frontiers | Research Topics

Effects of perinatal opioid exposure, volume II

Edited by
Henrietta S. Bada and Loretta Finnegan

Published in
Frontiers in Pediatrics

FRONTIERS EBOOK COPYRIGHT STATEMENT

The copyright in the text of individual articles in this ebook is the property of their respective authors or their respective institutions or funders. The copyright in graphics and images within each article may be subject to copyright of other parties. In both cases this is subject to a license granted to Frontiers.

The compilation of articles constituting this ebook is the property of Frontiers.

Each article within this ebook, and the ebook itself, are published under the most recent version of the Creative Commons CC-BY licence. The version current at the date of publication of this ebook is CC-BY 4.0. If the CC-BY licence is updated, the licence granted by Frontiers is automatically updated to the new version.

When exercising any right under the CC-BY licence, Frontiers must be attributed as the original publisher of the article or ebook, as applicable.

Authors have the responsibility of ensuring that any graphics or other materials which are the property of others may be included in the CC-BY licence, but this should be checked before relying on the CC-BY licence to reproduce those materials. Any copyright notices relating to those materials must be complied with.

Copyright and source acknowledgement notices may not be removed and must be displayed in any copy, derivative work or partial copy which includes the elements in question.

All copyright, and all rights therein, are protected by national and international copyright laws. The above represents a summary only. For further information please read Frontiers' Conditions for Website Use and Copyright Statement, and the applicable CC-BY licence.

ISSN 1664-8714
ISBN 978-2-8325-4799-1
DOI 10.3389/978-2-8325-4799-1

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Effects of perinatal opioid exposure, volume II

Topic editors

Henrietta S. Bada — University of Kentucky, United States

Loretta Finnegan — Thomas Jefferson University, United States

Citation

Bada, H. S., Finnegan, L., eds. (2024). *Effects of perinatal opioid exposure, volume II*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-4799-1

Table of contents

frontiers | Frontiers in Pediatrics

TYPE Editorial
PUBLISHED 05 April 2024
DOI 10.3389/fped.2024.1396595

Check for updates

OPEN ACCESS

EDITED AND REVIEWED BY
Eugene Dempsey,
University College Cork, Ireland

*CORRESPONDENCE
Henrietta S. Bada
hbada2@email.uky.edu

RECEIVED 06 March 2024
ACCEPTED 13 March 2024
PUBLISHED 05 April 2024

CITATION
Finnegan LP and Bada HS (2024) Editorial: Effects of perinatal opioid exposure—volume II. Front. Pediatr. 12:1396595. doi: 10.3389/fped.2024.1396595

COPYRIGHT
© 2024 Finnegan and Bada. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Editorial: Effects of perinatal opioid exposure—volume II

Loretta P. Finnegan[1] and Henrietta S. Bada[2]*

[1]Finnegan Consulting, LLC, Avalon, NJ, United States, [2]Department of Pediatrics, College of Medicine, University of Kentucky, Lexington, KY, United States

KEYWORDS

perinatal opioid exposure, neonatal abstinence syndrome, methadone, clonidine, long-term outcome, toxicology, ECMO, imaging

Editorial on the Research Topic
Effects of perinatal opioid exposure—volume II

1 Introduction

This second volume of the research topic on the Effects of Perinatal Opioid Exposure covers issues that address the various aspects of managing individuals during pregnancy, considering not only the treatment of opioid use disorder (OUD) but also the many factors that may affect the outcomes of pregnancy and infants with in-utero drug exposure (IUDE). Topics in this volume include preclinical studies, management of substance use disorder (SUD) during pregnancy, management of infants with prenatal exposure, long-term outcome studies that take into consideration factors such as parenting and psychological distress, examination of executive functioning and the trajectory of behavioral problems, and support for a recommendation to evaluate for individual and various other factors that may influence outcomes.

2 Preclinical studies

Clinically, oral opioid therapies for prenatal opioid exposure (POE) with the development of neonatal abstinence syndrome (NAS) are a standard of care, with morphine being the most commonly used medication. A non-opioid agent, clonidine, has recently been used for treatment of infants with NAS. However, data regarding the cellular and molecular effects of these treatments on the developing brain are still lacking. To address this gap in knowledge, Sithisarn et al., determined the effects of morphine or clonidine on the cell death of neonatal cortical explant cultures from Sprague Dawley rats after in-utero exposure to oxycodone. Explants from the prefrontal cortex (PFC) demonstrated greater cell death after prenatal treatment with oxycodone and postnatal treatment with morphine compared to treatment with clonidine. The PFC is vital for controlling higher-order executive functions such as behavioral flexibility, learning, and working memory.

Chin et al. defined the effects of POE on whole-brain functional connectivity and white matter injury using quantitative whole-brain structural and functional MRI in an established rat model of POE. Decreased connectivity in cortical-cortical and cortico-basal ganglia circuitry was particularly prominent with large effect sizes. These

data support that POE reduces brain-wide functional connectivity as well as the microstructural integrity of major white matter tracts. Altered neural circuitry, dysregulated network refinement, and diffuse network dysfunction have been implicated in the executive function deficits that are common in children with POE. Functional brain connectivity may serve as a translatable biomarker in children with POE.

3 Clinical investigations

Many healthcare providers lack training in screening for or treating SUD during pregnancy. The proliferation of punitive policies toward SUD has led to decreased prenatal care, no improvement in birth outcomes, and a disproportionate impact on Black, Indigenous, and other families of color. Barber and Terplan described the principles of care during pregnancy from an obstetrician-gynecologist perspective related to SUD, including the need to understand the unique barriers of pregnancy-capable persons, care for the dyad, person-centered language, and the high risk of mortality in the postpartum period with drug overdose being one of the leading causes of maternal death in the United States.

The use, misuse, and abuse of substances, particularly opioids, is an ongoing public health concern in this country and around the world. Resources to assist perinatal health professionals with this very complex subject are limited. Jones provides up-to-date information on the selection of monitoring protocols, the specifics of appropriate testing methodologies, and the interpretation of toxicological findings. A better understanding of these concepts will enable perinatal healthcare professionals to be a voice for the voiceless in order to protect and enrich lives during this unprecedented opioid epidemic.

Since the first use of methadone to treat OUD in pregnancy in the 1970s, there has been a long, controversial, and confusing history of studies, regulatory actions, and changes in practice that have clouded an accurate perception of methadone's use in pregnancy. McCarthy and Finnegan trace this history with a focus on the effect of methadone exposure during pregnancy on NAS. A new laboratory measure, the serum methadone/metabolite ratio, has provided a tool for documenting the profoundly dynamic nature of perinatal metabolism. The continuous induction of metabolic enzymes during pregnancy requires dose adjustments and changes in dosing frequency. The concept of "fetal methadone dosing" emphasizes that the relative stability of methadone levels in the fetus is an important consideration for methadone dosing in pregnancy.

The sharp increase in NAS cases has resulted in increased healthcare expenditures, resource utilization, and hospitalization of infants requiring pharmacotherapy. To mitigate the consequences of maternal-infant separation during pharmacological treatment, the Eat, Sleep, and Console (ESC) tool has become popular and is promoted as a novel method that focuses on the maternal/infant dyad with the resultant reduction of treatment duration and hospital stay. Gomez Pomar reviewed the studies on ESC and highlighted the differences among the studies. The majority were based on quality care initiatives with conflicting results. Although staff training has been proposed and the interventions of ESC have been defined, there still exists a lack of standardization of this practice, specifically with regard to the type of associated non-pharmacological practices as well as the reports of its short- and long-term outcomes, which may be attributable to a lack of randomized research trials. In a recent large multicenter trial using cluster randomization, infant follow-up was limited to 3 months post-discharge with no standard infant assessment.

The incidence of in-utero drug exposure (IUDE) and the use of neonatal extracorporeal membrane oxygenation (ECMO) have both increased over the past decade. There are no studies of infants with IUDE who required a life-saving procedure such as ECMO. Walther et al. reported that infants with IUDE had greater use of sedative and analgesic adjuvant medications during ECMO than infants with no IUDE on ECMO. Trend results indicated that post-ECMO feeding complications and total hospital stay were also greater in the IUDE-ECMO group. These findings illustrate the complex influence of prenatal drug exposure on neonatal patient care and warrant the development of clinical care strategies optimized for this unique patient group.

During the current opioid epidemic, opioids are commonly used with other substances such as tobacco and, more recently, the increase in methamphetamine has been selective to opioid use, particularly in rural regions. Wouldes and Lester provide a comprehensive review of the perinatal effects of the use of opioids and/or methamphetamines during pregnancy highlighting these effects on pregnant individuals and their infants. The characteristics of the women in both the opioid and methamphetamine studies were associated with poor maternal health, higher rates of mental illness, trauma, and poverty. Cardiovascular disease is not uncommon among women with substance use disorders, including opioid, methamphetamine, cocaine, alcohol, cannabis, or polydrug use. Women who used opioids and methamphetamines were reported to have poor maternal health, and rates of mental illness, trauma, and poverty. Infant outcomes that differed between opioid and methamphetamine exposure included variations in neurobehavior at birth which could complicate the diagnosis and treatment of neonatal opioid withdrawal. Given the complexity of OUD in pregnant individuals and the increasing co-use of these opioids with methamphetamine, future studies need to address the many confounders of perinatal outcomes and employ neurodevelopmental markers at birth that may help predict long-term neurodevelopmental outcomes.

4 Long-term outcome studies

The review by Yen and Davis elucidates the many reasons why very little is known about the immediate and long-term outcomes of these children with NAS which include: (1) barriers to maintaining short-term and long-term follow-up; (2) unclear mechanisms by which prenatal opioids affect the developing brain; (3) the multiplicity of psychosocial factors that affect child

development, and the varying degrees of deficits in different domains that are reported following prenatal opioid exposure; and (4) the non-uniformity of standardized tests administered at follow-up. Although not all of these factors are addressed or controlled for in all follow-up studies, the information would make clinicians and researchers aware of the possibility of lasting effects of perinatal opioid exposure.

Sarfi et al. prospectively followed mothers with OUD who were receiving opioid maintenance therapy (OMT), their children, and a comparison group of mothers with no history of substance use and their children. From the trajectories of maternal parenting distress and mental health, mothers on OMT had higher parenting distress and psychological distress than the comparison group. Parenting distress did not seem to affect the subscale of dysfunctional parent-child interactions or the subscale difficult child. Few mothers needed clinical intervention for psychological distress. Children of mothers on OMT had significantly higher levels of behavioral problems noted at 4.5 years of age than did comparison children, and these problems persisted to 8 years of age. However, problem scores decreased by 8 years in the comparison children. The long-term direct effects of prenatal opioid exposure on behavior problems appear to be modest in what appears to be a stable caregiving environment while receiving OMT.

Spowart et al. evaluated children with methadone exposure at ages 8–10 years, and a control group matched for gestational age, birth weight, and socio-economic status. Results from the administration of a battery of tests indicated no differences between exposed and non-exposed children as to the proportion of emotional, conduct, peer relationships, total difficulties or prosocial problems. However, a marginally higher proportion of exposed children had hyperactivity problems. In terms of executive regulation, the exposed children were significantly worse on indices of behavioral, emotional and cognitive regulation, and on the global executive composite. However, the effect of methadone was reduced with higher tobacco use. The study highlighted the importance of controlling for confounders in the determination of the effects of prenatal methadone exposure. These findings in school-aged children indicate a modest effect of methadone exposure on executive regulation.

Author contributions

LF: Writing – original draft, Writing – review & editing. HB: Writing – original draft, Writing – review & editing.

Acknowledgments

All authors listed have made a substantial, direct, or indirect and intellectual contribution to the work, and have approved it for publication. We would like to thank Frontiers in Pediatrics for the opportunity to bring this topic to you, the readers for their interest in this burgeoning topic, and the contributors for their time and effort in researching the various aspects of perinatal opioid exposure and related issues.

Conflict of interest

Author LF was employed by Finnegan Consulting LLC.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Pediatrics

TYPE Mini Review
PUBLISHED 07 November 2022
DOI 10.3389/fped.2022.1039055

Check for updates

OPEN ACCESS

EDITED BY
Henrietta S. Bada,
University of Kentucky, United States

REVIEWED BY
Enrique Gomez-Pomar,
University of Kentucky, United States
Shekher Mohan,
Liberty University, United States

*CORRESPONDENCE
Elizabeth Yen
eyen@tuftsmedicalcenter.org

SPECIALTY SECTION
This article was submitted to Neonatology, a section of the journal Frontiers in Pediatrics

RECEIVED 07 September 2022
ACCEPTED 18 October 2022
PUBLISHED 07 November 2022

CITATION
Yen E and Davis JM (2022) The immediate and long-term effects of prenatal opioid exposure. Front. Pediatr. 10:1039055. doi: 10.3389/fped.2022.1039055

COPYRIGHT
© 2022 Yen and Davis. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

The immediate and long-term effects of prenatal opioid exposure

Elizabeth Yen[1,2]* and Jonathan M. Davis[1,3]

[1]Department of Pediatrics, Tufts Medical Center, Boston, MA, United States, [2]Mother Infant Research Institute, Tufts Medical Center, Boston, MA, United States, [3]Tufts Clinical and Translational Science Institute, Boston, MA, United States

The opioid epidemic has adversely affected neonates and children, yet the mechanisms by which it impacts this population are not well understood. Not only does prenatal opioid exposure result in short-term consequences shortly after birth, it also creates long-term sequelae that may predispose these children to physical, emotional, psychiatric, cognitive, and socioeconomic problems in the future. This article provides a scoping overview of the long-term effects of antenatal opioid exposure on neonates and children as well as quality improvement and research efforts to understand and mitigate this major public health concern.

KEYWORDS

neonatal abstinence syndrome, short-term effects, long-term outcomes, nutrition, growth trajectory, brain development, ophthalmologic disorders, physical therapy

Introduction

Between 1999 and 2014, the number of pregnant women with opioid use disorder (OUD) increased from 1.5 to 6.5 cases per 1,000 hospital births (1). This led to a steep increase in the number of neonates with Neonatal Abstinence Syndrome (NAS) from 1.2 to 8.0 per 1,000 hospital births, with some areas reaching 20.0 per 1,000 hospital births (2, 3). A diagnosis of NAS is based on a variety of systems that evaluate the presence and severity of withdrawal (4–11). Non-pharmacologic approaches remain the primary focus of NAS management followed the initiation of pharmacotherapy if signs are still significant. This review will discuss the definition of NAS, pharmacotherapy of NAS, longer-term neurodevelopmental outcomes, and new initiatives to monitor and potentially mitigate longer-term complications.

The definition of NAS

With standardization of medication-assisted treatment (MAT), many pregnant women are receiving methadone, buprenorphine, and buprenorphine/naloxone. Consequently, neonatal opioid withdrawal syndrome (NOWS) is used to characterize signs of withdrawal result specifically from maternal opioid use. However, due to frequent polysubstance use during pregnancy, most clinicians continue to use the term NAS instead of NOWS.

While a diagnosis of NAS is made frequently, there is no consensus on the precise criteria. Some apply the diagnosis to: (1) all infants with a history of maternal OUD during pregnancy; (2) those with signs of withdrawal based on systems of assessment; and 3) the need for pharmacotherapy when non-pharmacologic measures are insufficient. Such variation in the definition of NAS can impact diagnostic coding, reimbursement, bedside management, research, and public health/policy (12).

To address this critical gap in terminology and the definition of NAS, a recent effort led by the US Department of Health and Human Services involved researchers, clinicians, and policy experts who proposed a simplified definition of NAS. The consensus recommendations included two key elements: (1) *in utero* exposure to opioids (with or without other substances), and (2) the presence of 2 of 5 of the most common clinical signs of NAS, i.e., high-pitched/excessive cry, poor sleep, hypertonia, tremors, and gastrointestinal issues. This *clinical definition* was intended to promote standardization of bedside management of these neonates, enhance research efforts, and promote public policy. The goal is to support the mother-infant dyad and provide services to help families impacted by the opioid epidemic. The authors acknowledged the unintended consequences of this enhanced definition and proposed foundational ethical principles while calling for the need to further validate the definition (12).

Effects of polysubstance use on the severity of NAS

Women with OUD experience other mental health issues and the need for psychotropic medications (13, 14). Infants exposed to maternal opioids were more likely to require pharmacotherapy when co-exposed to benzodiazepines (15), tobacco (16), selective serotonin reuptake inhibitors (16–18), gabapentin (19), marijuana (20), or cocaine (21). The use of psychotropic medications in addition to prescription opioids increased the severity of NAS by two-fold compared to the use of prescription opioids alone (22). The absolute risk for severe NAS (need for pharmacologic treatment) was highest in infants co-exposed to opioids and gabapentin. Conversely, some studies showed that the risk of NAS was not affected by other psychotropic medications (23–25). It is unclear if drug-drug interactions or other factors (e.g., socioeconomic, maternal stressors, other medical or psychiatric disorders) contribute to the severity of withdrawal in infants with polysubstance exposure. There is very limited long-term data regarding these multiple exposures and comprehensive studies (adjusting for multiple confounders) are urgently needed and are being evaluated in several National Institutes of Health (NIH) supported Helping End Addiction Long Term (HEAL) studies.

Presentation and management of NAS

Due to the continuous transplacental flow of opioids from the mother to the fetus, birth involves a sudden termination of supply and development of NAS. The μ-opioid receptors are ubiquitously present in the central nervous, peripheral nervous, and gastrointestinal systems. Opioid binding to these receptors inhibits adenyl cyclase, which further inhibits cyclic adenosine monophosphate (cAMP) production and downstream release of neurotransmitters (26). Cessation of opioids activates adenyl cyclase and disrupts the central, peripheral, and autonomic nervous systems that ultimately results in NAS. The onset of NAS can occur 24 h to several days after birth, depending on the half-life of the maternal opioid and other concurrent substance use.

First-line management of NAS is non-pharmacologic measures. Neonatal morphine solution is the most common opioid-replacement agent used in the US followed by methadone and buprenorphine. Non-opioid or adjunct agents include phenobarbital, clonidine, and gabapentin. Pharmacotherapy alleviates signs of withdrawal and optimizes short term physical, physiologic, and psychological functioning. A comprehensive review on the pharmacotherapy of NAS was recently published (27).

Ongoing management and long-term effects of NAS

Breastfeeding and use of breastmilk

Research demonstrates the benefits of breastfeeding in mother-infant dyads, especially pregnant mothers receiving MAT and not using illicit drugs (28–30). Although limited by small sample sizes, breastmilk analyses have shown that the concentrations of buprenorphine and methadone are low and pose minimal risks to neonates (31, 32). There are clear benefits of breastfeeding including less severe withdrawal, less need for pharmacotherapy, and shorter length of hospital stay (33, 34). The American Academy of Pediatrics (AAP) has recommended breastfeeding based on long-term benefits such as lower risk of type II diabetes, hypertension, and cancer in mothers and lower respiratory tract infections, diarrhea, otitis media, sudden infant death syndrome, asthma, and obesity in infants and children (28).

Physical therapy

In response to the opioid epidemic, the American Physical Therapy Association has advocated for safer alternatives to pharmacologic management of pain (35). The Association promoted a non-pharmacologic approach to alleviate pain and treat NAS through its "#ChoosePT" campaign (36). Neonatal physical therapists can recognize different clinical manifestations of withdrawal from various pharmacologic agents. Such early recognition is crucial in allowing the physical therapist to help alleviate the signs of withdrawal. Physical therapists develop and personalize care plans based on the Synactive Theory of Development, focusing on an infant's interaction with the environment, particularly on four behavioral subsystems, i.e., 1) autonomic control, 2) muscle tone and motor control, 3) sleep-wake cycle and attention state control, and 4) sensory processing/modulation (37–39). Good communication between bedside clinical staff and physical therapists is essential in providing infants with the best care plan. Ideally infants should be calm, especially at the beginning of their waking time so that physical therapists can observe the natural sleep-wake transitions and the infant's regulation skills.

Using various standardized motor assessments such as the NICU Network Neurobehavioral Scale/NNNS (40) and Brazelton Neonatal Behavioral Assessment Scale (41), physical therapists can optimize a neonate's sensory-motor environment. Such interventions may include tactile stimulation, positioning aids to create supportive boundaries, vertical rocking, pacifier usage, and other calming strategies. Environmental controls that benefit opioid-exposed neonates include low-stimulation environments, e.g., minimal noise, dim lights, and the use of white noise. Additionally, sensory-motor integration may benefit from infant massage (41), swaddling, hydrotherapy (42), antigravity postural positioning, and slow and steady movements (43). All these interventions aim to integrate auditory, tactile, visual, and vestibular management to improve behavioral state regulation in opioid-exposed neonates.

Nutrition and growth

Infants with prenatal opioid exposure are at risk for premature birth, lower birth weight, and a smaller head circumference (44–46). These likely result from the influence of maternal opioid/drug use on placental function and nutritional transport, which in turn may lead to fetal growth restriction (47). These neonates often experience postnatal growth issues, believed to result from a withdrawal-induced hypermetabolic state, feeding difficulties, and/or gastrointestinal disturbances (48, 49). A recent study demonstrated the molecular impact of prenatal opioid exposure on the hypothalamic and reward genes that regulate feeding behavior, indicating that *in utero* opioids can affect feeding regulation resulting in subsequent feeding difficulties and growth failure (50).

Because of the smaller size and postnatal growth failure, studies examined whether higher caloric intake could provide better nutritional support for opioid-exposed neonates. Infants randomized to 24 kilocalories per ounce (kcal/oz) formula had greater weight gain compared to those receiving standard 20 kcal/oz formula indicating that more calories are needed to provide ideal nutritional support in NAS (48). Another study showed that the high-caloric formulas were associated with less treatment failure, less weight loss, and shorter LOS compared to lower caloric formula (51). Although low-lactose formulas are perceived to alleviate gastrointestinal issues during the withdrawal period (51), several studies showed that low-lactose formula did not improve NAS outcomes (30, 52, 53).

Although opioid-exposed neonates are born smaller and may have early weight loss, these infants may develop hyperphagia as a compensatory mechanism (54, 55). The growth trajectory of these infants can involve excessive catch-up growth in the first year of life with body composition analysis showing more rapid gain in fat compared to fat-free mass (56, 57). A longitudinal study of cocaine-exposed neonates demonstrated that those born small for gestational age (SGA) developed rapid catch-up growth with a four-fold risk of obesity at nine years of age (58). While this study focused on prenatal cocaine exposure, it would be interesting to examine if opioid-exposed neonates have a similar risk profile. Could the smaller size at birth and abnormal feeding regulation and growth patterns be followed by increased adiposity in childhood and obesity/metabolic syndrome in adulthood? Opioid-exposed neonates may undergo fetal reprogramming (i.e., epigenetic changes) that may contribute to metabolic syndrome, abnormal lipid profiles, and cardiovascular disease in adults with opioid use disorder (59, 60). These studies suggest that opioid-exposed neonates may be at increased risk for nutritional and growth challenges that may persist into adulthood. While physicians are increasingly aware of the need for higher calories and nutritional evaluation for opioid-exposed neonates, there is a great need to advocate for long-term follow-up of infant growth (48, 51).

Abnormal brain development

Emerging data demonstrate the adverse effects of prenatal opioid exposure on the developing brain at the macrostructural, microstructural, neurophysiological, and/or functional levels. *In utero* opioid exposure results in a smaller

head circumference (e.g., altered brain growth), although this effect may be mediated by co-exposure to maternal tobacco or other psychoactive medications (44, 61–64). Early studies using ultrasonography have shown enlargement of in the thalamus of exposed subjects over the first six months of life (65, 66). Amplitude electroencephalographic (aEEG) recordings in opioid-exposed neonates showed increased discontinuity and low voltage recordings, as well as reduced or absent sleep-wake cycling; all these factors were associated with the severity of withdrawal and the need for pharmacotherapy (67–69). aEEG also detected brief seizures in more than half of the infants developing NAS (69).

Magnetic resonance imaging (MRI) has also demonstrated smaller volumes in the basal ganglia, deep gray matter, thalamus, ventrolateral nuclei, brainstem, and cerebrospinal and larger volumes in the right cingulate gyrus and left occipital lobe white matter in NAS (70, 71). Merhar and colleagues reported punctate white matter lesions in the brain of 8 of 20 opioid-exposed neonates (72). In addition to the macrostructural changes, opioid-exposed neonates also have microstructural abnormalities. Diffusion tract imaging of opioid-exposed neonates demonstrated quantitatively and qualitatively reduced fractional anisotropy (FA), which reflects fiber density, axonal diameter, and the degree of myelination, evidence of compromised white matter tract integrity (73, 74). Because reduced FA is associated with motor and cognitive deficits (75), these findings may explain the neurodevelopmental issues experienced by infants with NAS and emphasize the need to monitor this population more closely. The Outcome of Babies with Opioid Exposure (OBOE) study is an ongoing longitudinal cohort study designed to evaluate the impact of prenatal opioid exposure on brain structure-function relationships over the first two years of life (76).

Advanced neuroimaging can provide an even more sophisticated way to demonstrate the adverse impact of prenatal opioid exposure on the developing brain. Radhakrishnan et al. utilized resting-state functional brain MRI and showed significantly higher connectivity between the right amygdala and medial prefrontal region in the exposed cohort (77). Given the role of the amygdala in emotion, stress, and fear and of the prefrontal cortex in the executive function and working memory, this finding has important implications for future addiction-related behavior and risks. Furthermore, alterations in thalamocortical functional connectivity in the brain correlated with the severity of NAS (78). This emphasizes the utility of delineating the subtle yet intricate alterations in neural circuitry caused by prenatal opioid exposure. Another study using resting-state functional MRI also showed that infants with prenatal opioid exposure had smaller network volumes, particularly in the primary visual network, which may explain the higher risk of developmental and visual problems (79).

Visual evoked potentials (VEP) are another method that has demonstrated altered brain functioning in NAS (80). Although VEP does not directly correlate with visual function, it reflects neural maturity and myelination when recording activity over the occipital area. This can provide an objective measure of the visual pathway from the retina to the visual cortex (81). Opioid-exposed neonates have been found to have abnormal VEP including altered morphology, decreased amplitudes, and prolonged peak times (82, 83). These findings either normalized in the first few years of life or persisted until a decade later (80–82, 84), highlighting the importance of ongoing surveillance throughout life in these high-risk infants.

Neurodevelopmental outcomes and early intervention (EI)

Opioid-exposed neonates are at increased risk for developmental, behavioral, educational, and psychological/mental health issues later in life (85–89). Neonates with NAS requiring pharmacotherapy are even more vulnerable due to *in utero* and postnatal exposures. A multisite, blinded, randomized controlled trial comparing methadone with morphine in NAS demonstrated the superiority of methadone on length of hospital stay, length of stay due to NAS, and length of treatment (90). Despite this finding, a follow-up analysis looking at developmental milestones at 18 months demonstrated that neonates in both treatment arms had similar neurobehavioral deficits and a higher rate of the atypical profile on the NNNS which is associated with worse neurodevelopmental outcomes (91). Furthermore, a higher NAS severity index may be predictive of developmental outcomes at 18 months (92), highlighting the necessity for longitudinal follow-up in these high-risk infants.

Updated AAP guidelines on NAS has emphasized the need for close developmental, behavioral, and mental health screenings after infants are discharged from the hospital (94). All opiod-exposed infants should be referred for comprehensive services (e.g., NICU developmental follow-up programs, EI, etc.) as available. This is a focus of part C of the Individuals with Disabilities Education Act (IDEA) (https://www.cdc.gov/ncbddd/cp/treatment.html) in order to further monitor developmental milestones in these high risk infants (93, 94). Even though EI services are available in all areas in the United States, not all opioid-exposed infants and their families receive these services. Peacock-Chambers et al. showed that in Massachusetts, where the diagnosis of NAS serves as automatic eligibility for one-year EI services, less than half of eligible infants enrolled (95). The rate of EI referral was also shown to vary by custody status (two-fold higher for those discharged with their biological families than foster families) and length of hospital stay (greater referral for those with longer stay). EI referral did not equate to EI

enrollment, with only half of referred infants actually enrollment. A national survey also confirmed suboptimal EI referral for opioid-exposed neonates and the discrepancy based on the need for pharmacotherapy, with those requiring pharmacotherapy getting a higher referral rate than those who did not (96). This finding is concerning since all opioid-exposed neonates are at risk for long-term adverse effects, irrespective of the severity of withdrawal and the need for pharmacotherapy (97). Other home-based services, such as the Maternal, Infant, and Early Childhood Home Visiting Program may also benefit these families.

Although a few follow-up studies did not demonstrate significant developmental deficits in children with prenatal opioid exposure, these children can actually demonstrate poorer school performance and worse functioning at adolescence (85, 87). However, these findings may be influenced by food and housing insecurity, psychological and physical stress, and many other environmental factors encountered in childhood. There is an urgent need to study the long-term impact of prenatal opioid exposure which should also include academic and family outcomes to determine if significant differences exist related to the types of treatments (non-pharmacologic/pharmacologic) as well as various therapeutic approaches (scheduled treatments compared to use as needed).

Ophthalmologic disorders

Neonates with prenatal opioid exposure are at risk for ophthalmologic abnormalities such as strabismus, nystagmus, reduced visual acuity, impaired smooth pursuit, and delayed visual development due to direct neurotoxic effects of opioids and/or other social and neurodevelopmental factors (98–101). A cross-sectional study of children with a history of prenatal opioid exposure showed a 10-fold risk of strabismus in the first three years of life, with the mean age of presentation at 8.3 months (102). Another study showed a 6-fold risk of strabismus and a 90-fold risk of nystagmus in the first five years of life (103). While exodeviations presented earlier in life (6.8 months), esodeviations presented later at 11.6 months (104). A cohort study in a million infants showed that those with NAS had an 8-fold risk of nystagmus, 4.7-fold risk of strabismus, and a 2-fold risk of ophthalmologic-related hospitalization before age 13 (86). A longitudinal cohort study in nearly 800,000 infants showed that substance-exposed infants had a significantly higher incidence of ophthalmologic-related hospital admissions compared to unexposed infants (47.0 vs. 32.0 per 10,000 person-years), with a much higher cumulative incidence that widened over time (399.8 per 10,000 by 12 years of age). Opioids were shown to have a greater impact on ophthalmologic-related hospitalizations than cocaine, cannabis, and others (105). Altogether, evidence supports the association between prenatal opioid exposure, abnormal visuomotor development, and the need for comprehensive anticipatory guidance and timely ophthalmology referrals for this population.

Conclusion

The study and understanding of NAS has advanced dramatically in the last several decades resulting in tremendous progress in the care of maternal-infant dyads affected by the opioid epidemic. The well-being of these families remains a major public health priority that must look beyond the short-term issues. In addition to efforts to reduce costs and length of hospital stay, clinicians and researchers must provide sound anticipatory guidance that prioritizes multifaceted care surrounding infants with NAS—nutrition, growth, cognitive and neurodevelopmental follow-up, physical therapy, ophthalmologic evaluation, and ample family support. Prenatal opioid exposure is a lifelong process with potentially deleterious effects if not closely monitored. All healthcare, government, industrial, and public health stakeholders must collaborate and advance care that focuses on both the short and longer-term preventive and curative measures for this vulnerable and high-risk population.

Author contributions

EY: paper concept, writing and editing of manuscript. JD: paper concept and manuscript editing. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Haight SC, Ko JY, Tong VT, Bohm MK, Callaghan WM. Opioid use disorder documented at delivery hospitalization—united States, 1999–2014. *MMWR Morb Mortal Wkly Rep*. (2018) 67:845–9. doi: 10.15585/mmwr.mm6731a1

2. Winkelman TNA, Villapiano N, Kozhimannil KB, Davis MM, Patrick SW. Incidence and costs of neonatal abstinence syndrome among infants with medicaid: 2004–2014. *Pediatrics*. (2018) 141:e20173520. doi: 10.1542/peds.2017-3520

3. Tolia VN, Patrick SW, Bennett MM, Murthy K, Sousa J, Smith PB, et al. Increasing incidence of the neonatal abstinence syndrome in U.S. Neonatal ICUs. *New Engl J Med*. (2015) 372:2118–26. doi: 10.1056/NEJMsa1500439

4. Finnegan LP, Connaughton Jr JF, Kron RE, Enich JP. Neonatal abstinence syndrome: assessment and management. *Addict Dis*. (1975) 2:141–58.

5. Finnegan LP, Kaltenbach K. Neonatal abstinence syndrome. In: RA Hoekelman, SB Friedman, NM Nelson, HM Seidel, ML Weitzman, editors. *Primary pediatric care*. St. Louis: Mosby (1992). p. 1367–78.

6. Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med*. (2010) 363:2320–31. doi: 10.1056/NEJMoa1005359

7. Jones HE, Seashore C, Johnson E, Horton E, O'Grady KE, Andringa K, et al. Psychometric assessment of the neonatal abstinence scoring system and the MOTHER NAS scale. *Am J Addict*. (2016) 25:370–3. doi: 10.1111/ajad.12388

8. Lipsitz PJ. A proposed narcotic withdrawal score for use with newborn infants: a pragmatic evaluation of its efficacy. *Clin Pediatr*. (1975) 14:592–4. doi: 10.1177/000992287501400613

9. Zahorodny W, Rom C, Whitney W, Giddens S, Samuel M, Maichuk G, et al. The neonatal withdrawal inventory: a simplified score of newborn withdrawal. *J Behav Pediatr*. (1998) 19:89–93. doi: 10.1097/00004703-199804000-00005

10. Green M, Suffet F. The neonatal narcotic withdrawal index: a device for the improvement of care in the abstinence syndrome. *Am J Drug Alcohol Abuse*. (1981) 8:203–13. doi: 10.3109/00952998108999125

11. Grossman MR, Lipshaw MJ, Osborn RR, Berkwitt AK. A novel approach to assessing infants with neonatal abstinence syndrome. *Hosp Pediatr*. (2018) 8:1–6. doi: 10.1542/hpeds.2017-0128

12. Jilani SM, Jones HE, Grossman M, Jansson LM, Terplan M, Faherty LJ, et al. Standardizing the clinical definition of opioid withdrawal in the neonates. *J Pediatr*. (2022) 243:33–9.e1. doi: 10.1016/j.jpeds.2021.12.021

13. Hwang CS, Kang EM, Kornegay CJ, Staffa JA, Jones CM, McAninch JK. Trends in the concomitant prescribing of opioids and benzodiazepines, 2002-2014. *Am J Prev Med*. (2016) 51:151–60. doi: 10.1016/j.amepre.2016.02.014

14. Hanley GE, Mintzes B. Patterns of psychotropic medicine use in pregnancy in the United States from 2006 to 2011 among women with private insurance. *BMC Pregnancy Childbirth*. (2014) 14:242. doi: 10.1186/1471-2393-14-242

15. Sanlorenzo LA, Cooper WO, Dudley JA, Stratton S, Maalouf FI, Patrick SW. Increased severity of neonatal abstinence syndrome associated with concomitant antenatal opioid and benzodiazepine exposure. *Hosp Pediatr*. (2019) 9:569–75. doi: 10.1542/hpeds.2018-0227

16. Patrick SW, Dudley J, Martin PR, Harrell FE, Warren MD, Hartmann KE, et al. Prescription opioid epidemic and infant outcomes. *Pediatrics*. (2015) 135:842–50. doi: 10.1016/j.whi.2021.03.002

17. Bhatt-Mehta V, Richards J, Sturza J, Schumacher RE. Impact of in-utero exposure to selective serotonin reuptake inhibitors and opioids on neonatal opioid withdrawal syndrome. *J Addict Med*. (2019) 13:227–34. doi: 10.1097/ADM.0000000000000484

18. Bakhireva LN, Sparks A, Herman M, Hund L, Ashley M, Salisbury A. Severity of neonatal opioid withdrawal syndrome with prenatal exposure to serotonin reuptake inhibitors. *Pediatr Res*. (2022) 91:867–73. doi: 10.1038/s41390-021-01756-4

19. Loudin S, Haas J, Payne M, Linz MF, Meaney-Delman D, Honein MA, et al. Identifying co-exposure to opiates and gabapentin during pregnancy. *J Pediatr*. (2020) 217:196–8. doi: 10.1016/j.jpeds.2019.09.029

20. O'Connor AB, Kelly BK, O'Brien LM. Maternal and infant outcomes following third trimester exposure to marijuana in opioid dependent pregnant women maintained on buprenorphine. *Drug Alcohol Depend*. (2017) 180:200–3. doi: 10.1016/j.drugalcdep.2017.08.012

21. Fulroth R, Phillips B, Durand DJ. Perinatal outcome of infants exposed to cocaine and/or heroin in utero. *Am J Dis Child*. (1989) 143:905–10. doi: 10.1001/archpedi.1989.02150200057018

22. Huybrechts KF, Bateman BT, Desai RJ, Hernandez-Diaz S, Rough K, Mogun H, et al. Risk of neonatal drug withdrawal after intrauterine co-exposure to opioids and psychotropic medications: cohort study. *Br Med J*. (2017) 358:j3326. doi: 10.1136/bmj.j3326

23. Heintzelman J, Persons L, Melnykov I. Substance use during pregnancy: impact on Colorado community hospital. *J Cannabis Res*. (2020) 11(2):39. doi: 10.1186/s42238-020-00047-9

24. Dryden C, Young D, Hepburn M, Mactier H. Maternal methadone use in pregnancy: factors associated with the development of neonatal abstinence syndrome and implications for healthcare resources. *BJOG*. (2009) 116:665–71. doi: 10.1111/j.1471-0528.2008.02073.x

25. Kaltenbach K, Holbrook AM, Coyle MG, Heil SH, Salisbury AL, Stine SM, et al. Predicting treatment for neonatal abstinence syndrome in infants born to women maintained on opioid agonist medication. *Addiction*. (2012) 107(Suppl 1):45–52. doi: 10.1111/j.1360-0443.2012.04038.x

26. Johnson K, Gerarda C, Greenough A. Treatment of neonatal abstinence syndrome. *Arch Dis Child Fetal Neonatal Med*. (2019) 24:133–41.

27. Yen E, Kraft W, Davis JM. Pharmacologic management of neonatal abstinence syndrome. In: SJ Yaffe, JV Aranda, editors. *Neonatal and pediatric pharmacology: Therapeutic principles in practice*, 5th ed. Philadelphia, PA: Wolters Kluwer (2021). p. 530–40.

28. Meek JY, Noble L. Section on breastfeeding. Policy statement: breastfeeding and the use of human milk. *Pediatrics*. (2022) 150:e2022057988. doi: 10.1542/peds.2022-057988

29. Holmes AP, Schmidlin HN, Kurzum EN. Breastfeeding considerations for mothers of infants with neonatal abstinence syndrome. *Pharmacotherapy*. (2017) 37:861–9. doi: 10.1002/phar.1944

30. Lembeck AL, Tuttle D, Locke R, Lawler L, Jimenez P, Mackley A, et al. Breastfeeding and formula selection in neonatal abstinence syndrome. *Am J Perinatol*. (2021) 38:1488–93. doi: 10.1055/s-0040-1713754

31. Ilett KF, Hackett LP, Gower S, Doherty DA, Hamilton D, Bartu AE. Estimated dose exposure of the neonate to buprenorphine and its metabolite norbuprenorphine via breastmilk during maternal buprenorphine substitution treatment. *Breastfeed Med*. (2012) 7:269–74. doi: 10.1089/bfm.2011.0096

32. Jansson LM, Choo R, Velez ML, Lowe R, Huestis MA. Methadone maintenance and long-term lactation. *Breastfeed Med*. (2008) 3:34–7. doi: 10.1089/bfm.2007.0032

33. Chu L, McGrath JM, Qiao J, Brownell E, Recto P, Cleveland LM, et al. A meta-analysis of breastfeeding effects for infants with neonatal abstinence syndrome. *Nurs Res*. (2022) 71:54–65. doi: 10.1097/NNR.0000000000000555

34. Short VL, Gannon M, Abatemarco DJ. The association between breastfeeding and length of hospital stay among infants diagnosed with neonatal abstinence syndrome: a population-based study of in-hospital births. *Breastfeed Med*. (2016) 11:343–9. doi: 10.1089/bfm.2016.0084

35. McCarty DB, Peat JR, O'Donnell S, Graham E, Malcolm WF. "Choose physical therapy" for neonatal abstinence syndrome: clinical management for infants affected by the opioid crisis. *Phys Ther*. (2019) 99:771–85. doi: 10.1093/ptj/pzz039

36. American Physical Therapy Association White Paper. Beyond opioids: how physical therapy transforms pain management to improve health (2021). Available at: https://www.apta.org/contentassets/b9421650038941469c75d06a0a191069/beyond-opioids-white-paper.pdf (Accessed August 13, 2022).

37. Als H. Toward a synactive theory of development: promise for the assessment and support of infant individually. *Infant Ment Health J*. (1982) 3:229–43. doi: 10.1002/1097-0355(198224)3:4<229::AID-IMHJ2280030405>3.0.CO;2-H

38. Maltese A, Gallai B, Marotta R, Lavano F, Lavano SM, Tripi G, et al. The synactive theory of development: the keyword for neurodevelopmental disorders. *Acta Medica Medit*. (2017) 33:257. doi: 10.19193/0393-63842017_2s_194

39. Velez M, Jansson LM. The opioid dependent mother and newborn dyad: non-pharmacologic care. *J Addict Med*. (2008) 2:113–20. doi: 10.1097/ADM.0b013e31817e6105

40. Wouldes TA, Woodward LJ. Neurobehavior of newborn infants exposed prenatally to methadone and identification of a neurobehavioral profile linked to poorer neurodevelopmental outcomes at age 24 months. *PLoS One*. (2020) 15:e0240905. doi: 10.1371/journal.pone.0240905

41. Barlow J, Herath NI, Bartram Torrance C, Bennett C, Wei Y. The neonatal behavioral assessment scale (NBAS) and newborn behavioral observations (NBO)

system for supporting caregivers and improving outcomes in caregivers and their infants. *Cochrane Database Syst Rev*. (2018) 3:CD011754. doi: 10.1002/14651858.CD011754.pub2

42. Hahn J, Lengerich A, Byrd R, Stoltz R, Hench J, Byrd S, et al. Neonatal abstinence syndrome: the experience of infant massage. *Create Nurs*. (2016) 22:45–50. doi: 10.1891/1078-4535.22.1.45

43. Çaka SY, G?zen D. Effects of swaddled and traditional tub bathing methods on crying and physiological responses of newborns. *J Spec Pediatr Nurs*. (2018) 23:e12202. doi: 10.1111/jspn.12202

44. Graeve R, Balalian AA, Richter M, Kielstein H, Fink A, Martins SS, et al. Infants' prenatal exposure to opioids and the association with birth outcomes: a systematic review and meta-analysis. *Paediatr Perinat Epidemiol*. (2022) 36:125–43. doi: 10.1111/ppe.12805

45. Azuine RE, Ji Y, Chang HY, Kim Y, Ji H, DiBari J, et al. Prenatal risk factors and perinatal and postnatal outcomes associated with maternal opioid exposure in an urban, low-income, multiethnic US population. *JAMA Netw Open*. (2019) 2:e196405. doi: 10.1001/jamanetworkopen.2019.6405

46. Leyenaar JK, Schaefer AP, Sawwerman JR, Moen EL, O'Malley AJ, Goodman DC. Infant mortality associated with prenatal opioid exposure. *JAMA Pediatr*. (2021) 175:706–14. doi: 10.1001/jamapediatrics.2020.6364

47. Harter K. Opioid use disorder in pregnancy. *Ment Health Clin*. (2019) 9:359–72. doi: 10.9740/mhc.2019.11.359

48. Bogen DL, Hanusa BH, Baker R, Medoff-Cooper B, Cohlan B. Randomized clinical trial of standard- versus high-calorie formula for methadone-exposed infants: a feasibility study. *Hosp Pediatr*. (2018) 8:7–14. doi: 10.1542/hpeds.2017-0114

49. Favara MT, Smieth J, Friedman D, Lafferty M, Carola D, Adeniyi-Jones S, et al. Growth failure in infants with neonatal abstinence syndrome in the neonatal intensive care unit. *J Perinatol*. (2022) 42:313–8. doi: 10.1038/s41372-021-01183-7

50. Yen E, Kaneko-Tarui T, Ruthazer R, Harvey-Wilkes K, Hassaneen M, Maron JL. Sex-dependent gene expression in infants with neonatal opioid withdrawal syndrome. *J Pediatr*. (2019) 214:60–65.e2. doi: 10.1016/j.jpeds.2019.07.032

51. Kaplan HC, Kuhnell P, Walsh MC, Crowley M, McClead R, Wexelblatt S, et al. Orchestrated testing of formula type to reduce length of stay in neonatal abstinence syndrome. *Pediatrics*. (2020) 146:e20190914. doi: 10.1542/peds.2019-0914

52. Pandey R, Kanike N, Ibrahim M, Swarup N, Super DM, Groh-Wargo S, et al. Lactose-free infant formula does not change outcomes of neonatal abstinence syndrome (NAS): a randomized clinical trial. *J Perinatol*. (2021) 41:598–605. doi: 10.1038/s41372-020-00797-7

53. Alsaleem M, Dusin J, Akangire G. Effect of low lactose formula on the short-term outcomes of neonatal abstinence syndrome: a systematic review. *Glob Pediatr Health*. (2021) 8:2333794X211035258. doi: 10.1177/2333794X211035258

54. Shephard R, Greenough A, Johnson K, Gerada C. Hyperphagia, weight gain, and neonatal drug withdrawal. *Acta Paediatr*. (2002) 91:951–3. doi: 10.1080/080352502760272641

55. Martinez A, Kastner B, Taeusch HW. Hyperphagia in neonates withdrawing from methadone. *Arch Dis Child Fetal Neonatal Ed*. (1999) 80:F178–82. doi: 10.1136/fn.80.3.f178

56. Corr TE, Schaefer W, Paul IM. Body composition during the first 4 months in infants affected by neonatal abstinence syndrome: a pilot study. *J Dev Orig Health Dis*. (2022) 13:120–7. doi: 10.1017/S2040174421000052

57. Vance JC, Chat DC, Tudehope DI, Gray PH, Hayes AJ. Infants born to narcotic dependent mothers: physical growth patterns in the first 12 months of life. *J Paediatr Child Health*. (1997) 33:504–8. doi: 10.1111/j.1440-1754.1997.tb01659.x

58. LaGasse L, Gaskins RB, Bada HS, Shankaran S, Liu J, Lester BM, et al. Prenatal cocaine exposure and childhood obesity at nine years. *Neurotoxicol Teratol*. (2011) 33:188–97. doi: 10.1016/j.ntt.2010.11.002

59. Najafipour H, Beik A. The impact of opium consumption on blood glucose, serum lipids and blood pressure, and related mechanisms. *Front Physiol*. (2016) 7:436. doi: 10.3389/fphys.2016.00436

60. Vallecillo G, Robles MJ, Torrens M, Samos P, Roquer A, Martires PK, et al. Metabolic syndrome among individuals with heroin use disorders on methadone therapy: prevalence, characteristics, and related factors. *Subst Abus*. (2018) 39:46–51. doi: 10.1080/08897077.2017.1363122

61. Kaltenbach K, Finnegan LP. Perinatal and developmental outcome of infants exposed to methadone in-utero. *Neurotoxicol Teratol*. (1987) 9:311–3. doi: 10.1016/0892-0362(87)90021-3

62. Towers CV, Hyatt BW, Visconti KC, Chernicky L, Chattin K, Fortner KB. Neonatal head circumference in newborns with neonatal abstinence syndrome. *Pediatrics*. (2019) 143:e20180541. doi: 10.1542/peds.2018-0541

63. Choo RE, Huestis MA, Schroeder JR, Shin AS, Jones HE. Neonatal abstinence syndrome in methadone-exposed infants is altered by level of prenatal tobacco exposure. *Drug Alcohol Depend*. (2004) 75:253–60. doi: 10.1016/j.drugalcdep.2004.03.012

64. Morimoto D, Washio Y, Hatayama K, Okamura T, Watanabe H, Yoshimoto J, et al. Head circumference in infants with nonopiate-induced neonatal abstinence syndrome. *CNS Spectr*. (2021) 26:509–12. doi: 10.1017/S1092852920001522

65. Schulson M, Liu A, Björkman T, Quinton A, Mann KP, Benzie R, et al. Mid-gestational enlargement of fetal thalami in women exposed to methadone during pregnancy. *Front Surg*. (2014) 1:28. doi: 10.3389/fsurg.2014.00028

66. Pasto ME, Deiling J, Graziani LJ, Ehrlich S, Finnegan LP. Disparity in hemispheric and thalamic growth in infants undergoing abstinence. *NIDA Res Monogr*. (1986) 67:342–8.

67. Limjoco J, Zawadzki L, Belden M, Eickhoff J, Ikonomidou C. Amplitude-integrated EEG use in neonatal abstinence syndrome: a pilot study. *J Matern Fetal Neonatal Med*. (2020) 33:3565–70. doi: 10.1080/14767058.2019.1579190

68. Lust C, Vesoulis ZA, Zempel J, Gu H, Lee S, Rao R, et al. An amplitude integrated EEG evaluation of neonatal opioid withdrawal syndrome. *Am J Perinatol*. (2022). Online ahead of print. doi: 10.1055/a-1877-9291

69. Rana D, Pollard L, Rowland J, Dhanireddy R, Pourcyrous M. Amplitude-integrated EEG in infants with neonatal abstinence syndrome. *J Neonatal Perinatal Med*. (2019) 12:391–7. doi: 10.3233/NPM-1834

70. Yuan Q, Rubic M, Seah J, Rae C, Wright IM, Kaltenbach K, et al. Do maternal opioids reduce neonatal regional brain volumes? A pilot study. *J Perinatol*. (2014) 34:909–13. doi: 10.1038/jp.2014.111

71. Merhar SL, Kline JE, Braimah A, Kline-Fath BM, Tkach JA, Altaye M, et al. Prenatal opioid exposure is associated with smaller brain volumes in multiple regions. *Pediatr Res*. (2021) 90:397–402. doi: 10.1038/s41390-020-01265-w

72. Merhar SL, Parikh NA, Braimah A, Poindexter BB, Tkach J, Kline-Fath B. White matter injury and structural anomalies in infants with prenatal opioid exposure. *AJNR Am J Neuroradiol*. (2019) 40:2161–5. doi: 10.3174/ajnr.A6282

73. Monnelly VJ, Anblagan D, Quigley A, Cabez MB, Cooper ES, Mactier H, et al. Prenatal methadone exposure is associated with altered neonatal brain development. *Neuroimage Clin*. (2017) 18:9–14. doi: 10.1016/j.nicl.2017.12.033

74. Sikka P, Madan N, Yen E. Early white matter tract changes in neonates with prenatal opioid exposure: a pilot study. *J Perinatol*. (2022). Online ahead of print. doi: 10.1038/s41372-022-01427-0

75. Loe IM, Adams JN, Feldman HM. Executive function in relation to white matter in preterm and full term children. *Front Pediatr*. (2019) 6:418. doi: 10.3389/fped.2018.00418

76. Bann CM, Newman JE, Poindexter B, Okoniewski K, DeMauro S, Lorch SA, et al. Outcomes of babies with opioid exposure (OBOE): protocol of a prospective longitudinal cohort study. *Pediatr Res*. (2022). Online ahead of print. doi: 10.1038/s41390-022-02279-2

77. Radhakrishnan R, Elsaid NMH, Sadhasivam S, Reher TA, Hines AC, Yoder KK, et al. Resting state functional MRI in infants with prenatal opioid exposure-a pilot study. *Neuroradiology*. (2021) 63:585–91. doi: 10.1007/s00234-020-02552-3,

78. Radhakrishnan R, Vishnubhotla RV, Guckien Z, Zhao Y, Sokol GM, Haas DM, et al. Thalamocortical functional connectivity in infants with prenatal opioid exposure correlates with severity of neonatal opioid withdrawal syndrome. *Neuroradiology*. (2022) 64:1649–59. doi: 10.1007/s00234-022-02939-4

79. Merhar SL, Jiang W, Parikh NA, Yin W, Zhou Z, Tkach JA, et al. Effects of prenatal opioid exposure on functional networks in infancy. *Dev Cogn Neurosci*. (2021) 51:100996. doi: 10.1016/j.dcn.2021.100996

80. Mactier H, Hamilton R. Prenatal opioid—increasing evidence of harm. *Early Hum Dev*. (2020) 15:105188. doi: 10.1016/j.earlhumdev.2020.105188

81. Whitham JN, Spurrier NJ, Sawyer MG, Baghurst PA, Taplin JE, White JM, et al. The effects of prenatal exposure to buprenorphine or methadone on infant visual evoked potentials. *Neurotoxicol Teratol*. (2010) 32:280–8. doi: 10.1016/j.ntt.2009.09.001

82. McGlone L, Mactier H, Hamilton R, Bradnam M, Boulton R, Borland W, et al. Visual evoked potentials in infants exposed to methadone in utero. *Arch Dis Child*. (2008) 93:784–6. doi: 10.1136/adc.2007.132985

83. McGlone L, Hamilton R, McCulloch DL, Boulton R, Bradnam MS, Weaver LT, et al. Neonatal visual evoked potentials in infants born to mothers prescribed methadone. *Pediatr*. (2013) 131:e857–63. doi: 10.1542/peds.2012-2113

84. McGlone L, Hamilton R, McCulloch DL, MacKinnon JR, Bradnam M, Mactier H. Visual outcome in infants born to drug-misusing mothers prescribed methadone in pregnancy. *Br J Ophthalmol*. (2014) 98:238–45. doi: 10.1136/bjophthalmol-2013-303967

85. Yeoh SL, Eastwood J, Wright IM, Morton R, Melhuish E, Ward M, et al. Cognitive and motor outcomes of children with prenatal opioid exposure: a systematic review and meta-analysis. *JAMA Netw Open*. (2019) 2:e197025. doi: 10.1001/jamanetworkopen.2019.7025

86. Uebel H, Wright IM, Burns L, Hilder L, Bajuk B, Breen C, et al. Reasons for re-hospitalization in children who had neonatal abstinence syndrome. *Pediatrics*. (2015) 136:e811–20. doi: 10.1542/peds.2014-2767

87. Oei JL, Melhuish E, Uebel H, Azzam N, Breen C, Burns L, et al. Neonatal abstinence syndrome and high school performance. *Pediatrics*. (2017) 139: e20162651. doi: 10.1542/peds.2016-2651

88. Sherman LJ, Ali MM, Mutter R, Larson J. Mental disorders among children born with neonatal abstinence syndrome. *Psychiatr Serv*. (2019) 70:151. doi: 10.1176/appi.ps.201800341

89. Merhar SL, McAllister JM, Wedig-Stevie KE, Klein AC, Meinzen-Derr J, Poindexter BB. Retrospective review of neurodevelopmental outcomes in infants treated for neonatal abstinence syndrome. *J Perinatol*. (2018) 38:587–92. doi: 10.1038/s41372-018-0088-9

90. Davis JM, Shenberger J, Terrin N, Breeze J, Hudak M, Wachman EM, et al. Comparison of safety and efficacy of methadone vs. Morphine for treatment of neonatal abstinence syndrome: a randomized clinical trial. *JAMA Pediatr*. (2018) 172:741–8. doi: 10.1001/jamapediatrics.2018.1307

91. Czynski AJ, Davis JM, Dansereau LM, Engelhardt B, Marro P, Bogen DL, et al. Neurodevelopmental outcomes of neonates randomized to morphine or methadone for treatment of neonatal abstinence syndrome. *J Pediatr*. (2020) 219:146–51. doi: 10.1016/j.jpeds.2019.12.018

92. Flannery T, Davis JM, Czynski AJ, Dansereau LM, Oliveira EL, Camardo SA, et al. Neonatal abstinence syndrome severity index predicts 18-month neurodevelopmental outcome in neonates randomized to morphine or methadone. *J Pediatr*. (2020) 227:101–7.e1. doi: 10.1016/j.jpeds.2020.08.034

93. Patrick SW, Barfield WD, Poindexter BB. Committee on Fetus and newborn, committee on substance use and prevention. Neonatal opioid withdrawal syndrome. *Pediatrics*. (2020) 146:e2020029074. doi: 10.1542/peds.2020-029074

94. Zubler JM, Wiggins LD, Macias MM, Whitaker TM, Shaw JS, Squires JK, et al. Evidence-informed milestones for developmental surveillance tools. *Pediatrics*. (2022) 149:e2021052138. doi: 10.1542/peds.2021-052138

95. Peacock-Chambers E, Leyenaar JK, Foss S, Feinberg E, Wilson D, Friedmann PD, et al. Early intervention referral and enrollment among infants with neonatal abstinence syndrome. *J Dev Behav Pediatr*. (2019) 40:441–50. doi: 10.1097/DBP.0000000000000679

96. Yen E, Murphy HJ, Friedman H, Lucke AM, Rodday AM. Neonatal abstinence syndrome practice variations across pediatric subspecialty. *J Perinatol*. (2021) 41:1512–4. doi: 10.1038/s41372-020-00831-8

97. Hall ES, McAllister JM, Wexelblatt SL. Developmental disorders and medical complications among infants with subclinical intrauterine opioid exposures. *Popul Health Manag*. (2019) 22:19–24. doi: 10.1089/pop.2018.0016

98. Walhovd KB, Watts R, Amlien I, Woodward LJ. Neural tract development of infants born to methadone-maintained mothers. *Pediatr Neurol*. (2012) 47:1–6. doi: 10.1016/j.pediatrneurol.2012.04.008

99. McGlone L, Mactier H, Weaver LT. Drug misuse in pregnancy: losing sight of the baby? *Arch Dis Child*. (2009) 94:708–12. doi: 10.1136/adc.2008.156851

100. Walhovd KB, Bjørnebekk A, Haabrekke K, Siqveland T, Slinning K, Nygaard E, et al. Child neuroanatomical, neurocognitive, and visual acuity outcomes with maternal opioid and polysubstance detoxification. *Pediatr Neurol*. (2015) 52:326–32. doi: 10.1016/j.pediatrneurol.2014.11.008

101. Melinder A, Konijnenberg C, Sarfi M. Deviant smooth pursuit in preschool children exposed prenatally to methadone or buprenorphine and tobacco affects integrative visuomotor capabilities. *Addiction*. (2013) 108:2175–82. doi: 10.1111/add.12267

102. Gill AC, Oei J, Lewis NL, Younan N, Kennedy I, Lui K. Strabismus in infants of opiate-dependent mothers. *Acta Paediatr*. (2003) 92:379–85. doi: 10.1111/j.1651-2227.2003.tb00561.x

103. Cornish KS, Hrabovsky M, Scott NW, Myerscough E, Reddy AR. The short- and long-term effects on the visual system of children following exposure to maternal substance misuse in pregnancy. *Am J Ophthalmol*. (2013) 156:190–4. doi: 10.1016/j.ajo.2013.02.004

104. Yoo SH, Jansson LM, Park H-J. Sensorimotor outcomes in children with prenatal opioid exposure. *J AAPOS*. (2017) 21:316–21. doi: 10.1016/j.jaapos.2017.05.025

105. Auger N, Rhéaume M, Low N, Lee GE, Ayoub A, Luu TM. Impact of prenatal exposure to opioids, cocaine, and cannabis on eye disorders in children. *J Addict Med*. (2020) 14:459–66. doi: 10.1097/ADM.0000000000000621

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 22 November 2022
DOI 10.3389/fped.2022.1068330

Check for updates

OPEN ACCESS

EDITED BY
Dick Tibboel,
Erasmus Medical Center, Netherlands

REVIEWED BY
Balaji Govindaswami,
Valley Medical Center Foundation, United States
Rachana Singh,
Tufts University, United States

*CORRESPONDENCE
Thitinart Sithisarn
tsith2@uky.edu

SPECIALTY SECTION
This article was submitted to Neonatology, a section of the journal Frontiers in Pediatrics

RECEIVED 12 October 2022
ACCEPTED 04 November 2022
PUBLISHED 22 November 2022

CITATION
Sithisarn T, Legan SJ, Westgate PM, Bada HS and Wilson ME (2022) Understanding the effects of opioids vs non-opioids in the treatment of neonatal abstinence syndrome, an in vitro model.
Front. Pediatr. 10:1068330.
doi: 10.3389/fped.2022.1068330

COPYRIGHT
© 2022 Sithisarn, Legan, Westgate, Bada and Wilson. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Understanding the effects of opioids vs non-opioids in the treatment of neonatal abstinence syndrome, an in vitro model

Thitinart Sithisarn[1]*, Sandra J. Legan[2], Philip M. Westgate[3], Henrietta S. Bada[1] and Melinda E. Wilson[2]

[1]Department of Pediatrics, University of Kentucky, Lexington KY, United States, [2]Department of Physiology, University of Kentucky, Lexington KY, United States, [3]Department of Biostatistics, University of Kentucky, Lexington KY, United States

Neonatal abstinence syndrome (NAS) refers to cadre of withdrawal manifestations in infants born to mothers who used illicit and licit substances during pregnancy. The increasing prevalence of NAS has been largely due to the maternal use of opioids during pregnancy. NAS contributes to increased morbidity and long-term disability in surviving infants. Clinically, oral opioid therapies for opioid exposure have been a standard treatment with morphine (MO) being the most commonly used medication. Recently, a non-opioid agent, clonidine (CD) has also been used with potentially favorable short- and long-term outcomes in infants. However, data regarding the cellular and molecular effects of these treatments on the developing brain is still lacking due to a lack of a reliable animal model that targets the neonatal brain. To address this gap in knowledge we determined the effects of MO or CD on the cell death of neonatal cortical explant cultures that were exposed to oxycodone (OXY) *in utero*. Sprague Dawley rats were randomized and implanted with programmable infusion pumps before mating to receive either the OXY (dose increasing from 1.21–1.90 mg/kg/day to a maximum dose of 2.86–3.49 mg/kg/day) or normal saline (NS) throughout pregnancy and until one week after delivery. Male and female rat pups were sacrificed on postnatal day 4, and the prefrontal cortex (PFC) and hippocampus (HC) were dissected and treated with MO (0.10–1.00 μM) or CD (1.20–120.00 μM) in culture media. After 5 days of treatment the explants were labeled with propidium iodide to detect cell death. Dead cells were analyzed and counted under fluorescence microscopy. In explants from the PFC, cell death was greater in those prenatally exposed to OXY and postnatally treated with MO (OXY/MO) (736.8 ± 76.5) compared to OXY/CD (620.9 ± 75.0; $p = 0.005$). In the HC explants, mean cell death counts were not significantly different between groups regardless of prenatal exposure or postnatal treatment ($p = 0.19$). The PFC is vital in controlling higher-order executive functions such as behavioral flexibility, learning and working memory.

Abbreviations
NAS, Neonatal Abstinence Syndrome; NOWS, Neonatal Opioid Withdrawal Syndrome; MO, Morphine; CD, Clonidine; OXY, Oxycodone; CON, Control Postnatal treatment; PFC, Prefrontal Cortex; HC, Hippocampus; NS, Normal Saline.

Therefore, our finding is consistent with executive function problems in children with prenatal opioid exposure.

KEYWORDS

neonatal abstinence syndrome (NAS), opioid withdrawal, morphine, clonidine, *in vitro* model, cell death, prefrontal cortex, hippocampus

Introduction

Opioid use during pregnancy is reaching record levels in the United States (1, 2). The recent data showed that the incidence of illicit drug use including opioids and marijuana among women of reproductive age was around 16.3% with 5.8% use during pregnancy (3). The increase in maternal opioid use during pregnancy has led to a dramatic increase in Neonatal Abstinence Syndrome (NAS) or more recently termed Neonatal Opioid Withdrawal Syndrome (NOWS) in those infants exposed to opioids *in utero* (4). The incidence of NOWS ranged from 4 to 423 cases (mean 31.8 ± 75.9) per 1,000 birth admissions from the cross-sectional study in the United State from 2016 to 2017 (5). In 2017, the Healthcare Cost and Utilization Project estimated that for every 1,000 newborn hospital stays, 7 were diagnosed with NAS. These babies experience a constellation of symptoms characterized by central nervous system hyperirritability (characterized by incessant and high-pitched cries, tremor), autonomic nervous system dysfunction (temperature instability, nasal stuffiness) and gastrointestinal disturbances (vomiting, diarrhea, poor feeding) (6). Seizures may occur in up to 2%–11% in infants with NAS (7, 8). The current literature supports the use of opioids as a first line pharmacologic treatment in tapering doses for NAS (9). Morphine is the most commonly used medication with small percentages of infants being treated with methadone, and a very small percentage receiving buprenorphine (10). However, it remains unclear how opioid treatment of NAS affects long-term outcomes for these infants. Pre- or perinatal exposure to opioids is associated with long-term effects on neurodevelopment and cognitive functions in children (11–13), decreased brain volumes (14) and lower fractional anisotropy in several areas on the brain magnetic neuroimaging reflecting decreased myelination (15). Preclinical studies also reveal concerning effects of opioid exposure on the developing brain (16) including inhibition of neural progenitor cell differentiation (17), decrease in neurogenesis (18) and impairment of synaptic plasticity (19, 20). Moreover, perinatal exposure to opioids alters the ontogeny of the stress-axis (21, 22) and immune response (23). Therefore, it is important to consider other effective non-opioid treatments for NAS to avoid further exposing the developing brain to opioids and to ultimately improve both short- and long-term clinical outcomes.

Clonidine, an alpha-2 adrenergic agonist that has sedative properties, has been used in animal models of naloxone-induced precipitated withdrawal to ameliorate withdrawal symptoms from adult opioid-addicted rats (24, 25). Clinical studies report that clonidine is an effective treatment for NAS as an adjunct therapy with morphine (26) or chloral hydrate (27). We report that in the pilot clinical study, clonidine treatment is also effective as a monotherapy for NAS and results in improved short-term neurodevelopmental assessment and a shorter length of treatment as compared to morphine treatment (28). The mechanisms whereby neonatal exposure to opioids or clonidine may alter neurological development have not been clearly determined. Virtually no data exist on the molecular and cellular effects underlying the long-term deficits in these children and there are currently only limited animal models to determine such effects.

To begin to address this deficiency in model systems we utilized neonatal explant cultures from animals that were exposed to oxycodone (OXY) *in utero* and determined the effects of postnatal morphine or clonidine exposure on cell death. Organotypic explant cultures have been used extensively to study mechanisms of cell death following neurotoxic insults (29–32). Furthermore, they have advantages over isolated *in vitro* culture systems in that the microenvironment is maintained between neurons and glia, the cultures can be maintained for weeks at a time and they can be pharmacologically manipulated with drug treatments to assess cell death, cell function and gene expression (32). Additionally, the use of an *in vitro* model avoids the complex maternal care and behaviors that can confound *in vivo* models of early brain development (33). The development of a reliable *in vitro* model is critical to understanding the long-term molecular changes that occur in the brain in babies experiencing NAS. We hypothesized that postnatal treatment with clonidine decreased cell death in stress-responsive brain regions including the prefrontal cortex and the hippocampus as compared to the treatment with morphine using an organotypic explant culture model.

Materials and methods

Animals and perinatal treatment

The study protocol was approved by the University of Kentucky Institutional Animal Care and Use Committee. Virgin Sprague Dawley rats (Harlan, Indianapolis, IN)

weighing 216.5–259 g (mean 242.7 g) ($n = 10$) were housed individually at 22–25 °C and maintained in a 14L:10D photoperiod (lights on at 0500 am) with regulated 30%–70% humidity. Rat chow and water were provided *ad libitum*.

Once released from quarantine, the females were implanted with programmable micro-infusion pumps (iPrecio® Model SMP-200) (iPRECIO®, Alzet, Cupertino, CA) under isoflurane anesthesia. The tips of the tubes were tunneled and positioned for subcutaneous infusion on the nape of the neck. The animals were randomly assigned to receive either oxycodone (OXY) (Mallinckrodt, St. Louis, MO) (100 mg/ml, diluted in normal saline ($n = 5$) or normal saline control (NS) ($n = 5$) on a day of implantation, continued for one week before mating, throughout pregnancy and one week after delivery. In OXY group, the rats received the basal dose of 0.2 μl/hr for one day (OXY dose from basal rate was approximately 1.21–1.9 mg/kg/day), then started to receive escalating doses by pulsatile infusion twice a day during mating and pregnancy. Since the pumps needed to be pre-programmed before implantation, the doses were escalated according to the expected weight gain during pregnancy and the possible development of tolerance to opioid. Each female was housed with the male breeder one week after the implantation of the infusion pumps.

To mimic human use the pulsed dose was escalated as follows. Weeks 1–2: A basal rate of 0.2 μl/hr and a pulse of 1 μl/hr for one hour twice a day was administered for 2 weeks (daily dose from pulse infusion of approximately 0.77–0.87 mg/kg, total daily dose 2.46–2.77 mg/kg/day). Week 3: A basal rate of 0.2 μl/hr and a pulse of 2 μl/hr for one hour twice a day was administered for 1 week (daily dose from pulse infusion of approximately 1.36–1.54 mg/kg, total daily dose 2.85–3.23 mg/kg/day). Week 4: A basal rate of 0.2 μl/hr and a pulse of 3 μl/hr for one hour twice a day was administered for 1 week (dose from pulse infusion of approximately 1.65–2.00 mg/kg, total daily dose 2.86–3.49 mg/kg/day). Finally, Week 5: A basal rate of 0.2 μl/hr and a pulse of 2 μl/hr for one hour twice a day was administered until sacrificed (daily dose from pulse infusion of approximately 1.54 mg/kg, total daily dose 3.23 mg/kg/day). The NS rats group received NS subcutaneously at the same pre-programmed infusion rates.

GD 0 was designated as the day that sperm were detected in the vaginal smear, and the females were individually housed thereafter. On postnatal day (PD) 1, average of 22 days after GD 0, the pups were counted and weighed. The dams were allowed to nurse their own pups while continuing to receive treatment from the infusion pump.

From the 5 dams in prenatal NS group, there were total of 24 pups (12 male and 12 female pups). From the 5 dams in prenatal OXY group, there were total of 28 pups (16 male and 12 female pups). At least one explant from each pup (both PFC and HC) was treated with each one of the six postnatal treatments, the explants were run in duplicate for each treatment. So the n of the pups for prenatal NS (control) for all postnatal treatments = 24 (combined male and female), and n for prenatal oxycodone for all postnatal treatments = 28 (combined male and female), **Figure 1**.

Organotypic cortical explants

See **Figure 1**. Cortical explants are isolated from PND 3–4 rat pups, as previous described (29, 34, 35) with slight modifications. PD 3–4 is chosen because it is the optimal age of development for them to survive, but still can differentiate adequately and can potentially harvest both the PFC and HC from the same animal. Additionally, cutting the explants from younger animals is technically challenging. Pups were sexed and brains were isolated and sectioned, 300 µm, in cold dissection media containing Gey's balanced salt solution (G9779, Sigma-Aldrich, Saint Louis, MO), 0.2 M MgCl2 and 37.5% glucose on a vibratome from Bregma −.36 to −2.64 mm. Approximately 8–10 slices were harvested per brain. In cold dissection media plus ketamine HCl (Ketaset, NLS Animal Heath). Each brain was isolated for the prefrontal cortex and for the hippocampus. Individual cortices were plated on Millicell-CM membranes (PICMO3050, Fisher, Hampton, NH) in wells containing 1X Basal Medium Eagle (B9638, Sigma-Aldrich), Hanks' Balanced Salt Solution (14,025, Invitrogen), heat-inactivated horse serum (3H30074.03, Fisher), 37.5% glucose in Geys BSS, glutamax (35,050, Invitrogen, Carlsbad, CA), and penicillin/streptomycin (15,140, Invitrogen). Explants remained in culture at 34 °C with 5% CO_2. Media was changed every three days. Healthy explants are transparent with smooth edges while overfed explants become opaque and underfed explants thin to the point that they are undetectable (35). After 3 days on the culture media, the explants were treated with one these 6 treatments: vehicle either alone (CON), or with 0.1 or 1 µM morphine (MO), or 1.2, 12 or 120 µM clonidine (CD). These concentrations of morphine treatment were used to cover the range of the mean plasma concentrations of 125 up to above 300 and 167 ± 77 ng/ml that were reported in the neonates that received the therapeutic doses of morphine (36, 37). These concentrations of clonidine were used to cover the extrapolated intra-cerebroventricular concentration reported to prevent the reduction in the hypothalamic noradrenaline after naloxone-induced withdrawal in chronically morphine treated rats (38).

Assessment of cell death

After 5 days of treatment, explants were washed with 0.1 M PBS and incubated with 5 µg/ml of propidium

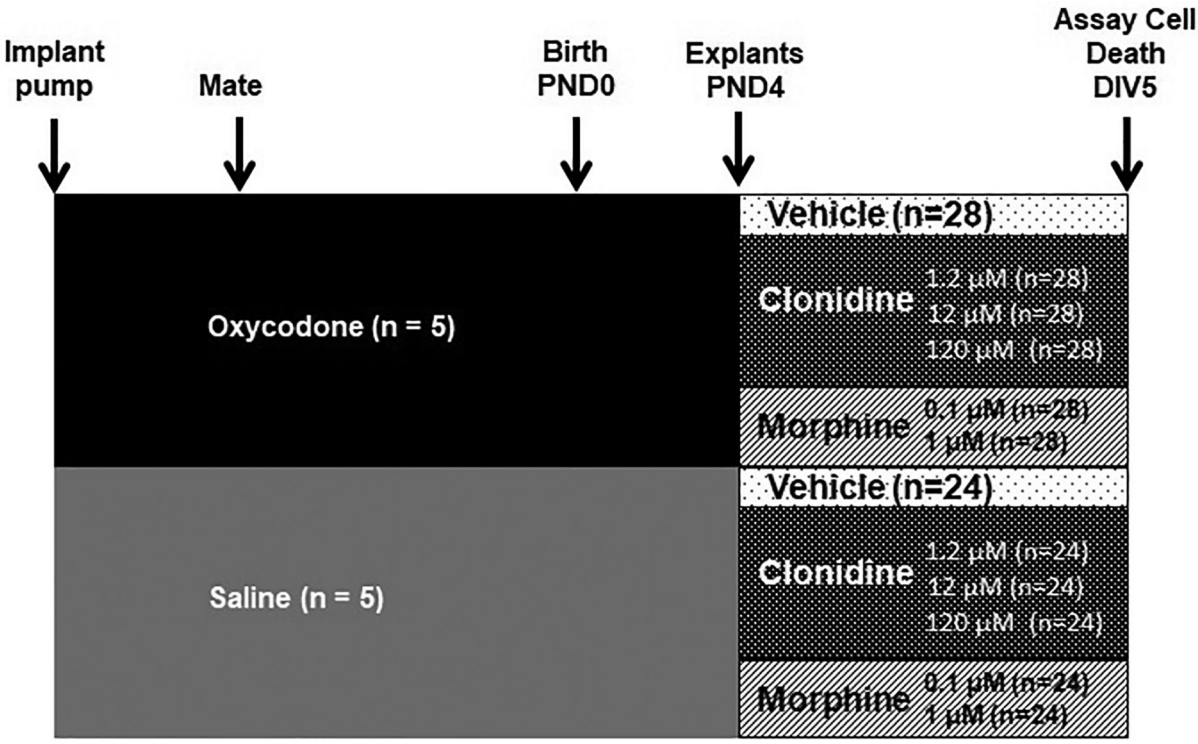


FIGURE 1
Schematic of pre- and post-natal treatment regimen.

iodide (PI) (1 mg/ml in H2O, P4170, Sigma-Aldrich) in BME for 30 min. Explants were washed (0.1M PBS) and visualized using a fluorescent microscope. PI entered cells that had a porous cell membranes, indicating damage, and bound to DNA. PI uptake indicated cell death and fluoresced red (emission at 630 nm) under green light (excited at 495 nm). Pictures, 20X magnification of explants, were captured using an image capture program, SPOT Advanced. Red (dead) cells per frame were then counted using a Nikon NIS-Element software®. Pictures were coded and analyzed blindly.

Statistical analysis

Linear mixed effects models with a random effect for litter were used for statistical analyses with statistical significance defined as $p < 0.05$. Because there were no significant dose effects in MO or CD treatment groups, the results from the 2 MO concentrations (0.1 or 1 μM) and the 3 CD (1.2, 12 or 120 μM) groups were combined for further analysis. The interactions between gender and treatment groups were not significant; therefore, the results from both male and female offspring were combined.

Results

In the PFC

Figure 2A shows the cell death counts with MO or CD treatment in the PFC explants. In explants from prenatally exposed OXY pups, only postnatal treatment with morphine, not clonidine, increased cell death compared to CON. Postnatal morphine also increased cell death compared to clonidine. In explants from prenatally exposed normal saline (NS) pups, both morphine and clonidine increased cell death compared to CON.

In the hippocampus

Figure 2B shows the effect of MO or CD on the HC explants from prenatal exposure to either OXY or NS. In either prenatal OXY or NS groups, postnatal treatment with MO or CD had no effect on cell death when compared to CON. However, in the prenatal NS explants, postnatal CD treatment decreased cell death compared to MO. Postnatal treatment with CD also decreased cell death in the prenatal NS explants when compared to either postnatal treatment with MO or CON in prenatal OXY explants. The decline in

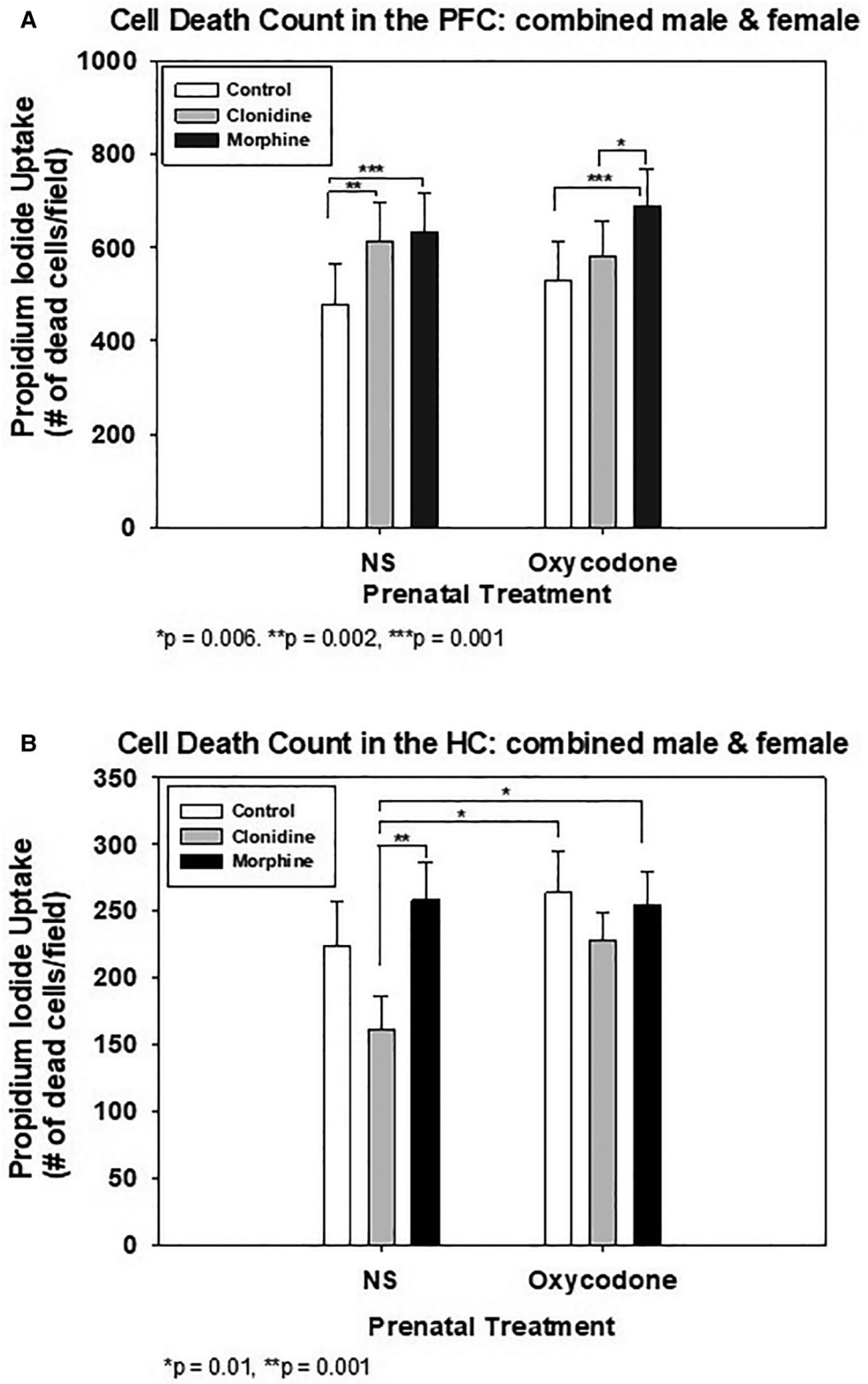


FIGURE 2
Quantification of cell death in organotypic explants following treatment with clonidine or morphine. (A) Prefrontal Cortex (PFC) Explants. (B) Hippocampus (HC) explants.

cell death in the prenatal NS-postnatal CD group did not differ from the prenatal NS –postnatal CON group.

Assessment of cell death by propidium iodide staining under fluorescence microscopy were as shown, from the PFC (**Figure 3A**) and from the hippocampus (**Figure 3B**). Worst staining for cell death noted in postnatal MO treatment group, see **Figure 2** for cell death count.

Discussion

To the best of our knowledge this is the first study to use an invitro model of organotypic cortical explants to study the effects of non-opioid vs. opioid treatment for NAS/ NOWS on cell death. Our results showed the anatomical site- and prenatal exposure- specific protective effects of clonidine on cell death. Although organotypic explant cultures have been used to study the effects of certain treatments on neuronal toxicity and cell death (31, 39), they have not been previously used to study the effects of prenatal opioid exposure and postnatal treatment for NAS.

From this pilot study, postnatal exposure to clonidine decreased cell death in the prefrontal cortex cortical explants compared to postnatal exposure to morphine when the rats were prenatally exposed to oxycodone; this possible protective effect was not noted when the rats were prenatally exposed to NS. In the hippocampus, clonidine also decreased cell death compared to morphine, when rats were prenatally exposed to NS. However, this effect was not present when the rats were prenatally exposed to oxycodone. Postnatal clonidine also decreased cell death in the hippocampus of prenatal NS rats when compared to postnatal treatment with morphine or control in prenatal oxycodone group.

As hypothesized, our results suggested that when the animals were prenatally exposed to opioid, postnatal treatment with the non-opioid clonidine led to a decrease in cell death in the prefrontal cortex as compared to treatment with morphine. This finding supports the possibility of using a non-opioid therapeutic agent as an alternative or adjunctive therapy for NAS/ NOWS as a growing body of evidence have suggested adverse effects of opioids on the developing brain. Our results support the findings from the previous preclinical study by Bajic et al. that morphine exposure during the neonatal period (PD1–7) increased the density of neuronal cell death in the neonatal rat cortex and amygdala (40). Others also reported increased neuronal cell death (41) and reduced cortical thickness and the numbers of neurons in the fetal frontal cerebral cortex in the offspring (42) after prolonged intrauterine morphine exposure. Although we did not explore the mechanisms of cell death in this study, one of the mechanisms by which morphine enhances neuronal cell death is reported to be increased apoptosis *via* a caspase-3

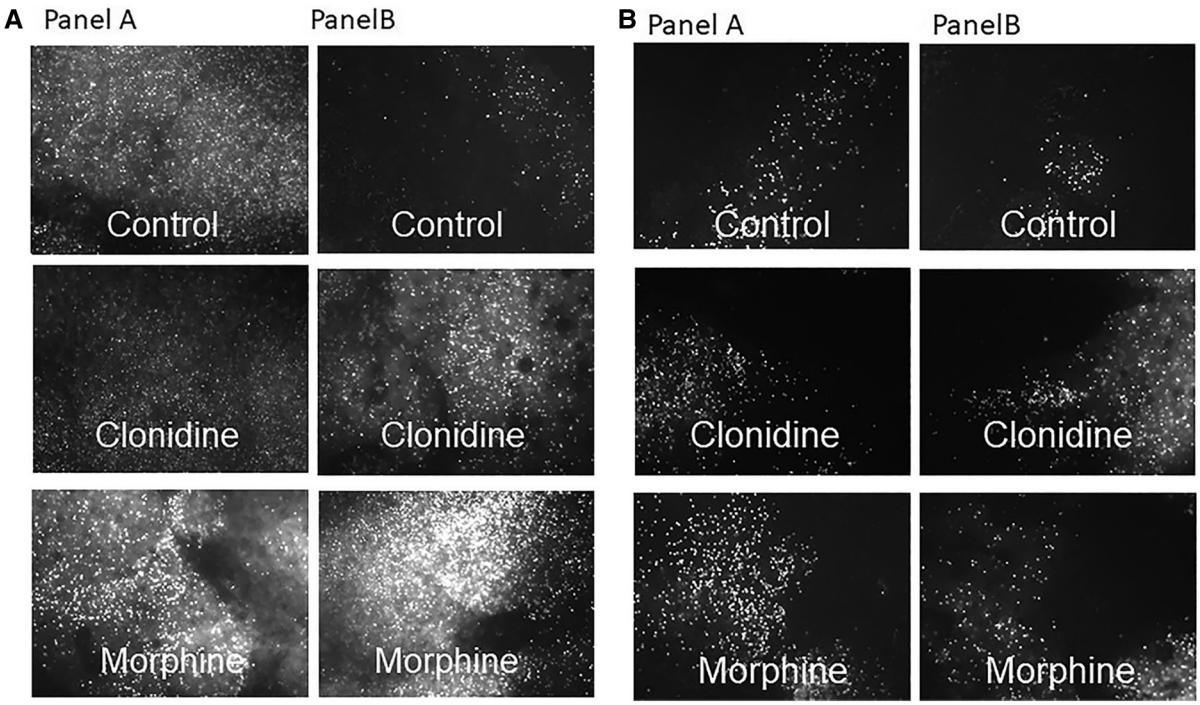


FIGURE 3
Propidium iodide staining for cell death from the PFC (A) and hippocampus (B) under fluorescence microscopy, explants were prenatally exposed to NS (panel A) and to OXY (panel B) with postnatal treatment with control, clonidine and morphine respectively.

dependent pathway (40, 43, 44). Oxidative stress has been described as another cellular mechanism involved in opioid neurotoxicity (45). We found brain region-specific effects of the pre- and postnatal opioid treatment on cell death in this study. Our findings are in line with Bajic et al. that the prefrontal cortex but not the hippocampus, is one of the supra-spinal regions susceptible to opioid toxicity. This may be due to the relative densities of glutamatergic neurons which may lead to increased neurotoxicity as has been shown in other paradigms (46). A limitation of our study is that we did not perform immunohistochemistry to identify the specific cell types of dead cells. However, previous studies showed that opioids disrupt neuronal and glial maturation by context-dependent, modulatory effects throughout ontogeny (47). Future study should aim to identify cell types and possible mechanisms underlying our findings. There seemed to be significant amount of background, which can be potentially explained by the thickness of the samples. All explants do not thin at the same rate. Another limitation is that we used propidium iodide staining which only crosses the membranes of the dead cells and detects both apoptotic and necrotic cell death. Annexin V technic should be considered for future experiments to specifically assess apoptotic cell death (48). Of note, there were significant amount of cell death in the explants from NS exposed rat pups suggesting that this may be part of a normal process or may reflect what happens to the cells in the explant cultures.

Clonidine, on the other hand, has been reported to provide dose and brain region-specific neuroprotective effects for cerebral ischemia in the *in vivo* model (49, 50). In vitro, clonidine decreases the neuronal cell injury caused by N-methyl-d-aspartate (NMDA) receptor agonist exposure, an effect which is abolished by the selective alpha2-adrenoceptor antagonist yohimbine in primary cortical neuron cultures (51). The mechanism by which clonidine may have less toxic effects as a treatment for neonatal drug withdrawal requires further elucidation. In addition to preventing the elevation of norepinephrine, thereby ameliorating sympathetic hyperactivity in NAS (52) which in turn can alleviate withdrawal symptoms, clonidine may provide neuroprotection by reducing the release of glutamate resulting in decreased NMDA activation and neuronal damage (53). Further studies are needed to explore the mechanisms by which clonidine may provide neuroprotective effects after perinatal opioid exposure.

Interestingly, the treatment group with highest cell death in the PFC was among the pups that were prenatally exposed to OXY and treated postnatally with morphine. The significance of this finding may be related to the fetal programming by prenatal opioid exposure (54). This concept was grounded on the pathophysiology of the effects of prenatal cocaine exposure (55) and early life stress (56), wherein prenatal exposure to stress or substances of abuse can potentially lead to altered programming of brain development and adverse short- and long-term neurodevelopmental outcomes. Fetal programming involves the processes by which conditions during critical periods of cellular proliferation, differentiation, and maturation affect the developing brain and how the brain responds to and interacts with these conditions, which in turn can affect cell survival (57). Besides the effects on the stress-axis (58), prenatal stress (59) and opioids (60, 61) can alter the availability of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) which may be one of the key signaling pathways that alters cell survival. Further study including the use of animal models is required to elucidate how prenatal opioid exposure can possibly make the brain more susceptible to a postnatal averse environment and investigate its effects on the long term outcomes (62).

We did not find significant interactions between treatment groups and gender in this study which could be due to our small sample size, therefore the results were combined. However, previous studies have described the gender-specific susceptibilities or vulnerabilities that impact cognitive, executive and behavioral outcomes after prenatal substance exposure (63). Our group previously reported more notable hyperactivity in the open field test in prenatal oxycodone-exposed male offspring compared to females (64). Prenatal opioid exposure is consistently associated with behavioral issues, primarily with the symptoms of attention–deficit hyperactivity disorder (ADHD) in children (65, 66). Behavior and attention is significantly regulated by the PFC; weaker structure and function of the PFC is associated with attention deficit/ hyperactivity (67). There exists emerging evidence that the corticolimbic system undergoes age and gender –specific development (68). Altogether, more studies are needed to verify the effects of perinatal opioid exposure/ treatment on the development on the corticolimbic system,interaction with genders and other potential postnatal interventions that may improve the long term outcomes (69, 70).

Conclusions

In this pilot study we attempted to develop an *in vitro* model to study the effects of opioid (morphine) vs. non-opioid (clonidine) treatment for NAS/NOWS after prenatal exposure to oxycodone on cell death by using organotypic explant cultures from two of the corticolimbic- regions, the prefrontal cortex and the hippocampus. We found that post-natal treatment with clonidine may have effects to decrease cell deaths in the PFC as compared to morphine treatment, a result which supports consideration to use clonidine as another option for NAS/NOWS treatment. No differences in the effects of postnatal treatment on cell death were found in the hippocampus when prenatally exposed to oxycodone, but in prenatal NS-treated explants, postnatal clonidine treatment also decreased cell death compared to morphine. Although

our experiments showed interesting findings from the small sample sizes, future studies are warranted as there are certain limitations. Those studies may utilize this model to investigate other pharmacologic treatment choices for NAS/NOWS and further determine the mechanisms for cell death/ cell survival and other pathophysiology by which prenatal opioid exposure and postnatal treatment may affect brain development.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The animal study was reviewed and approved by the University of Kentucky Institutional Animal Care and Use Committee.

Author contributions

TS planned and conducted all the experiments, collected all data, wrote the manuscript. SJL helped significantly with planning and conducting the experiments, edited the manuscript. PMW is a statistician who was responsible for all the statistical analysis. HSB contributed significantly toward forming the concepts of all the experiments and edited the manuscript. MEW helped significantly with planning and conducting the experiments, edited the manuscript. All authors contributed to the article and approved the submitted version.

Acknowledgment

This work was supported by Children's Miracle Network Fund for Sithisarn, T. Bada, H., Sithisarn, T. and Westgate, P.M. also received funding from NO-POPPY study (Non-Opiate Treatment After Prenatal Opiate Exposure to Prevent Injury to the Young Brain, NIH R01-DA043519)

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Patrick SW, Schumacher RE, Benneyworth BD, Krans EE, McAllister JM, Davis MM. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000–2009. *JAMA*. (2012) 307(18):1934–40. doi: 10.1001/jama.2012.3951

2. Ko JY, D'Angelo DV, Haight SC, Morrow B, Cox S, Salvesen von Essen B, et al. Vital signs: prescription opioid pain reliever use during pregnancy - 34 U.S. Jurisdictions, 2019. *MMWR Morb Mortal Wkly Rep*. (2020) 69 (28):897–903. doi: 10.15585/mmwr.mm6928a1

3. SAMSHA. Results from the 2016 National Survery on Drug Use and Health: Detailed Tables. 2019.

4. Patrick SW, Barfield WD, Poindexter BB, Committee On F, Newborn COSU, Prevention. Neonatal opioid withdrawal syndrome. *Pediatrics*. (2020) 146(5):1–18. doi: 10.1542/peds.2020-029074

5. Young LW, Hu Z, Annett RD, Das A, Fuller JF, Higgins RD, et al. Site-level variation in the characteristics and care of infants with neonatal opioid withdrawal. *Pediatrics*. (2021) 147(1):1–10. doi: 10.1542/peds.2020-008839

6. Stover MW, Davis JM. Opioids in pregnancy and neonatal abstinence syndrome. *Semin Perinatol*. (2015) 39(7):561–5. doi: 10.1053/j.semperi.2015.08.013

7. Jansson LM, Velez M, Harrow C. The opioid-exposed newborn: assessment and pharmacologic management. *J Opioid Manag*. (2009) 5(1):47–55. doi: 10.5055/jom.2009.0006

8. Kocherlakota P. Neonatal abstinence syndrome. *Pediatrics*. (2014) 134(2): e547–61. doi: 10.1542/peds.2013-3524

9. Kraft WK, Stover MW, Davis JM. Neonatal abstinence syndrome: pharmacologic strategies for the mother and infant. *Semin Perinatol*. (2016) 40 (3):203–12. doi: 10.1053/j.semperi.2015.12.007

10. Tolia VN, Patrick SW, Bennett MM, Murthy K, Sousa J, Smith PB, et al. Increasing incidence of the neonatal abstinence syndrome in U.S. neonatal ICUs. *N Engl J Med*. (2015) 372(22):2118–26. doi: 10.1056/NEJMsa1500439

11. Hunt RW, Tzioumi D, Collins E, Jeffery HE. Adverse neurodevelopmental outcome of infants exposed to opiate in-utero. *Early Hum Dev*. (2008) 84 (1):29–35. doi: 10.1016/j.earlhumdev.2007.01.013

12. Bunikowski R, Grimmer I, Heiser A, Metze B, Schafer A, Obladen M. Neurodevelopmental outcome after prenatal exposure to opiates. *Eur J Pediatr*. (1998) 157(9):724–30. doi: 10.1007/s004310050923

13. Ornoy A, Segal J, Bar-Hamburger R, Greenbaum C. Developmental outcome of school-age children born to mothers with heroin dependency: importance of environmental factors. *Dev Med Child Neurol*. (2001) 43 (10):668–75. doi: 10.1017/S0012162201001219

14. Walhovd KB, Moe V, Slinning K, Due-Tonnessen P, Bjornerud A, Dale AM, et al. Volumetric cerebral characteristics of children exposed to opiates and other substances in utero. *Neuroimage*. (2007) 36(4):1331–44. doi: 10.1016/j.neuroimage.2007.03.070

15. Walhovd KB, Westlye LT, Moe V, Slinning K, Due-Tonnessen P, Bjornerud A, et al. White matter characteristics and cognition in prenatally opiate- and polysubstance-exposed children: a diffusion tensor imaging study. *AJNR Am J Neuroradiol*. (2010) 31(5):894–900. doi: 10.3174/ajnr.A1957

16. Hammer Jr. RP, Ricalde AA, Seatriz JV. Effects of opiates on brain development. *Neurotoxicology*. (1989) 10(3):475–83.

17. Willner D, Cohen-Yeshurun A, Avidan A, Ozersky V, Shohami E, Leker RR. Short term morphine exposure in vitro alters proliferation and differentiation of neural progenitor cells and promotes apoptosis via mu receptors. *PLoS One*. (2014) 9(7):e103043. doi: 10.1371/journal.pone.0103043

18. Wu CC, Hung CJ, Shen CH, Chen WY, Chang CY, Pan HC, et al. Prenatal buprenorphine exposure decreases neurogenesis in rats. *Toxicol Lett*. (2014) 225 (1):92–101. doi: 10.1016/j.toxlet.2013.12.001

19. Niu L, Cao B, Zhu H, Mei B, Wang M, Yang Y, et al. Impaired in vivo synaptic plasticity in dentate gyrus and spatial memory in juvenile rats induced by prenatal morphine exposure. *Hippocampus*. (2009) 19(7):649–57. doi: 10.1002/hipo.20540

20. Tan JW, Duan TT, Zhou QX, Ding ZY, Jing L, Cao J, et al. Impaired contextual fear extinction and hippocampal synaptic plasticity in adult rats induced by prenatal morphine exposure. *Addict Biol*. (2015) 20(4):652–62. doi: 10.1111/adb.12158

21. Rimanoczy A, Slamberova R, Riley MA, Vathy I. Adrenocorticotropin stress response but not glucocorticoid-negative feedback is altered by prenatal morphine exposure in adult male rats. *Neuroendocrinology*. (2003) 78(6):312–20. doi: 10.1159/000074884

22. Sithisarn T, Bada HS, Dai H, Reinhardt CR, Randall DC, Legan SJ. Effects of perinatal oxycodone exposure on the response to CRH in late adolescent rats. *Neurotoxicol Teratol*. (2008) 30(2):118–24. doi: 10.1016/j.ntt.2007.12.010

23. Li Y, Merrill JD, Mooney K, Song L, Wang X, Guo CJ, et al. Morphine enhances HIV infection of neonatal macrophages. *Pediatr Res*. (2003) 54 (2):282–8. doi: 10.1203/01.PDR.0000074973.83826.4C

24. Milne B, Cervenko FW, Jhamandas K, Sutak M. Intrathecal clonidine: analgesia and effect on opiate withdrawal in the rat. *Anesthesiology*. (1985) 62 (1):34–8. doi: 10.1097/00000542-198501000-00007

25. Pinelli A, Trivulzio S. Quantitative evaluation of opioid withdrawal signs in rats repeatedly treated with morphine and injected with naloxone, in the absence or presence of the antiabstinence agent clonidine. *J Pharmacol Toxicol Methods*. (1997) 38(3):117–31. doi: 10.1016/S1056-8719(97)00050-6

26. Agthe AG, Kim GR, Mathias KB, Hendrix CW, Chavez-Valdez R, Jansson L, et al. Clonidine as an adjunct therapy to opioids for neonatal abstinence syndrome: a randomized, controlled trial. *Pediatrics*. (2009) 123(5):e849–56. doi: 10.1542/peds.2008-0978

27. Esmaeili A, Keinhorst AK, Schuster T, Beske F, Schlosser R, Bastanier C. Treatment of neonatal abstinence syndrome with clonidine and chloral hydrate. *Acta Paediatr*. (2010) 99(2):209–14. doi: 10.1111/j.1651-2227.2009.01547.x

28. Bada HS, Sithisarn T, Gibson J, Garlitz K, Caldwell R, Capilouto G, et al. Morphine versus clonidine for neonatal abstinence syndrome. *Pediatrics*. (2015) 135(2):e383–91. doi: 10.1542/peds.2014-2377

29. Wilson ME, Dubal DB, Wise PM. Estradiol protects against injury-induced cell death in cortical explant cultures: a role for estrogen receptors. *Brain Res*. (2000) 873(2):235–42. doi: 10.1016/S0006-8993(00)02479-3

30. Humpel C. Organotypic brain slice cultures: a review. *Neuroscience*. (2015) 305:86–98. doi: 10.1016/j.neuroscience.2015.07.086

31. Pena F. Organotypic cultures as tool to test long-term effects of chemicals on the nervous system. *Curr Med Chem*. (2010) 17(10):987–1001. doi: 10.2174/092986710790820679

32. Lossi L, Alasia S, Salio C, Merighi A. Cell death and proliferation in acute slices and organotypic cultures of mammalian CNS. *Prog Neurobiol*. (2009) 88 (4):221–45. doi: 10.1016/j.pneurobio.2009.01.002

33. Curley JP, Champagne FA. Influence of maternal care on the developing brain: mechanisms, temporal dynamics and sensitive periods. *Front Neuroendocrinol*. (2016) 40:52–66. doi: 10.1016/j.yfrne.2015.11.001

34. Staal JA, Alexander SR, Liu Y, Dickson TD, Vickers JC. Characterization of cortical neuronal and glial alterations during culture of organotypic whole brain slices from neonatal and mature mice. *PLoS One*. (2011) 6(7):e22040. doi: 10.1371/journal.pone.0022040

35. Fuller L, Dailey ME. Preparation of rodent hippocampal slice cultures. *CSH Protoc*. (2007) 2007:pdb prot4848. doi: 10.1101/pdb.prot4848

36. Chay PC, Duffy BJ, Walker JS. Pharmacokinetic-pharmacodynamic relationships of morphine in neonates. *Clin Pharmacol Ther*. (1992) 51 (3):334–42. doi: 10.1038/clpt.1992.30

37. Saarenmaa E, Neuvonen PJ, Rosenberg P, Fellman V. Morphine clearance and effects in newborn infants in relation to gestational age. *Clin Pharmacol Ther*. (2000) 68(2):160–6. doi: 10.1067/mcp.2000.108947

38. Gonzalvez ML, Milanes MV, Martinez-Pinero MG, Marin MT, Vargas ML. Effects of intracerebroventricular clonidine on the hypothalamic noradrenaline and plasma corticosterone levels of opiate naive rats and after naloxone-induced withdrawal. *Brain Res*. (1994) 647(2):199–203. doi: 10.1016/0006-8993(94)91318-8

39. Cronberg T, Rytter A, Asztely F, Soder A, Wieloch T. Glucose but not lactate in combination with acidosis aggravates ischemic neuronal death in vitro. *Stroke*. (2004) 35(3):753–7. doi: 10.1161/01.STR.0000117576.09512.32

40. Bajic D, Commons KG, Soriano SG. Morphine-enhanced apoptosis in selective brain regions of neonatal rats. *Int J Dev Neurosci*. (2013) 31(4):258–66. doi: 10.1016/j.ijdevneu.2013.02.009

41. Nasiraei-Moghadam S, Kazeminezhad B, Dargahi L, Ahmadiani A. Maternal oral consumption of morphine increases Bax/Bcl-2 ratio and caspase 3 activity during early neural system development in rat embryos. *J Mol Neurosci*. (2010) 41(1):156–64. doi: 10.1007/s12031-009-9312-6

42. Sadraie SH, Kaka GR, Sahraei H, Dashtnavard H, Bahadoran H, Mofid M, et al. Effects of maternal oral administration of morphine sulfate on developing rat fetal cerebrum: a morphometrical evaluation. *Brain Res*. (2008) 1245:36–40. doi: 10.1016/j.brainres.2008.09.052

43. Katebi SN, Razavi Y, Zeighamy Alamdary S, Khodagholi F, Haghparast A. Morphine could increase apoptotic factors in the nucleus accumbens and prefrontal cortex of rat brain's Reward circuitry. *Brain Res*. (2013) 1540:1–8. doi: 10.1016/j.brainres.2013.09.045

44. Hu S, Sheng WS, Lokensgard JR, Peterson PK. Morphine induces apoptosis of human microglia and neurons. *Neuropharmacology*. (2002) 42(6):829–36. doi: 10.1016/S0028-3908(02)00030-8

45. Cunha-Oliveira T, Rego AC, Oliveira CR. Cellular and molecular mechanisms involved in the neurotoxicity of opioid and psychostimulant drugs. *Brain Res Rev*. (2008) 58(1):192–208. doi: 10.1016/j.brainresrev.2008.03.002

46. Fowler AK, Thompson J, Chen L, Dagda M, Dertien J, Dossou KS, et al. Differential sensitivity of prefrontal cortex and hippocampus to alcohol-induced toxicity. *PLoS One*. (2014) 9(9):e106945. doi: 10.1371/journal.pone.0106945

47. Hauser KF, Knapp PE. Opiate drugs with abuse liability hijack the endogenous opioid system to disrupt neuronal and glial maturation in the central nervous system. *Front Pediatr*. (2017) 5:294. doi: 10.3389/fped.2017.00294

48. Rieger AM, Nelson KL, Konowalchuk JD, Barreda DR. Modified annexin V/propidium iodide apoptosis assay for accurate assessment of cell death. *J Vis Exp*. (2011) 50:1–4. doi: 10.3791/2597

49. Dean JM, George S, Naylor AS, Mallard C, Gunn AJ, Bennet L. Partial neuroprotection with low-dose infusion of the alpha2-adrenergic receptor agonist clonidine after severe hypoxia in preterm fetal sheep. *Neuropharmacology*. (2008) 55(2):166–74. doi: 10.1016/j.neuropharm.2008.05.009

50. Yanli L, Xizhou Z, Yan W, Bo Z, Yunhong Z, Zicheng L, et al. Clonidine preconditioning alleviated focal cerebral ischemic insult in rats via up-regulating p-NMDAR1 and down-regulating NMDAR2A / p-NMDAR2B. *Eur J Pharmacol*. (2016) 793:89–94. doi: 10.1016/j.ejphar.2016.10.036

51. Laudenbach V, Mantz J, Lagercrantz H, Desmonts JM, Evrard P, Gressens P. Effects of alpha(2)-adrenoceptor agonists on perinatal excitotoxic brain injury: comparison of clonidine and dexmedetomidine. *Anesthesiology*. (2002) 96 (1):134–41. doi: 10.1097/00000542-200201000-00026

52. Langer SZ. Presynaptic regulation of the release of catecholamines. *Pharmacol Rev*. (1980) 32(4):337–62.

53. Jellish WS, Murdoch J, Kindel G, Zhang X, White FA. The effect of clonidine on cell survival, glutamate, and aspartate release in normo- and hyperglycemic rats after near complete forebrain ischemia. *Exp Brain Res*. (2005) 167 (4):526–34. doi: 10.1007/s00221-005-0064-4

54. Conradt E, Crowell SE, Lester BM. Early life stress and environmental influences on the neurodevelopment of children with prenatal opioid exposure. *Neurobiol Stress*. (2018) 9:48–54. doi: 10.1016/j.ynstr.2018.08.005

55. Lester BM, Padbury JF. Third pathophysiology of prenatal cocaine exposure. *Dev Neurosci*. (2009) 31(1-2):23–35. doi: 10.1159/000207491

56. Gluckman PD, Hanson MA. Living with the past: evolution, development, and patterns of disease. *Science*. (2004) 305(5691):1733–6. doi: 10.1126/science.1095292

57. Buss C, Entringer S, Wadhwa PD. Fetal programming of brain development: intrauterine stress and susceptibility to psychopathology. *Sci Signal*. (2012) 5(245): pt7. doi: 10.1126/scisignal.2003406

58. Cottrell E, Seckl J. Prenatal stress, glucocorticoids and the programming of adult disease. *Front Behav Neurosci*. (2009) 3:19. doi: 10.3389/neuro.08.019.2009

59. Luoni A, Berry A, Calabrese F, Capoccia S, Bellisario V, Gass P, et al. Delayed BDNF alterations in the prefrontal cortex of rats exposed to prenatal stress: preventive effect of lurasidone treatment during adolescence. *Eur Neuropsychopharmacol*. (2014) 24(6):986–95. doi: 10.1016/j.euroneuro.2013.12.010

60. Schrott LM, Franklin L, Serrano PA. Prenatal opiate exposure impairs radial arm maze performance and reduces levels of BDNF precursor following training. *Brain Res*. (2008) 1198:132–40. doi: 10.1016/j.brainres.2008.01.020

61. Subedi L, Huang H, Pant A, Westgate PM, Bada HS, Bauer JA, et al. Plasma brain-derived neurotrophic factor levels in newborn infants with neonatal abstinence syndrome. *Front Pediatr*. (2017) 5:238. doi: 10.3389/fped.2017.00238

62. Phillips NLH, Roth TL. Animal models and their contribution to our understanding of the relationship between environments, epigenetic modifications, and behavior. *Genes (Basel)*. (2019) 10(1):1–15. doi: 10.3390/genes10010047

63. Traccis F, Frau R, Melis M. Gender differences in the outcome of offspring prenatally exposed to drugs of abuse. *Front Behav Neurosci*. (2020) 14:72. doi: 10.3389/fnbeh.2020.00072

64. Sithisarn T, Legan SJ, Westgate PM, Wilson M, Wellmann K, Bada HS, et al. The effects of perinatal oxycodone exposure on behavioral outcome in a rodent model. *Front Pediatr*. (2017) 5:180. doi: 10.3389/fped.2017.00180

65. Nygaard E, Slinning K, Moe V, Walhovd KB. Behavior and attention problems in eight-year-old children with prenatal opiate and poly-substance exposure: a longitudinal study. *PLoS One*. (2016) 11(6):e0158054. doi: 10.1371/journal.pone.0158054

66. Schwartz AN, Reyes LM, Meschke LL, Kintziger KW. Prenatal opioid exposure and ADHD childhood symptoms: a meta-analysis. *Children (Basel)*. (2021) 8(2):1–19. doi: 10.3390/children8020106

67. Arnsten AF. The emerging neurobiology of attention deficit hyperactivity disorder: the key role of the prefrontal association Cortex. *J Pediatr*. (2009) 154 (5):I-S43. doi: 10.1016/j.jpeds.2009.01.018

68. Premachandran H, Zhao M, Arruda-Carvalho M. Sex differences in the development of the rodent corticolimbic system. *Front Neurosci*. (2020) 14:583477. doi: 10.3389/fnins.2020.583477

69. Chou IC, Trakht T, Signori C, Smith J, Felt BT, Vazquez DM, et al. Behavioral/environmental intervention improves learning after cerebral hypoxia-ischemia in rats. *Stroke*. (2001) 32(9):2192–7. doi: 10.1161/hs0901.095656

70. Ilyka D, Johnson MH, Lloyd-Fox S. Infant social interactions and brain development: a systematic review. *Neurosci Biobehav Rev*. (2021) 130:448–69. doi: 10.1016/j.neubiorev.2021.09.001

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 23 December 2022
DOI 10.3389/fped.2022.1087956

Check for updates

OPEN ACCESS

EDITED BY
Henrietta S. Bada,
University of Kentucky, United States

REVIEWED BY
Thitinart Sithisarn,
University of Kentucky, United States
Eric W. Reynolds,
University of Texas Health Science Center at Houston, United States

*CORRESPONDENCE
Monica Sarfi
a.m.sarfi@medisin.uio

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Neonatology, a section of the journal Frontiers in Pediatrics

RECEIVED 02 November 2022
ACCEPTED 29 November 2022
PUBLISHED 23 December 2022

CITATION
Sarfi M, Eikemo M and Konijnenberg C (2022) Children born to women in opioid maintenance treatment: A longitudinal study of child behavioral problems and parenting stress. Front. Pediatr. 10:1087956. doi: 10.3389/fped.2022.1087956

COPYRIGHT
© 2022 Sarfi, Eikemo and Konijnenberg. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Children born to women in opioid maintenance treatment: A longitudinal study of child behavioral problems and parenting stress

Monica Sarfi[1*†], Marie Eikemo[2†] and Carolien Konijnenberg[3]

[1]Norwegian Centre for Addiction Research (SERAF), Faculty of Medicine, University of Oslo, Oslo, Norway, [2]Department of Psychology, Faculty of Social Sciences, University of Oslo, Oslo, Norway, [3]Department of Psychology, Inland Norway University of Applied Sciences, Lillehammer, Norway

In the wake of the "opioid epidemic", there is considerable concern regarding potential harmful long-term effects of prenatal opioid exposure. Opioid misuse and addiction confer increased exposure to lifestyle stressors and health burdens. Accordingly, it is challenging to disentangle effects of prenatal opioid exposure *per se* from factors related to maternal stress. In this study, we followed 36 women enrolled in comprehensive opioid maintenance treatment (OMT) program and their children alongside 36 age-matched mother-child dyads from a community sample (COMP) from pregnancy until child-age 8 years. Across five sessions, we used a battery of well-established questionnaires to investigate trajectories of parenting stress and mental health symptoms as well as child behavior problems. The 8-year retention was relatively high (OMT: 72%, COMP: 67%), and the OMT sample remarkably stable and well-functioning, with minimal concomitant illicit drug use. Mixed effects regressions showed significantly different trajectories of child behavior problems ($F = 3.8$, $p = 0.024$) and parenting stress ($F = 3.1$, $p = 0.016$) in the two groups. Differences in experienced stress were largely explained by more distress specifically related to the parenting role in the OMT group ($F = 9.7$, $p = 0.003$). The OMT sample also reported higher psychological distress ($F = 15.6$, $p < 0.001$) than the comparison group, but notably few participants presented with problems that warranted clinical intervention. The results underscore the benefits of tailored follow-up of children prenatally exposed to opioids and their families beyond infancy and toddlerhood. Long-term direct effects of prenatal opioid exposure on behavior problems are likely modest, given an otherwise stable caregiving environment conducive to healthy development.

KEYWORDS
prenatal opioid exposure, development, methadone, buprenorphine, parenting distress

1. Introduction

The increased access to both licit and illicit opioids globally has received pronounced public health and scientific attention as it has affected the lives of millions of individuals. Of these, many are parents or child caregivers. Opioid dependence, and the resulting impact on parental capacity raises major concerns regarding the well-being and safety

of the children in these households (1, 2). Opioid maintenance treatment (OMT) with methadone or buprenorphine is an established and recommended "best practice" intervention for pregnant women with opioid use disorders (OUD) (3). Like illicit opioids, methadone and buprenorphine mimic naturally occurring endorphins and activate the same opioid receptors. However, they do so more slowly than other opioids, thereby preventing erratic maternal opioid levels and protecting the fetus from repeated episodes of withdrawal (4). OMT is associated with healthier pregnancies, lower risk for miscarriage, better access to prenatal care for the woman and significantly improved birth outcomes compared to untreated opioid use disorder (5) and tapering in pregnancy (6). Stability in OMT has shown to reduce reported lifestyle problems and stress associated with illicit drug use (7) and has improved the quality of the home environment for children of parents in OMT. Despite the beneficial effects, concerns are often raised regarding the possible negative consequences of prenatal exposure to OMT medications on the developmental outcomes of the children.

Prenatal exposure to any opioid agonist has an immediate effect on the newborn, often resulting in neonatal abstinence syndrome (NAS), indicating opioid withdrawal. While symptoms of NAS often abate within days or weeks, there is lacking consensus regarding possible harmful long-term consequences on developmental outcomes and studies show varying results, depending on methodology and outcome measures (8, 9). However, results from a rigorous longitudinal randomized controlled trial showed that children exposed to opioid agonists prenatally follow a pattern of normal development during the first 3 years of life (10).

Studies of effects of prenatal opioid exposure beyond 3 years are few and show divergent findings (11). Some reports indicate that opioid-exposed children have higher risk of difficulties in childhood such as cognitive, neuro—and psychomotor development (12), mediated in part through suboptimal maternal caregiving. Other studies show heightened internalizing and externalizing behavior problems, conduct disorders and ADHD diagnoses (13). However, there is little evidence to support direct relationships between prenatal opioid exposure and adverse developmental trajectories into later stages of childhood and adolescence. Rather, the adverse effects observed on child outcomes appear to be mediated and moderated by a number of individual and environmental factors and the interplay between these factors, not the opioid exposure *per se* (11).

Addiction treatment alone may not be sufficient to address the underlying factors that can affect child safety and development in families with OUD. This vision is embedded in the Norwegian OMT program, which aims to provide comprehensive, collaborative care for opioid-addicted parents and their children within the framework of the free national public health care system. Pregnant patients enrolled in the national OMT program in this country are subjected to strict control routines such as regular urine tests, counselling, regular pregnancy checkups and child welfare referral when required. These national guidelines for pregnant OMT patients and their children outline a structured follow-up regimen from birth to school-age (14), involving hospital services as well as a range of health professionals in the field of addiction treatment, mental health and education services. As a result, studies on OMT cohorts in this country have shown very little concomitant drug use in pregnancy and birth parameters of children born to mothers in OMT are within the normal ranges (15, 16). A substantial number of mothers retain custody 8 years after delivery and a recent study showed that children growing up with parents in stable OMT have significantly better mental health in early school age than other vulnerable groups such as children placed in foster care (17).

Despite good retention and rehabilitation, mothers in OMT often share many of the difficulties of addicted mothers outside OMT such as socioeconomic and interpersonal challenges. There is also a prominent fear of losing custody of children in this group of mothers, which is dependent on adherence to the schedules and rules in the OMT program. On top of contextual risk factors, women with OUD have high risk for comorbid psychopathology—in particular mood disturbances —that influence child care which in turn may account for reduced distress tolerance in the parenting role (18). At the neurobiological level, caregiving challenges observed in parents with opioid addiction may reflect the general dysregulation of neural circuits underpinning reward and stress responses seen in addiction (19), which are also important for parenting (20, 21).

Parenting stress is one of the most prominent sources of stress and is experienced by all parents to some degree (22–24). Parenting stress accounts for the stress associated specifically with the parenting role and is influenced by factors residing both within each parent and factors in their environments (25, 26). There is compelling evidence that mothers with opioid addiction typically have more stress in their lives compared to mothers from normative samples (27). Less is known about how OUD treatment and treatment stability enable opioid-addicted mothers to manage parenting over time,—especially faced with personal and child related challenges. Studies of early mother-child interaction have consistently found patterns of poor sensitivity and responsiveness to infants' emotional and behavioral cues in dyads of substance-dependent mothers compared to normative dyads (28, 29). However, difficulties with sensitive parenting are multiply determined and may be compounded by infants' display of "difficult behaviors" such as fussiness and disrupted sleep pattern—often occurring in infants exposed to opioids *in utero* and known as neonatal abstinence syndrome (NAS) (30). Parenting an infant with regulatory problems or raising a child with behavioral challenges tends to increase parenting stress, and parents who experience

greater parenting-related stress may be more likely to parent in ways that maintain child problems or even put the child at risk for maltreatment (31, 32).

While many studies have assessed parenting in substance using populations, outcomes reported are frequently confounded by factors as parental concomitant substance use and psychiatric comorbidity in the study groups. As such, longitudinal studies of children of mothers in stable OMT are needed to explore developmental consequences of prenatal opioid exposure *per se*.

The longitudinal data presented here stem from a prospective observational study of mothers enrolled in OMT in pregnancy and their children exposed to opioid agonists prenatally who were raised in relatively stable home environments. In parallel, an age matched comparison group of non-exposed children and mothers with no history of drug addiction was followed. Participants in the OMT study group had been in this treatment on average 2.5 years at study inclusion and were stable in treatment throughout the study period. Further, this is a group with very limited concomitant substance use and less psychological distress symptoms than reported in similar study groups, i.e., (33). Also, 80% of the included children lived with biological parents when they were 8 years. Both study cohorts were followed from pregnancy to school-age.

Specifically, we aimed to describe (a) parenting stress, (b) perceived child behavioral problems, and (c) post-natal mental health of mothers in OMT and a comparison group of non-dependent mothers from infancy to early school age and to explore the association between child behavior problems and parenting stress in the two groups across time.

2. Methods and materials

To date, OMT in Norway includes ~8,000 individuals, one-third being women. The number of pregnancies in the OMT program has been low and stable in the period 2005–2015 with a mean number of 28 pregnancies per year, representing 0.06% of the general pregnant population in Norway during the same time period (34).

2.1. Participants

2.1.1. Participants in opioid maintenance treatment

Data included in this study is part of a prospective, longitudinal cohort study of children born to mothers in opioid maintenance treatment in Norway who were included during a 2-year period (2005–07). Around 30% of the OMT population of 7,500 individuals in the country were women. The annual birth rate of children exposed to OMT-medications has varied between 25 and 40 since OMT was introduced as treatment option in 1998.

Women in the OMT-group were contacted if they had a pregnancy due date between January 2005 and January 2007 and had used either methadone or buprenorphine during pregnancy. Recruitment took place through local GP contacts, regional OMT centers and treatment facilities throughout Norway. Of the 47 pregnant women in OMT in Norway identified at the start of the longitudinal project, six declined to be included, two miscarried, one child was excluded due to a severe congenital disorder which yielded a 76% participation rate ($N = 36$). A majority of the mothers (68%) in OMT had been in stable in this treatment for a considerable time before pregnancy was confirmed (31.1 months, range: 3–81 months) and used methadone as their OMT-medication while the rest used buprenorphine. There was very little concomitant illicit drug use (35), but almost all mothers in the OMT group smoked cigarettes daily during pregnancy.

2.1.2. The community sample comparison group

Describing the trajectories of parenting stress and child behavior problems *within* the OMT group was the main goal of this study. It was not feasible to recruit a control group matched on socio-economic/demographic variables for a long-term follow-up study in Norway, due to high living standard and free healthcare and social services. Nevertheless, an age matched community sample of healthy pregnant women without illicit drug use or psychiatric illness were recruited to serve as a "comparison group" (COMP, $N = 36$) as a means to address general developmental trajectories throughout the follow-up period. The COMP participants were recruited through local health care centers in and around the capital city. Importantly, potential main effects of group may therefore be confounded by socioeconomic and opioid-related influences. On the other hand, an absence of overall group effects may suggest a rather well-functioning OMT group. Accordingly, we are primarily interested in age*group interaction effects that could indicate differences in developmental trajectories. Information about the infants (i.e., weight, presence of neonatal abstinence symptoms) was obtained directly from hospital medical records. Recruitment and inclusion procedures are described in more detail in previous publications (36, 37).

Descriptive statistics and socio-demographic variables are in the two groups at study inclusion and 8 years later are shown in **Table 1**. The proportion of women in OMT in employment or education-related activities increased during the study period, and more disclosed having a stable partner. The rate of smoking was unchanged and high in the OMT group.

Some of the children in the OMT group were placed out-of-home during study period, and foster-parent reported

TABLE 1 Key characteristics of the two study groups at delivery and 8 years later.

Variables	Birth		8 years	
	OMT ($n = 36$)	COMP ($n = 36$)	OMT ($n = 26$)	COMP ($n = 24$)
NAS yes/no	23/13 (63.9%)	–	–	–
Birthweight (g) *M* (SD)	3,146 (599)	3,618 (343)	–	–
Age mother *M* (SD)	32.2 (4.7)	32.6 (4.7)	40.0 (5.0)	40.0 (4.7)
Gestational age *M* (SD)	38.6 (2.5)	40.0 (0.7)	–	–
Methadone *N*	26	–	15	–
Dose mg, *M* (range)	108.5 (0–660)	–	120 (0–440)	–
Buprenorphine, *N*	10	–	11	–
Dose mg, *M* (range)	13.3 (3–24)	–	12.0 (4–20)	–
Smoking yes/no	35/1	0/36	22/4	3/21[a]
Work or study yes/no	3/33	35/1	10/16	24/0
Partner yes/no	11/25	36/0	18/8	23/1

Methadone and buprenorphine doses are not comparable because some of the women converted medication during the study period. All participants were white, Norwegian women.
[a]Women in the comparison group who reported smoking were party smokers.

information was collected after placement. Nevertheless, only information given by the biological mothers (original mother-child dyads) at each assessment point was used in the present study. All available data from these mothers was used, even those with missing data for some assessments. The total number of participants with complete data sets amounted to 26 mothers in the OMT group and 24 comparison mothers (see Figure 1).

2.2. Procedures

Participants received verbal and written information about the study at the time of recruitment and signed consent forms with permission to be contacted again for further assessments as the child grew older. They also signed separate consent forms prior to each assessment. Data was collected in pregnancy, during infancy (3 and 6 months), in toddlerhood (1 and 2.5 years), preschool period (4.5 years), and school age (8 years). The study was approved by the Regional Ethics Committee (2013/1606/REK Sør-Øst B) and conducted in accordance with the Declaration of Helsinki (1964).

Previous publications from this study group have addressed various aspects of both parental and child functioning (17, 35, 38–40) throughout the 8-year follow-up-period. Here we analyze key outcomes across the whole study period, focusing primarily on parenting stress and child behavioral problems.

2.2.1. Attrition and retention rates

During the 8-year study period, five boys and two girls in the OMT group were placed out-of-home by Child Welfare Services. Three children were removed from home between the 1 and 2-year assessments, and one mother withdrew from the study shortly after the child was 1 year old (see Figure 1). Two children were placed in foster care before the 4-year assessment, and another two children before the 8-year assessment. The two mothers who discontinued the study prior to the 8-year assessment did so because they feared potential stigma. The COMP group was reduced to 31 participants at the 4-year

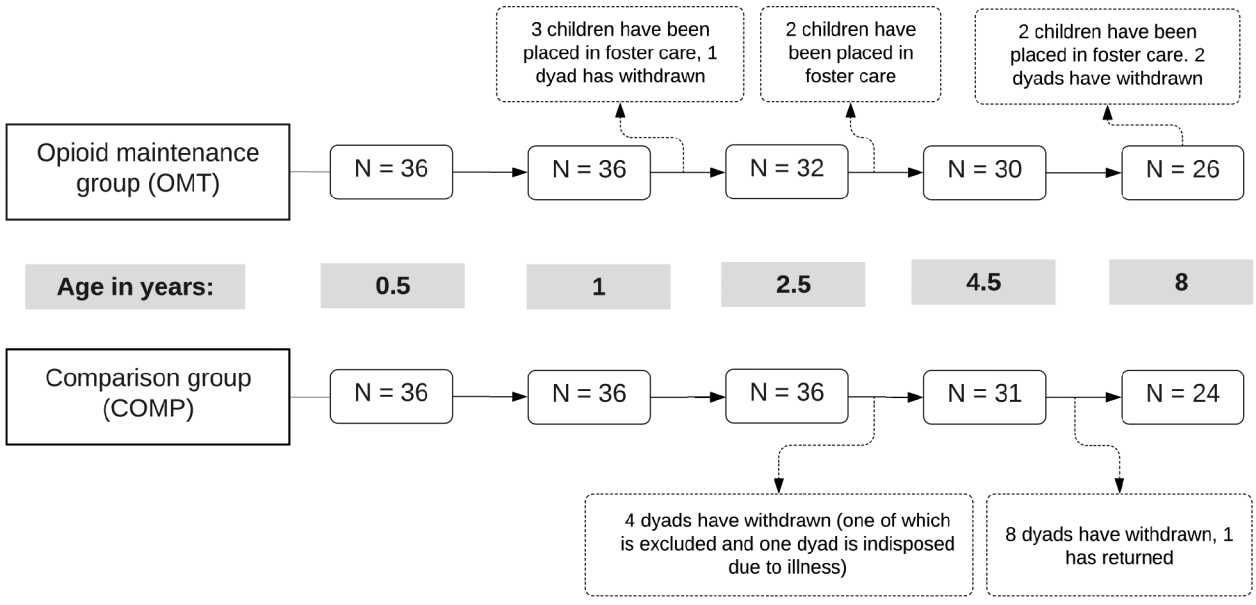


FIGURE 1
Schematic of retention and discontinuation in the two groups across the five assessment points. Age refers to child age in years.

assessment (85%) because four families withdrew from the study, one mother was temporarily indisposed by illness (but returned at the next assessment point) and one other child from this group was excluded prior to the third assessment due to cerebral palsy. The number of participants in the COMP group was further decreased at the last assessment as 8 more mothers withdrew from the study. All the mothers in the COMP group who discontinued stated time constraints as their main reason to leave the study.

2.3. Measures

2.3.1. The parenting stress index (PSI)

The PSI is a self-report questionnaire specifically developed to identify potential child and parent characteristics that might lead to stress in the parenting system (41, 42). The original PSI consists of 120-items scored on a five-point Likert type scale, with responses ranging from strongly agree (1) to strongly disagree (5). Higher scores indicate higher stress. The PSI has a Parent and Child Domain that in sum reflects the overall degree of stress in the parenting system. An abbreviated version of the PSI was developed in 1990 and is referred to the Short form version (PSI-SF) (41). The PSI-SF is a direct derivative of the full-length version and takes approximately 10 min to complete. It consists of 36 items built upon Castaldi's 1990 factor analysis of the original (here referred to as the long form: PSI-LF) which demonstrated that the parenting stress construct consisted of three central factors. The PSI-SF consists of three subscales namely *Parental Distress, PD* ("I feel trapped by my responsibilities as a parent"; "I feel lonely and without friends"), *Parent-Child Dysfunctional Interaction, PCDI* ("Sometimes I feel my child doesn't like me and doesn't want to be close to me", "When I do things for my child, I get the feeling that my efforts are not appreciated"). *Difficult Child, DC* ("My child makes more demands on me than most children", "My child gets upset easily over the smallest thing").

Each subscale consists of 12 items in statement form. Agreement is rated from 1 (strongly disagree) to 5 (strongly agree), with subscales scores ranging from 12 to 60. A total PSI-SF score is calculated by summing the three subscales' scores, ranging from 36 to 180. Scores above the 85th percentile on the Total Stress scale are considered borderline clinically significant Similarly, the cut-off scores for the subscales are 33 (PD), 26 (P-CDI) and 33 (DC) (43).

The two versions of the PSI have been in use at different time points in the present study due to time constraints. The PSI-SF was completed by parents at the first and last assessment (6 months and 8 years). The full-length PSI was administered at age 1, 2.5 and 4.5. The PSI-SF is a direct derivative of the full-length version and has been used in many studies (44). Here we converted all data to short form to formally model parenting stress over time. The 36 equal-wording items that constitute the PSI-SF were extracted from the full-length versions and plotted into PSI-SF templates. The scale reliability of the PSI-LF and the PSI-SF supports this construction procedure as shown by good inter-item reliability (Cronbach's alpha) for the original PSI-LF and PSI-SF as well as the three constructed PSI-SF questionnaires (see **Table 2**).

TABLE 2 Cronbach's alpha for the different PSI versions.

	PSI Version	
Age (years)	PSI_LF	PSI_SF
0.5	NA	0.9
1.0	0.94	0.88[a]
2.5	0.93	0.83[a]
4.5	0.94	0.91[a]
8.0	NA	0.94

Cronbach's alpha.
[a]Denotes the values computed for short form versions constructed from items in the long form of the PSI.

2.3.2. The Edinburgh postnatal depression scale (EPDS)

The EPDS is a set of ten screening questions that can indicate whether a parent has symptoms that are common in women with depression and anxiety during pregnancy and in the year following the birth of a child (45). To complete this set of questions, the parent should select the number next to the response that comes closest to how they have felt in the past 7 days. Responses are scored 0, 1, 2 and 3 based on the seriousness of the symptom). The total score is found by adding together the scores for each of the 10 items. Based on a number of studies, a cut-off of 13 or higher could be used to identify pregnant and postpartum women with higher symptom levels, whereas lower cut-off values could be used if the intention is to avoid false negatives and identify most patients who meet diagnostic criteria (46).

2.3.3. The hopkins symptom checklist-25 (SCL-25)

The SCL-25 is a widely used screening tool for measuring anxiety and depression in both clinical and normative samples (SCL-25, 47). It comprises a 10-item subscale for anxiety and a 15-item subscale for depression. In the version used here, each item relating to a symptom is rated from 0 (none) to 4 (very much). Scores for each subscale were computed as averages across the 15 depression items and 10 anxiety items. In accordance with a previous study using this questionnaire version, a cut-off of $\geq$1.0 was used to identify participants with at least some distress (48). In the present study, SCL-25 data was available from measurements in pregnancy, 6 months after delivery and at child ages 2.5 and 8 years.

2.3.4. Child behavior checklist (CBCL 1 ½-5)

This 100-item checklist (49) measures specific emotional and behavioral problems of children ages 18 months through 5 years. The questionnaire is administered to parents or other caregivers who know the child well. Caregivers rate items describing statements relating to behavior on a scale from zero to two, with higher scores indicating greater problem severity. Items are summed to make up seven subscales (emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems and aggressive behavior) which in turn can be combined into two higher-order scales; internalizing and externalizing problems, and a total difficulty score. The minimum possible score is 0 and the maximum is 200. In this study, the Child Behavior Checklist (CBCL 1 ½-5) was administered to mothers at child ages 2.5 and 4 years.

2.3.5. Strengths and difficulties questionnaire (SDQ)

The parent version of the SDQ is designed for children aged 4–16 years. The questionnaire consists of 25 items distributed on 5 subscales of five items each (emotional problems, conduct problems, hyperactivity/inattention problems, peer problems and prosocial behavior). The first four scales are summed to calculate a *total difficulties score* (0–40), used here. Higher scores one the SDQ indicate more difficulties. This questionnaire was completed by mothers at the last assessments (8 years).

2.3.5.1. Common scale for behavior scores

The CBCL and the SDQ are used to measure the same underlying construct: behavioral difficulties. The number of items and composite scales differ. However, previous studies show that the sum scores from the two instruments are strongly correlated (50, 51). To enable longitudinal analysis across time points, we chose to rescale both scores to 0–1. Ratings were converted to a number between 0 and 1, based on the minimal and maximal possible score in each instrument such that new score would reflect the "relative problem load". Here we used the new score for inferential statistics, but also report raw scores from each questionnaire (total scores). Sensitivity analyses of main group differences were conducted to assess the face validity of the common scale score (see **Supplementary Material**).

2.4. Statistical analysis

All analyses were performed using R version 4.1.0 (packages are described in the **Supplementary Material**). For PSI, child behavior scores and SCL data, mixed effects regressions were used to account for dependencies in the data. Models were implemented in the *lme4* package in R and assessments nested within mother (subject). Mixed effects models allow easy inclusion of covariates at within- and between subject levels as well as different random effect variables. Mixed models are also flexible with regards to unequal group size and some types of missing data. A random intercept for participant was used in all models to account for the non-independence of data within participant. Age was modeled as a categorical predictor due to the limited number of assessments and relative variability in the measurement times. All models included the design relevant fixed effects *group* and *age* and *group*-by-*age* interaction. Variance explained by inter-individual differences in *birthweight* and *sex*, (and *years in treatment)* were tested during model selection for the analyses of PSI scores and problem behavior. A decrease in Bayesian Information Criterion (BIC) of 2 or more was used as an indication of a superior model. For the final models, the results from REML model are reported. Overall contrasts were performed with Satterthwaite's method for denominator degrees of freedom. Tukey correction for multiple comparisons were used for *post hoc* contrasts. A separate regression was performed on the OMT data to assess whether neonatal abstinence syndrome (NAS) explained variance in the reports of behavior difficulties or stress. Group differences in the EDPS data were assessed with an independent samples Welch's *t*-test, which is robust to unequal variances, was used to test for group differences in the postnatal depression (EDPS) data. A significance level of 5% was used for all analyses. Internal consistency of the converted PSI scales was assessed by Cronbach alpha (α). We also report Pearson correlations to describe the associations between the two main outcomes (total PSI score and child behavior scores) at the three time points where both measures were collected (2.5, 4.5 and 8 years).

A third of the participants discontinued or were excluded during the follow-up period ($n = 22$). To assess whether the participants who discontinued had worse mental health at the first assessment (in pregnancy) compared to those that completed the whole study, we conducted a sensitivity analysis comparing SCL-25 scores at the first assessment (Welch's *t*, *completed* vs. *discontinued*).

3. Results

3.1. Reported parenting stress

3.1.1. Total parenting stress

Figure 2 shows the distribution of parenting stress scores at each assessment. Total PSI-SF scores were on average 7 points higher in the OMT group ($M_{OMT} = 69$, $M_{COMP} = 62$). The mixed regression for the total PSI score showed a significant main effect of *group* ($F_{1,74.1} = 5.5$, $p = 0.022$) and *age* ($F_{4,253.5} = 24.5$, $p < 0.0001$) and *age*group* interaction ($F_{4,253.5} = 3.1$, $p = 0.016$). Pairwise comparisons showed significant group differences at the first (6 months: $Mean_{Diff}$ OMT > COMP = 6.5, $p = 0.038$) and last assessment (8 years, OMT > COMP

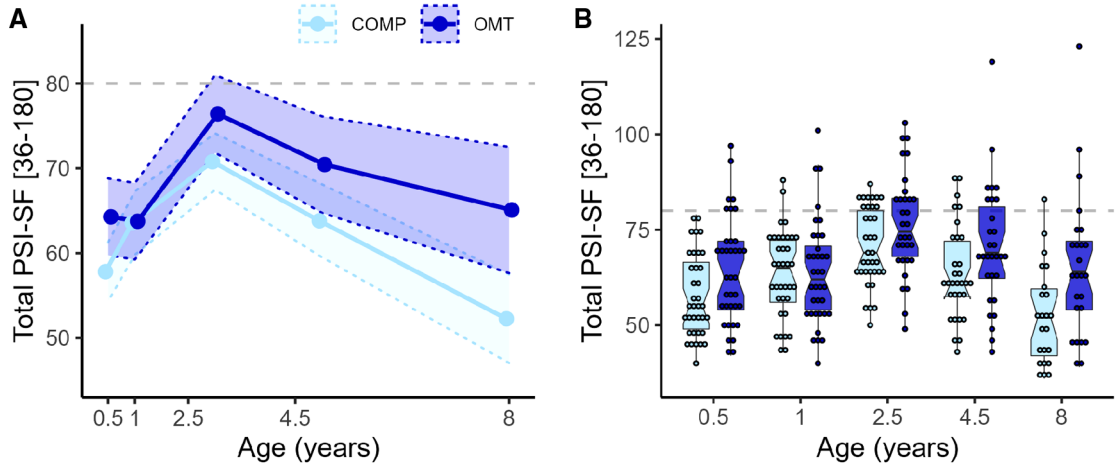


FIGURE 2
Showing the trend in PSI over time and scores for each participant (**A**) group-wise mean total PSI-SF with 95% confidence bands for the five time points. Age is presented on numerical scale on the x-axis to illustrate relative timing of assessments. (**B**) Box- and dot plots of total PSI-SF scores presented group-wise at each time point. OMT: dark blue, COMP: light blue. The box plot notches represent the 95% CI of the median in the middle line). Dots show the total PSI-SF score for each participant and each point of assessment, presented on a categorical x-axis. Dashed grey lines indicate the 80-point threshold, often used as a cut-off for clinical problems.

11.9, $p = 0.0008$). A separate regression of PSI in the OMT group only, showed that neither *time in OMT treatment* nor neonatal abstinence syndrome (*NAS*) were significant predictors of parenting stress, and did not improve model fit. The intraclass correlation (ICC) was 0.52, indicating relatively high consistency in reports across assessments within-subject.

3.1.1.1. Sub-scales of the PSI

For the Parenting Distress (PD) subscale there was a significant main effect of *group* ($F_{1,71.7} = 9.7$, $p = 0.003$) and *age* ($F_{4,244.7} = 8.7$, $p < 0.0001$) and *group*age* interaction ($F_{4,244.7} = 3.6$, $p = 0.007$). *Post hoc* contrasts showed significant group differences at every assessment apart from 1 year. For the DC sub-scale there was no significant main ($F_{1,71.9} = 0.8$, $p = 0.38$) or interaction effects ($F_{4,246.5} = 1.4$, $p = 0.25$) involving *group*, but a main effect of *age* ($F_{4,246.5} = 47.4$, $p < 0.0001$). For the PCDI subscale there were no significant main ($F_{1,73.6} = 3.4$, $p = 0.07$) or interaction effects ($F_{4,249} = 2.3$, $p = 0.06$) of *group*, but a main effect of *age* ($F_{4,249} = 23.4$, $p < 0.0001$). **Figure 3** shows the average scores and confidence intervals on the three subscales which compose the PSI total score across the study period.

3.2. Symptoms of psychological distress

3.2.1. Reported depression and anxiety: The hopkins symptom checklist (SCL-25)

The SCL-25 was administered in the last trimester of pregnancy, when the child was 6 months, 2.5 years, 4.5 and 8 years. **Figure 4** shows that the average SCL-25 score was higher in the OMT group across the whole study period from pregnancy (age = 0) to 8 years (main effect: $F_{1,70} = 15.6$, $p = 0.0002$) with a large spread of scores. Group contrasts showed that there were significant differences at each measurement point (ranging between 5 and 13 points difference in sum score, all p's < 0.0046). Seven women in the OMT group scored ≥1 on average across all measurements. There was a significant main effect of age ($F_{3,181} = 15.6$, $p < 0.0001$), and a *group*age* interaction effect for the total SCL-25 score ($F_{3,181} = 3.17$, $p = 0.026$). Separate models for anxiety and depression subscales showed similar and robust group differences across the measurements (p's < 0.0006).

The sensitivity analysis of baseline scores for the participants who completed all assessments and those who discontinued at some point during the study, showed no significant difference in SCL-25 score for either group [OMT: mean difference (Δ) = 0.06, $p = 0.77$; COMP: $\Delta = -0.01$, $p = 0.91$]. Therefore, it is not evident that those who discontinued or were excluded from the study had worse mental health than those who did not.

3.2.2. The Edinburgh postnatal depression scale (EPDS)

We observed large differences in the average scores on the EPDS for the two groups (see **Figure 5**. Welch's $t_{46.3} = 4.8$, $p < 0.0001$, Cohen's $d = 1.1$), but also a large difference in the spread of scores. While the average of the OMT group was just barely below the cut-off for maternal post-partum depression (scores > 10) on the EPDS, none of the participants in the

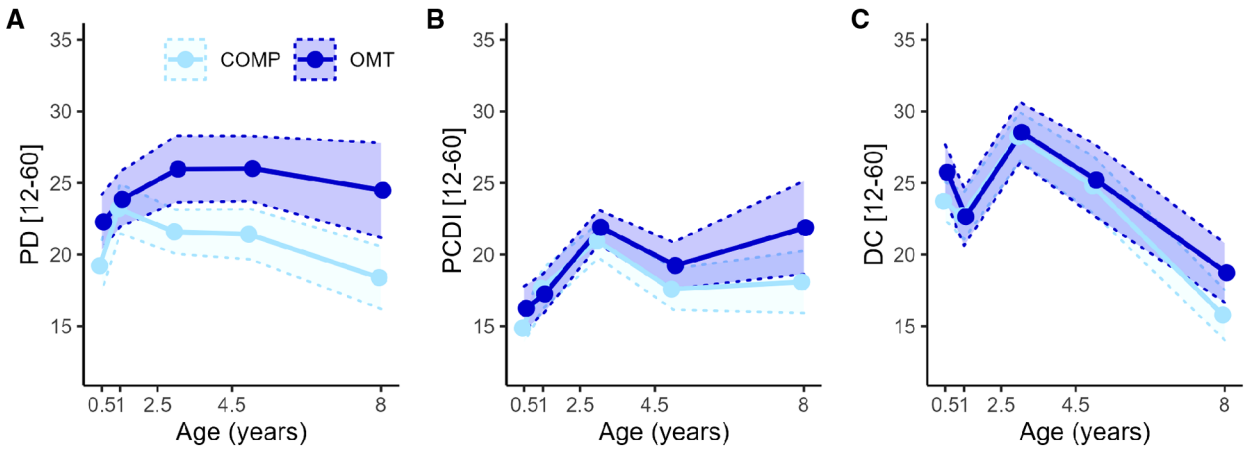


FIGURE 3
The lines with points in figures A–C show the average PSI-SF score across the five assessment points for the three subscales of the PSI-SF. (A) Parental distress, (B) Parent Child Dysfunctional Interaction and (C) Difficult Child. The shaded areas within the dotted lines represent the 95% confidence intervals. The *x*-axis is linearly scaled with time to illustrate the measurement intervals.

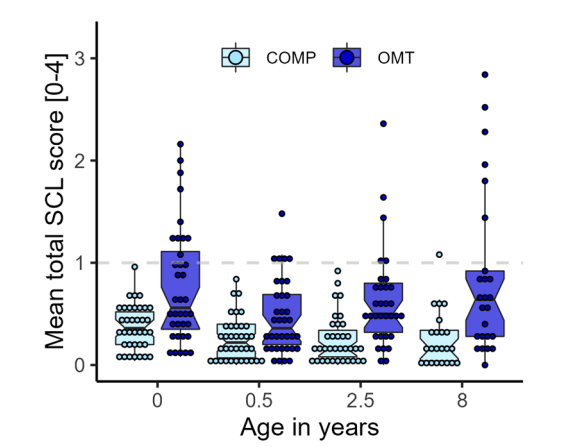


FIGURE 4
Overview of the average SCL-25 scores by group and measurement occasion. Dots display average score per participant at each assessment. SCL-25 ratings from 4 ½ years were not available.

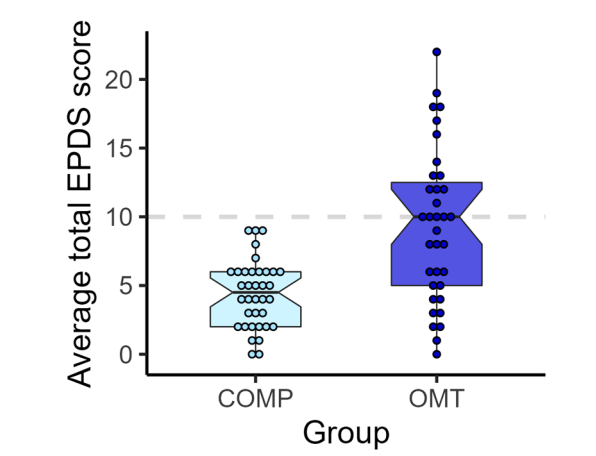


FIGURE 5
Boxplots and dots showing individual EPDS sum scores for each participant in the two study groups.

comparison group scored above this cutoff 3 months after delivery (M ± SD: COMP = 4.49 ± 2.44, OMT = 9.34 ± 5.58).

3.2.2.1. Associations between EPDS and parental distress

There was a moderate significant correlation between the EPDS score and the total PSI-SF score at 6 months ($r = 0.24$, $p = 0.040$) and the EPDS score and the parental distress (PD) subscale at 6 months ($r = 0.29$, $p = 0.013$). Group-wise analyses showed that this association was solely due to a significant correlation in the comparison group (COMP: $r = 0.4.0$, $p = 0.016$; OMT: $r = 0.11$, $p = 0.5$).

3.3. Parent reports of child problem behavior

Figure 6 shows the distribution of parent–reported problem scores collected when the children were 2.5, 4.5 and 8 years old. The mixed model of the (normalized) behavioral problem scores showed a significant effect of *group* ($F_{1,70.5} = 15.0$, $p = <0.001$) and *age* ($F_{2,119.4} = 52.3$, $p < 0.001$), and a significant interaction effect ($F_{2,119.4} = 3.8$, $p = 0.024$). The problem

10.3389/fped.2022.1087956

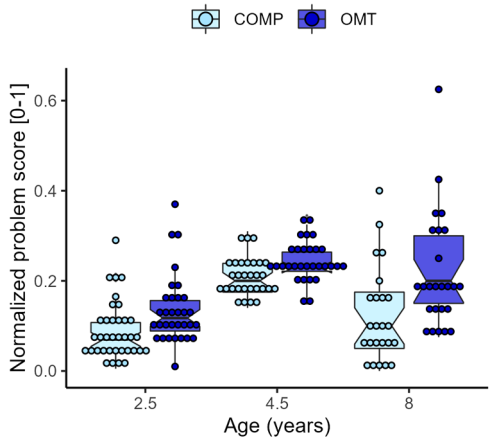


FIGURE 6
Boxplots of the average rescaled (0–1) problem score per group and age. Individual averages are superimposed as dots on the boxplots.

reports were on average 7% higher in the OMT group. In both groups, average scores were higher at the 4.5-year assessment. While reported difficulties significantly decreased from 4.5 to 8 years in the comparison group ($t_{105} = 4.3$, $p < 0.001$), scores in the OMT did not ($t_{105} = 1.18$, $p = 0.47$, Tukey adjustment). The variability in scores was notably higher in both groups at the 8-year assessment (see **Figure 6**). The ICC was 0.38. A separate regression analysis in the OMT data, showed that neonatal abstinence syndrome (NAS) was not a significant predictor of behavior problems, and did not improve the model fit. Two sensitivity analyses showed group differences in the raw problem score data (CBCL and SDQ), results and descriptive statistics can be found in the **Supplementary Material**.

3.3.1. Associations between parenting stress and child behavior problems

Pearson correlations between total parenting stress and child behavior problems at the three assessment points: 2.5, 4.5 and 8 years are displayed in **Table 3**. Coefficients are shown separately for the two groups. Overall, there were medium and strong correlations between scores across time within both outcome measures in the two groups. There was strong association between total PSI score and child behavior problems both at child ages 4.5 ($r = 0.74$, $p < 0.0001$) and 8 ($r = 0.72$, $p < 0.0001$) in the OMT data. Similarly, for the comparison group the correlation between total PSI score and child behavior problems was highest at 4.5 ($r = 0.68$, $p < 0.0001$) and 8 years ($r = 0.63$, $p = 0.0014$). Because the group differences were noticeably more robust on the PD (parental distress) subscale, we also tested the correlation between the PD and SDQ reports at 8 years which showed a significant positive association ($t_{45} = 4.5$, $p < 0.0001$).

4. Discussion

This study describes the trajectories of parenting stress, mental health and reports of child behavior problems in a cohort of women in opioid agonist treatment during pregnancy and their children. The mother-child dyads were followed for 8 years alongside a comparison group of mothers without history of substance use. On average, mothers in the OMT group reported poorer mental health, more child behavior problems and more parenting stress and distress throughout the study period. At the same time, group differences were rather small, and few scored above clinical cuff-offs. Indeed, the group differences were largely due to a handful of participants with high scores across outcomes. Altogether, mothers in stable OMT share many of the same challenges of parenthood with mothers from a normative sample.

Although mothers in the OMT group reported somewhat higher parenting stress than mothers in the comparison group, there were large within-group variability in scores (see **Figure 2**, 2). Both study groups demonstrated similar patterns in parenting stress over time: increasing levels of stress towards toddlerhood and decreasing stress as children grew older. However, the distribution of scores at the subscales

TABLE 3 Pearson correlations for main outcomes within the two study groups.

		OMT group					
		Prob 2	**Prob 4**	**Prob 8**	**PSI_tot 2**	**PSI_tot 4**	**PSI_tot 8**
Comparison group	Prob 2		***0.74***	***0.56***	**0.53**	***0.57***	**0.47**
	Prob 4	**0.45**		***0.69***	***0.60***	***0.74***	***0.67***
	Prob 8	0.36	0.36		**0.39**	**0.50**	***0.72***
	PSI_tot 2	**0.44**	**0.49**	**0.52**		***0.63***	**0.46**
	PSI_tot 4	0.26	***0.68***	**0.54**	***0.60***		***0.68***
	PSI_tot 8	0.29	0.41	***0.63***	***0.72***	**0.61**	

The matrix shows the correlations between problem and stress (PSI total) measures at the three measurement points where both outcomes were assessed. Upper right part of the matrix shows correlations for the OMT group the lower left part shows the corresponding correlations for the comparison group [all correlations significant at the unadjusted 0.05 level are marked in bold. Correlations significant after Bonferroni correction 0.05/30 tests ($p < 0.0017$) are marked in *italic*].

level of the PSI differed in the two groups. While there were no significant group differences in parent-child dysfunctional interaction (PCDI) or perceptions of child difficulties (DC), we found a significant and robust difference in reported parental distress (PD) from toddlerhood onwards. Further inspection of the longitudinal trajectory of parenting stress showed a peak in both groups when the children were 2 ½ years old. This finding is consistent with studies showing that parents experience higher stress in toddlerhood that typically decreases with increasing child age (26, 52). Considering that most 2- and 3-year-olds have tantrums, can resist parental direction and say no to many things, toddlerhood is challenging for most parents. The resistance and protesting behavior that typically characterizes toddlerhood would likely increase the demands of parenting and exacerbate parenting stress. In addition, whether the child is able to successfully regulate emotions is important because it is implicated in behaviors which are characteristics of externalizing behavior problems (53, 54).

It is unsurprising that mothers with opioid addiction have more stress in their lives compared to a low-risk group of mothers without a history of addiction. Individuals in established OMT typically have a more stable lifestyle than individuals with opioid addiction outside treatment (55), but more psychosocial and psychiatric vulnerability than healthy comparison groups (56). Sociodemographic risk factors act as distal stressors in both addicted and non-addicted mothers, which likely reduces tolerance for subjective stress experienced in the parenting role (26, 57). Other distal sources of stress for mothers in OMT may be associated with aspects of the treatment itself. We suggest that the types of surveillance mothers are subjected to in the national OMT of this country acts for better and for worse: On the one hand, the guidelines require close monitoring of women and children, especially during pregnancy and the first year after birth. This may cause stress and fear of making mistakes (41) in mothers who have had histories with child welfare involvement or have experienced removal of children earlier. On the other hand, a coordinated treatment program facilitates access to many services that can help mothers to cope with parenting challenges that arise. Observation, guidance and parental training services are offered both as residential treatment and home-based assistance. Seven women in this study stayed in a mother-infant facility before and after delivery for shorter or longer time, and more than half the women in the OMT group received support from Child Welfare Services (CWS). In a previous paper based on the same cohort, it was reported that CWS had been involved in 19 out of 26 families when the children were 4 years old (58) primarily by offering assistance such as daycare, visiting homes and parental counseling, but also with out-of-home placements of the children. At the last assessment point in this study, seven of the original 36 children in this study had been moved into foster care.

Despite moderate differences in total parenting stress over time, there were group differences in reported anxiety and depression symptoms (SCL-25) that persisted throughout the study. These were largely driven by a subgroup of mothers with high symptom load (**Figure 4**). Seven mothers in the OMT group scored higher than the cutoff (>1) on depression symptoms and four on the anxiety subscale of the SCL-25. Further, nine of the 36 mothers in the OMT group scored above the clinical cut-off for postnatal depression when their children were 3 months old as measured by the EPDS. At the same time, none of the mothers in the comparison group scored in the clinical range for postnatal depression. A risk factor commonly associated with maternal addiction is psychological maladjustment especially increased symptoms of anxiety and depression (59). These conditions are comorbid and associated with adverse child outcomes (60).

Parental distress was significantly correlated with postnatal depressive symptoms—but only in the comparison group. Both these measures may reflect more general life circumstances and psychosocial burden, not specifically related to the parenting role as such. For example, many of the mothers in the OMT group lived in residential care prior to and after delivery. While the stay at an institution entails a lot of care, verbal reports indicate that these women experience considerable worries about potential relapse and consequently losing custody of their children. It is also likely that the prevalence of neonatal abstinence symptoms, causing worries or difficulties with stress coping. Interestingly, in a previous paper on the same women it was found that while depressive symptoms were significantly reduced from the last month of pregnancy to 6 months later, the trend reversed from 6 months after birth to 2 years later (38).

Reports of child behavior problems were significantly higher in the OMT group at all three points of assessment. In both groups, the highest level of behavior problems was reported at 4.5 years. However, while behavior problems decreased between 4.5 and 8 years in the comparison group, they remained higher and relatively stable in the OMT group in the same period. This result may be a sign of *de facto* more behavior problems among opioid-exposed children compared to non-exposed peers. Alternatively, mothers in OMT who struggle more with the parental role (high PD scores) may also perceive children as "difficult". According to a transactional model of development, there are dynamic, reciprocal processes of continuous interaction between a child and the caregiving environment (61). It was previously found that parents report somewhat more behavior problems than teachers when the children were 8 years old, but the overall interrater agreement was high (41).

There was a strong positive correlation between parenting stress and child behavior problems among mothers in OMT and a somewhat weaker association in the comparison group. These data align well with previous studies (62, 63) showing that parenting stress was positively associated with behavior

problems from infancy to childhood (64). Future studies with larger sample sizes are needed to study the causal relationships between child behavior problems and parenting stress over time and include relevant mediating and moderating factors into the models. Variability in behavior problem scores was notably higher in both groups at 8 years. Also, previous studies showed increasing variation with increasing age (65, 66).

The findings presented here have implications for clinical practice and future research. First, the continuous heightened rates of psychological distress symptoms that characterize mothers in OMT should be given attention from the addiction treatment field and is also relevant for child mental health services. Importantly, the large spread in scores indicates notable individual differences that need to be addressed in terms of differentiated services and measures tailored to each family's individual needs. The bidirectional nature of parenting stress and child behavior problems necessitates a keen-eyed perspective on this complexity.

The SDQ and CBCL are among the most commonly used screening methods for assessing the presence of potential behavior problems in children. Although these instruments provide descriptions of a child's behavior, clinical use is often pragmatic and context dependent: Whilst a cut-off score on symptom-loaded questionnaires may differentiate between children needing intervention and those who do not, the clinical decisions largely depend on a collection of additional information. Notably, scores above or below the clinical thresholds do not always correspond to the parent's own perception of the significance of the child's behavior problems.

One key finding here is that although overall parenting stress was higher in the OMT group, the differences were largely explained by higher parental distress ratings from toddlerhood onwards. It is suggested here that parental distress in this vulnerable group of mothers-child dyads may be a key factor for clinicians when planning counseling, guidance and supportive measures.

4.1. Strengths and limitations

The longitudinal design of the study is a key strength of the study. A selection of outcomes related to demographics, life circumstances, psychosocial development, health and well-being were collected over almost a decade. As such, the OMT group who provided data for the present study is unique in a national and international context Compared to many other studies of outcomes related to OMT, this group led a relatively stable lifestyle with fewer psychosocial vulnerability factors. Also, most of the women in this study maintained custody of their children. More than two-thirds of the women recruited nationally completed the whole study and retention rate was highest in the OMT group. Mothers in current OMT knew that their responses would not be shared with treatment providers or CWS. The result was an excellent working alliance with the participants as reflected in the high retention rate. Further, the OMT group were subjected to very tight follow-up during the first years of the study period and had minimal on-top use of illicit drugs (38, 56).

Several limitations should be acknowledged. Firstly, the small sample size from a single country limits the external validity of the study and the generalizability of the results. However, all women who gave birth while in OMT program in Norway during the inclusion interval were invited to participate, and 76% did. Our study has limited statistical power with 24–36 datapoints per assessment. However, the correlations between within-subject measurements across time was high (ICC) and statistical models that can accommodate all the available data were used. However, the modest number of participants also limited the choices of statistical approach. More advanced methods (such as structural equation models) would allow assessment of the directional effects of the main outcomes measured at multiple timepoints but require larger study samples. Future studies are needed to assess potential causal relationships between parenting stress, child behavioral problems and mental health.

Because there was some loss of data over time, the results from the latest timepoints should be interpreted with some caution as missing data may not be unrelated to the main outcomes. To assess this, a sensitivity analysis was conducted to check whether the parents that were excluded or discontinued the study had worse mental health at the first assessment (in pregnancy) compared to those that completed the whole study. This analysis showed no difference in mental health at study entry between those who completed the study and those who discontinued. Further, the PSI data analyzed here come from two different versions, with overlapping items. While using the same version of the PSI would have been ideal, the Cronbach alpha (α) showed satisfactory consistency.

Here parental stress, mental health and child behavior problems were based solely on self-reports from the same individuals (mothers). Using several data sources can diminish the effects of reporting bias. However, in a recent paper findings showed high agreement between parents and teachers on reported SDQ at child age 8 years in this cohort (41).

A key limitation to consider is that the "normative" comparison group was only matched on age and time of pregnancy. There were considerable differences in sociodemographic factors and life circumstances in the two groups. For instance, nearly all mothers in the OMT group and none in the comparison group were smokers. This is in line with previous research showing that 97% of pregnant women in opioid maintenance treatment used tobacco (67). Studies have suggested that prenatal exposure to tobacco is associated with attentional deficits, behavioral problems, as well as impaired memory function (68). Children born to opioid-maintained women may therefore be potentially at

double risk for negative developmental outcomes from both prenatal opioid and nicotine exposure. Altogether, this could mean that the group differences found here may be inflated and could be smaller if the comparison group had been matched on smoking, sociodemographic variables, and other risk factors. It is noteworthy that despite the high rate of smoking among women in the maintenance treatment, group differences remained small. This may indicate that smoking has less effect on child behavior over time when other maternal lifestyle factor are under control.

The families in this study have been followed by the same two researchers over nearly a decade. This has undoubtedly led to high retention in the study but may also have had some influence on the outcomes of this study. At each timepoint, most participants consented to be contacted again, and expected invitation to follow-up assessments. This may by itself have conferred support and constituted a stabilizing factor in life of individuals who have experienced a lot of turbulence with treatment providers and authorities. Also, the study's explicit aim to study developmental trajectories in children could prompt caregiving competency in parents who have many concerns about their children and the potential harm caused by prenatal opioid exposure.

These data may also be relevant in light of the stark increase in prescription opioid misuse in many countries. The relatively stable group tested here with a history of heroin addiction and long-term OMT may share characteristics with patients who develop opioid addiction following pain treatment, and the results may therefore better generalize to these patients than individuals with current illicit drug use. The OMT group tested here present with higher problem load and stress than the community sample, yet most individuals have scores that fall within the non-clinical range. It is also possible that the mothers in this OMT group is exposed to fewer and different life stressors than most women currently using drugs illicitly. Accordingly, high stress and problem behavior is not a necessary, direct consequence of prenatal exposure to opioids.

4.2. Conclusion

Increasing use and misuse of opioids can have ripple effects on families. In pregnancy, opioid addiction is recognized as a major risk factor, and there is concern for the growing number of children exposed to opioids prenatally and potential adverse developmental outcomes. While findings showed somewhat higher parental distress and child behavior problems in the OMT group assessed here, scores are largely in the sub-clinical range across a time period of 8 years. Compared to other study samples, mothers in this group had little problems with illicit drug use and provided a stable caregiving environment for their children over time. Consequently, it is suggested that prenatal opioid exposure by itself does not cause developmental problems. This notwithstanding, a small number of the dyads studied here scored in the clinical range across several measures which underscore the need to identify high-risk mother-child dyads in order to render specialized services and tailored follow-up measures.

Data availability statement

The data analyzed in this study is not publicly accessible due to privacy constraints. The R code for the analyses presented here is available from the authors on request. Requests to access these datasets should be directed to marie.eikemo@psykologi.uio.no.

Ethics statement

The study was approved by the Norwegian Regional Ethics Committee (2013/1606/REK Sør-Øst B) and conducted in accordance with the Declaration of Helsinki (1964). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

MS designed and initiated the study, MS acquired funding for the study, MS and CK collected the data; ME analyzed the data and made the figures, MS and ME drafted the manuscript, MS, ME and CK critically revised the manuscript. All authors contributed to the article and approved the submitted version.

Acknowledgments

The authors express our gratitude to the caregivers and children who faithfully participated in this research for over a decade.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the

editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.1087956/full#supplementary-material.

References

1. Crowley DM, Connell CM, Jones D, Donovan MW. Considering the child welfare system burden from opioid misuse: research priorities for estimating public costs. *Am J Manag Care*. (2019) 25(13 Suppl):S256. PMID: 31361428; PMCID: PMC7895335

2. Guo C, Moses-Kolko E, Phillips M, Swain JE, Hipwell AE. Severity of anxiety moderates the association between neural circuits and maternal behaviors in the postpartum period. *Cogn Affect Behav Neurosci*. (2018) 18(3):426–36. doi: 10.3758/s13415-017-0516-x

3. Whittaker A. *Guidelines for the identification and management of substance use and substance use disorders in pregnancy*. Geneva, Switzerland: WHO Press (2014). 224 p.

4. Mozurkewich EL, Rayburn WF. Buprenorphine and methadone for opioid addiction during pregnancy. *Obstet Gynecol Clin North Am*. (2014) 41 (2):241–53. doi: 10.1016/j.ogc.2014.02.005

5. Jansson LM, Di Pietro JA, Elko A, Williams EL, Milio L, Velez M. Pregnancies exposed to methadone, methadone and other illicit substances, and poly-drugs without methadone: a comparison of fetal neurobehaviors and infant outcomes. *Drug Alcohol Depend*. (2012) 122(3):213–9. doi: 10.1016/j.drugalcdep.2011.10.003

6. Jones HE, O'Grady KE, Malfi D, Tuten M. Methadone maintenance vs. methadone taper during pregnancy: maternal and neonatal outcomes. *Am J Addict*. (2008) 17(5):372–86. doi: 10.1080/10550490802266276

7. Muller AE, Skurtveit S, Clausen T. Building abstinent networks is an important resource in improving quality of life. *Drug Alcohol Depend*. (2017) 180:431–8. doi: 10.1016/j.drugalcdep.2017.09.006

8. Conradt E, Crowell SE, Lester BM. Early life stress and environmental influences on the neurodevelopment of children with prenatal opioid exposure. *Neurobiol Stress*. (2018) 9:48–54. doi: 10.1016/j.ynstr.2018.08.005

9. Monnelly VJ, Hamilton R, Chappell FM, Mactier H, Boardman JP. Childhood neurodevelopment after prescription of maintenance methadone for opioid dependency in pregnancy: a systematic review and meta-analysis. *Dev Med Child Neurol*. (2019) 61(7):750–60. doi: 10.1111/dmcn.14117

10. Kaltenbach K, O'Grady KE, Heil SH, Salisbury AL, Coyle MG, Fischer G, et al. Prenatal exposure to methadone or buprenorphine: early childhood developmental outcomes. *Drug Alcohol Depend*. (2018) 185:40–9. doi: 10.1016/j.drugalcdep.2017.11.030

11. Arter SJ, Tyler B, McAllister J, Kiel E, Güler A, Cameron Hay M. Longitudinal outcomes of children exposed to opioids in-utero: a systematic review. *J Nurs Scholarsh*. (2021) 53(1):55–64. doi: 10.1111/jnu.12609

12. Baldacchino A, Arbuckle K, Petrie D, McCowan C. Neurobehavioral consequences of chronic intrauterine opioid exposure in infants and preschool children: a systematic review and meta-analysis. *BMC Psychiatry*. (2014) 14 (1):1–12. doi: 10.1186/1471-244X-14-104

13. Azuine R, Ji Y, Chang H-Y, Kim Y, Ji H, DiBari J, et al. Prenatal risk factors and perinatal and postnatal outcomes associated with maternal opioid exposure in an urban, low-income, multiethnic US population. *JAMA Network Open*. (2019) 2: e196405. doi: 10.1001/jamanetworkopen.2019.6405

14. Bakstad B, Welle-Strand GK. Nasjonal retningslinje for gravide i legemiddelassistert rehabilitering (LAR) og oppfølging av familiene frem til barnet når skolealder [Only in Norwegian: National guidelines for pregnant women in opioid maintenance treatment (OMT) and follow-up of their families until the children reach school age]. Oslo, Norway: Norwegian Directorate of Health (2011).

15. Lund IO, Skurtveit S, Sarfi M, Bakstad B, Welle-Strand G, Ravndal E. Substance use during and after pregnancy among a national cohort of pregnant women in opioid maintenance treatment and their partners. *J Subst Use*. (2012) 17(3):277–86. doi: 10.3109/14659891.2011.580415

16. Welle-Strand GK, Skurtveit S, Jones HE, Waal H, Bakstad B, Bjarkø L, et al. Neonatal outcomes following in utero exposure to methadone or buprenorphine: a national cohort study of opioid-agonist treatment of pregnant women in Norway from 1996 to 2009. *Drug Alcohol Depend*. (2013) 127(1):200–6. doi: 10.1016/j.drugalcdep.2012.07.001

17. Sarfi M, Eikemo M, Welle-Strand GK, Muller AE, Lehmann S. Mental health and use of health care services in opioid-exposed school-aged children compared to foster children. *Eur Child Adolesc Psych*. (2022) 31(3):495–509. doi: 10.1007/s00787-021-01728-3

18. Peisch V, Sullivan A D, Breslend NL, Benoit R, Sigmon SC, Forehand GL, et al. Parental opioid abuse: a review of child outcomes, parenting, and parenting interventions. *J Child Fam Stud*. (2018) 27(7):2082–99. doi: 10.1007/s10826-018-1061-0

19. Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry*. (2016) 3(8):760–73. doi: 10.1016/S2215-0366(16)00104-8

20. Rutherford HJV, Kim S, Yip SW, Potenza MN, Mayes LC, Strathearn L. Parenting and addictions: current insights from human neuroscience. *Curr Addict Rep*. (2021) 8(3):380–8. doi: 10.1007/s40429-021-00384-6

21. Swain JE, Ho SS. Early postpartum resting-state functional connectivity for mothers receiving buprenorphine treatment for opioid use disorder: a pilot study. *J Neuroendocrinol*. (2019) 31(9):e12770. doi: 10.1111/jne.12770

22. Crnic KA, Greenberg MT. Minor parenting stresses with young children. *Child Dev*. (1990) 61(5):1628–37. doi: 10.2307/1130770

23. Hakvoort EM, Bos HMW, Van Balen F, Hermanns JMA. Spillover between mothers' postdivorce relationships: the mediating role of parenting stress. *Pers Relatsh*. (2012) 19(2):247–54. doi: 10.1111/j.1475-6811.2011.01351.x

24. Killeen TCS, Brady KT. Parental stress and child behavioral outcomes following substance abuse residential treatment: follow-up at 6 and 12 months. *J Subst Abuse Treat*. (2000) 19(1):23–9. doi: 10.1016/S0740-5472(99)00078-1

25. Rutherford HJV, Mayes LC. Parenting stress: a novel mechanism of addiction vulnerability. *Neurobiol Stress*. (2019) 11:100172. doi: 10.1016/j.ynstr.2019.100172

26. Mackler JS, Kelleher RT, Shanahan L, Calkins SD, Keane SP, O'Brien M. Parenting stress, parental reactions, and externalizing behavior from ages 4 to 10. *J Marriage Fam*. (2015) 77(2):388–406. doi: 10.1111/jomf.12163

27. Kelley SJ. Stress and coping behaviors of substance-abusing mothers. *J Spec Pediatr Nurs*. (1998) 3(3):103. doi: 10.1111/j.1744-6155.1998.tb00215.x

28. Kelley SJ. Parenting stress and child maltreatment in drug-exposed children. *Child Abuse Negl*. (1992) 16(3):317–28. doi: 10.1016/0145-2134(92)90042-P

29. Hatzis D, Dawe S, Harnett P, Barlow J. Quality of caregiving in mothers with illicit substance use: a systematic review and meta-analysis. *Subst Abus*. (2017) 11:1178221817694038. doi: 10.1177/1178221817694038

30. Velez M, Jansson L. The opioid dependent mother and newborn dyad: nonpharmacologic care. *J Addict Med*. (2008) 2(3):113–20. doi: 10.1097/ADM.0b013e31817e6105

31. Abidin RR. The determinants of parenting behavior. *J Clin Child Psychol*. (1992) 21(4):407–12. doi: 10.1207/s15374424jccp2104_12

32. Holly LE, Fenley AR, Kritikos TK, Merson RA, Abidin RR, Langer DA. Evidence-base update for parenting stress measures in clinical samples. *J Clin Child Adolesc Psychol*. (2019) 48(5):685–705. doi: 10.1080/15374416.2019.1639515

33. Wouldes TA, Woodward LJ. Maternal methadone dose during pregnancy and infant clinical outcome. *Neurotoxicol Teratol*. (2010) 32(3):406–13. doi: 10.1016/j.ntt.2010.01.007

34. Odsbu I, Mahic M, Skurtveit SO, Lund I-O, Handal M. An 11-year nationwide registry-linkage study of opioid maintenance treatment in pregnancy in Norway. *Norsk Epidemiologi*. (2021) 29(1-2):63–70. doi: 10.5324/nje.v29i1-2.4047

35. Bakstad B, Sarfi MA, Welle-Strand GK, Ravndal E. Opioid maintenance treatment during pregnancy: occurrence and severity of neonatal abstinence syndrome. *Eur Addict Res*. (2009) 15(3):128–34. doi: 10.1159/000210042

36. Sarfi M, Smith L, Waal H, Sundet JM. Risks and realities: dyadic interaction between 6-month-old infants and their mothers in opioid maintenance treatment. *Infant Behav Dev*. (2011) 34(4):578–89. doi: 10.1016/j.infbeh.2011.06.006

37. Sarfi M. *Vulnerable but adaptable. A longitudinal study of a national cohort of children born to women in opiod maintenance (OMT) treatment. [dissertation]*. Oslo: University of Oslo (2012).

38. Lund IO, Skurtveit S, Sarfi AM, Bakstad B, Welle-Strand G, Ravndal E. A 2-year prospective study of psychological distress in pregnant women in opioid maintenance treatment and their partners. *J Subst Use*. (2013) 18(2):148–60. doi: 10.3109/14659891.2011.642928

39. Konijnenberg C, Lund IO, Melinder A. Behavioural outcomes of four-year-old children prenatally exposed to methadone or buprenorphine: a test of three risk models. *Early Child Dev Care*. (2015) 185(10):1641–57. doi: 10.1080/03004430.2015.1016506

40. Welle-Strand GK, Skurtveit S, Abel KF, Chalabianloo F, Sarfi M. Living a normal life? Follow-up study of women who had been in opioid maintenance treatment during pregnancy. *J Subst Abuse Treat*. (2020) 113:108004. doi: 10.1016/j.jsat.2020.108004

41. Abidin RR. *Parenting stress index-short form*. Charlottesville, VA: Pediatric Psychology Press (1990).

42. Abidin RR. *Parenting stress index: Manual*. 3rd ed. Odessa, FL: Psychological Assessment Resources, Inc. (1995).

43. Abidin RR. *Parenting stress index-fourth edition (PSI-4)*. Lutz, FL: Psychological Assessment Resources (2012).

44. Haskett ME, Ahern LS, Ward CS, Allaire JC. Factor structure and validity of the parenting stress index-short form. *J Clin Child Adolesc Psychol*. (2006) 35(2):302–12. doi: 10.1207/s15374424jccp3502_14

45. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: development of the 10-item Edinburgh postnatal depression scale. *Br J Psychiatry*. (1987) 150(6):782–6. doi: 10.1192/bjp.150.6.782

46. Levis B, Negeri Z, Sun Y, Benedetti A, Thombs BD. Accuracy of the Edinburgh postnatal depression scale (EPDS) for screening to detect major depression among pregnant and postpartum women: systematic review and meta-analysis of individual participant data. *Br Med J*. (2020) 371:m4022. doi: 10.1136/bmj.m4022

47. Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The hopkins symptom checklist (HSCL): a self-report symptom inventory. *Behav Sci*. (1974) 19(1):1–15. doi: 10.1002/bs.3830190102

48. Lund IO. *Pregnant women in opioid maintenance treatment (OMT): maternal and neonatal outcomes*. Oslo: University of Oslo (2013).

49. Achenbach TM. *Manual for the child behavior checklist/2-3*. Burlington, VT: University of Vermont, Department of Psychiatry (1992).

50. Lavigne JV, Meyers KM, Feldman M. Systematic review: classification accuracy of behavioral screening measures for use in integrated primary care settings. *J Pediatr Psychol*. (2016) 41(10):1091–109. doi: 10.1093/jpepsy/jsw049

51. Sheldrick RC, Benneyan JC, Kiss IG, Briggs-Gowan MJ, Copeland W, Carter AS. Thresholds and accuracy in screening tools for early detection of psychopathology. *J Child Psychol Psychiatry*. (2015) 56(9):936–48. doi: 10.1111/jcpp.12442

52. Williford AP, Calkins SD, Keane SP. Predicting change in parenting stress across early childhood: child and maternal factors. *J Abnorm Child Psychol*. (2007) 35(2):251–63. doi: 10.1007/s10802-006-9082-3

53. Calkins SD, Gill KL, Johnson MC, Smith CL. Emotional reactivity and emotional regulation strategies as predictors of social behavior with peers during toddlerhood. *Soc Dev*. (1999) 8(3):310–34. doi: 10.1111/1467-9507.00098

54. Calkins SD, Dedmon SE. Physiological and behavioral regulation in two-year-old children with aggressive/destructive behavior problems. *J Abnorm Child Psychol*. (2000) 28(2):103–18. doi: 10.1023/A:1005112912906

55. Skinner ML, Haggerty KP, Fleming CB, Catalano RF, Gainey RR. Opiate-addicted parents in methadone treatment: long-term recovery, health, and family relationships. *J Addict Dis*. (2010) 30(1):17–26. doi: 10.1080/10550887.2010.531670

56. Sarfi M, Sundet JM, Waal H. Maternal stress and behavioral adaptation in methadone- or buprenorphine-exposed toddlers. *Infant Behav Dev*. (2013) 36(4):707–16. doi: 10.1016/j.infbeh.2013.08.006

57. Suchman N, Luthar SS. The mediating role of parenting stress in methadone-maintained mothers' parenting. *Parenting*. (2001) 1(4):285–315. doi: 10.1207/S15327922PAR0104_2

58. Lund IO, Brendryen H, Ravndal E. A longitudinal study on substance use and related problems in women in opioid maintenance treatment from pregnancy to four years after giving birth. *J. Subst. Abuse Treat*. (2014) 8:35–40. doi: 10.4137/SART.S15055

59. Seay KD, Kohl PL. The comorbid and individual impacts of maternal depression and substance dependence on parenting and child behavior problems. *J Fam Violence*. (2015) 30(7):899–910. doi: 10.1007/s10896-015-9721-y

60. Barker ED, Jaffee SR, Uher R, Maughan B. The contribution of prenatal and postnatal maternal anxiety and depression to child maladjustment. *Depress Anxiety*. (2011) 28(8):696–702. doi: 10.1002/da.20856

61. Sameroff AJ. The transactional model. In: AJ Sameroff, editors. *The transactional model of development how children and contexts shape each other*. 1st ed. Washington, DC: American Psychological Association (2009). p. 3–21.

62. Benzies KM, Harrison MJ, Magill-Evans J. Parenting stress, marital quality, and child behavior problems at age 7 years. *Public Health Nurs*. (2004) 21(2):111–21. doi: 10.1111/j.0737-1209.2004.021204.x

63. Stone LL, Mares SHW, Otten R, Engels RCME, Janssens JMAM. The co-development of parenting stress and childhood internalizing and externalizing problems. *J Psychopathol Behav Assess*. (2016) 38(1):76–86. doi: 10.1007/s10862-015-9500-3

64. Bayer JK, Hiscock H, Ukoumunne OC, Price A, Wake M. Early childhood aetiology of mental health problems: a longitudinal population-based study. *J Child Psychol Psychiatry*. (2008) 49(11):1166–74. doi: 10.1111/j.1469-7610.2008.01943.x

65. Neece CL, Green SA, Baker BL. Parenting stress and child behavior problems: a transactional relationship across time. *Am J Intellect Dev Disabil*. (2012) 117(1):48–66. doi: 10.1352/1944-7558-117.1.48

66. Newton EK, Laible D, Carlo G, Steele JS, McGinley M. Do sensitive parents foster kind children, or vice versa? Bidirectional influences between children's prosocial behavior and parental sensitivity. *Dev Psychol*. (2014) 50(6):1808–16. doi: 10.1037/a0036495

67. Jones HE, Heil SH, Tuten M, Chisolm MS, Foster JM, O'Grady KE, et al. Cigarette smoking in opioid-dependent pregnant women: neonatal and maternal outcomes. *Drug Alcohol Depend*. (2013) 131(3):271–7. doi: 10.1016/j.drugalcdep.2012.11.019

68. Zhou S, Rosenthal DG, Sherman S, Zelikoff J, Gordon T, Weitzman M. Physical, behavioral, and cognitive effects of prenatal tobacco and postnatal secondhand smoke exposure. *Curr Probl Pediatr Adolesc Health Care*. (2014) 44(8):219–41. doi: 10.1016/j.cppeds.2014.03.007

frontiers | Frontiers in Pediatrics

TYPE Mini Review
PUBLISHED 08 February 2023
DOI 10.3389/fped.2022.1071564

Check for updates

OPEN ACCESS

EDITED BY
Loretta Finnegan,
Finnegan Consulting, LLC, United States

REVIEWED BY
Pilar Saenz Gonzalez,
La Fe Hospital, Spain
Leslie Edinboro,
Edinboro Consulting, LLC, United States

*CORRESPONDENCE
Joseph Jones
✉ Joe.jones@usdtl.com

SPECIALTY SECTION
This article was submitted to Neonatology, a section of the journal Frontiers in Pediatrics

RECEIVED 16 October 2022
ACCEPTED 23 December 2022
PUBLISHED 08 February 2023

CITATION
Jones J (2023) Toxicology as a diagnostic tool to identify the misuse of drugs in the perinatal period.
Front. Pediatr. 10:1071564.
doi: 10.3389/fped.2022.1071564

COPYRIGHT
© 2023 Jones. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Toxicology as a diagnostic tool to identify the misuse of drugs in the perinatal period

Joseph Jones*

United States Drug Testing Laboratories, Des Plaines, IL, United States

The use, misuse, and abuse of substances are a continued public health concern in this country and around the world. Perinatal exposure to substances of abuse is associated with several long-term negative consequences for the neonate. Limited resources exist to assist perinatal health professionals on this very complex subject. The purpose of this document is to provide additional information about selecting monitoring protocols, the specifics of appropriate testing methodologies, and the interpretation of toxicological findings. Understanding these concepts better allows perinatal healthcare professionals to be a voice for the voiceless in order to protect and enrich lives during this unprecedented opioid epidemic.

KEYWORDS

newborn toxicology, maternal substance use, substance abuse, prenatal drug exposure, umbilical cord testing, meconium testing, forensic testing

1. Introduction

The use, misuse, and abuse of substances, including both prescription opioids and non-prescription opioids, are a continued public health concern (1). Prenatal exposure to these substances may lead to a number of negative health consequences, including neonatal opioid withdrawal syndrome (NOWS), a subcategory of neonatal abstinence syndrome (NAS); premature birth; stillbirth; and an array of other long term negative health consequences (2, 3). Additionally, children of parents suffering from substance use disorders are at a three-fold higher risk of experiencing child maltreatment (4, 5).

A long-standing objective of the HealthyPeople initiative has been to promote an increase of maternal abstinence from illicit substances. HealthyPeople 2030 (6) has targeted an increase from the baseline of 93% of pregnant women reporting abstinence in the National Survey on Drug Use and Health (NSDUH) to 95.3% reporting abstinence by 2030. The most recent findings published in the aggregated 2018–2019 NSDUH was 94.0% [95% CI: 92.9%, 95.6%] (CBHSQ, 2020). This improvement was not statistically significant but it is in the desired direction.

The 2020 NSDUH reported 8.3% (SE 2.05) of pregnant mothers claimed to have used an illicit substance in the past month, which was up from 5.8% (SE 1.04) in 2019 (7). A good portion of these mothers are at or near the poverty level and without private insurance. This highlights the fact that this population is very vulnerable with regard to inadequate access to prenatal care and treatment for substance use disorders and presents an opportunity for public health intervention efforts.

Fulfilling the objectives of HealthyPeople 2030 suggests that perinatal healthcare professionals must understand the scope and extent of prenatal substance exposure (8). Specifically needed are processes to provide effective prevention efforts, identify exposure in both an epidemiological and specific case perspective, recognize medical issues associated with perinatal exposure to substances, provide protection for the infant, and refer the exposed infants for appropriate follow-up when needed (8). To accomplish these objectives, the

perinatology professional must obtain credible information. Questionnaires and the analysis of various biological specimen types are currently the two approaches for obtaining perinatal substance exposure information. Using questionnaires to obtain credible perinatal substance exposure information is very difficult due to the potential promotion of stigma and guilt which undermines a patient/healthcare professional trust relationship and the potential legal ramifications. Testing biological specimens have less than perfect sensitivity due primarily to detection window limitations.

Further complicating testing biological specimens is the complexity of the maternal-fetal dyad. The placenta, a temporary organ, resides between the mother and baby serving as an interface. Molecules, including substances of abuse and their metabolites, are transported through the placental barrier through simple diffusion (such as oxygen and carbon dioxide) and more complex transport mechanisms (9). The placenta is also a structure that is capable of metabolizing certain compounds that in some cases varies with gestational age (9). The structure of the human placenta is sufficiently different from other mammals which limits generalizability of the study of transport functions in animal models (9). Random controlled trials of prenatal exposure to substances of abuse are lacking due to the ethical considerations of providing pregnant persons a known toxic compound for research purposes.

Testing of biological specimens to monitor perinatal substance exposure is a very specialized field. Limited resources are available to perinatal health professionals to design perinatal substance exposure-monitoring strategies and assist with interpretation. The author consults routinely in cases where Child Protection Service action was taken based on specimens analyzed without chain of custody, presumptive positive results that have not been confirmed by a sufficiently specific method, and lacking review of the medical record to determine if the positive was due to hospital administered medicine. The aim of this manuscript is three-fold. We will review both commonly available options for perinatal substance monitoring and important concepts to consider when designing a monitoring policy, as well as discuss some frequently asked questions regarding the interpretation of newborn toxicology results.

2. Detection and monitoring of perinatal substance exposure

2.1. Questionnaire

The American College of Obstetricians and Gynecologists (ACOG) recommends screening all pregnant women for substance use with a validated questionnaire for the purpose of intervention and referral (10). There are several validated questionnaires available for use, such as the Drug Abuse Screening Test (DAST-10), the 4P's, Substance Use Risk Profile-Pregnancy, the CRAFFT screening tool, NIDA Quick Screen, and the Wayne Indirect Drug Use Screener (10). Strengths associated with the use of these tools are that they are inexpensive, quick to administer, and can monitor for substance use throughout the entire perinatal period (8, 10). However, limitations include recall bias and under-reporting due to stigma and fear of legal repercussions (8–12). Many unvalidated "local questionnaires" are in use, which may unwittingly negatively impact sensitivity and specificity (13).

2.2. Biological specimen types

2.2.1. Maternal urine

Maternal urine testing is the primary biological specimen type used for monitoring maternal substance use during the perinatal period, including at intake upon arrival at the birthing center (14, 15). Perinatal professionals have used urine testing for many decades. Urine testing has proven to be a reliable specimen type, many laboratories are proficient with the testing procedures, and costs are low compared to other specimen types. Additionally, many clinicians have sufficient experience with the interpretation of the results.

Many laboratories test specimens in a clinical environment as opposed to a forensic environment. Presumptive positive specimens are routinely unconfirmed using a definitive technique, processed without documented chain of custody, and destroyed in a few days regardless of the outcome of the test (which eliminates the possibility of a retest when there is a question about the accuracy of a result). Under these circumstances, these tests are satisfactory to utilize for research or as a screening tool to initiate brief intervention, further testing, or additional monitoring. These specimen results, if not performed using forensic protocols (maintaining a documented chain of custody and automatic confirmation of presumptive positive specimens), should not initiate negative action towards the mother and/or child.

2.2.2. Maternal blood

In this environment, maternal blood is typically not a specimen type of choice for drug testing. The collection protocol is invasive and presents an unnecessary biohazard risk to transportation and laboratory staff; the detection windows are very short (shorter than urine); and the analysis is very expensive. There are new tests that show promise in this environment, such as phosphatidylethanol (PEth) in whole blood or dried blood spots. PEth is a direct ethanol biomarker that detects prenatal ethanol exposure and has a detection window measured in weeks rather than days (16).

2.2.3. Maternal hair

Maternal hair is a specimen type that offers a very long detection window. Analytes incorporate into hair by three main routes. First is environmental exposure. In an environment where a drug is used, smoked, handled, manufactured, or prepared, the environment becomes contaminated, and the drug over time will transfer to the hair. Next is consumption. When a user consumes a drug, the sweat and sebum contain drug and drug metabolites, and as these fluids bathe the hair shaft these analytes deposit on the hair. Lastly, also following consumption, the blood, which contains drug and drug metabolites, deposits the analytes into the root. Once in or on the hair, the analytes bind to proteins and pigments in the hair and remain for an extended period.

Hair testing has several advantages. The collection procedure is simple and noninvasive. The collection may directly observe the donor without gender issues (15, 17). The collector may execute the collection outside of clinical settings. The detection window of drug in hair is months instead of days depending on the source of hair and the compound of interest.

There are several limitations of using hair as a specimen type for drug testing. Cosmetic treatment may interfere with analysis depending on the substance or treatment. These processes contain varying amounts of reducing and/or oxidizing agents, which may alter the structure of the compound of interest (18, 19). The analysis requires a complex specimen preparation, which makes the testing expensive (20). Lastly, there is a potential for observing a positive maternal hair test result due to external contamination or environmental exposure. While providing important information concerning the maternal environment, it does not provide specific evidence of prenatal exposure (15).

2.2.4. Newborn urine

For many years, newborn urine was the primary strategy to objectively identify prenatal drug exposure. The advantages of newborn urine testing are similar to the advantages listed for maternal urine testing, but there are several limitations to testing newborn urine.

Several limitations exist regarding newborn urine to monitor prenatal substance exposure (15). The ideal newborn urine specimen is the neonate's first urine void, and it is difficult to know if the specimen captured was indeed the first void. Missing the first urine void is commonplace. The newborn produces a limited volume of urine with the first void. This results in an excess of specimen rejections due to insufficient quantity for testing. Dilute newborn urine is typical, which shortens an already short detection window even further. Collection protocols are clumsy, and the adhesives are irritating to delicate newborn skin. These limitations led to the development of other testing strategies, such as newborn hair, meconium, and umbilical cord tissue segments as alternatives for monitoring prenatal substance exposure.

2.2.5. Newborn hair

Newborn hair testing offers many of the benefits mentioned in the maternal hair discussion above. Hair forms in the third trimester, and substances and their metabolites may become entrapped in the hair, thus offering a long window of detection (15). References to using newborn hair for prenatal drug exposure appears in the literature (21–24), but its use is not routine. While newborn hair provides a long window of detection and is a simple non-invasive collection process, newborn hair is routinely not present or in sufficient quantity to complete all testing. Approximately one-fourth of all children born do not have sufficient hair for testing. This obstacle limits the use of hair as a primary strategy for most routine prenatal substance monitoring programs (20).

2.2.6. Newborn meconium

The first alternative specimen to routinely replace newborn urine as the specimen of choice for newborn toxicology was meconium (14, 25–28). Meconium is the first fecal matter excreted by the newborn and is a complex and highly variable material composed primarily of mucopolysaccharides, water, bile, salts, bile acids, epithelial cells, and other lipids (29). Meconium begins to form near mid-term of the pregnancy with the majority forming after week 38. As the laboratory equipment and laboratory processes evolved to meet the demand and challenges of high throughput workplace drug testing resulting from the Federal Drug Free Workplace Act in the late 1980s, these processes and equipment were available to develop feasible and practical newborn toxicology testing strategies.

The primary advantage of meconium is the long detection window which includes the entire last trimester. Advantages include a non-invasive collection procedure. Additionally, enough specimen is available for testing in most cases and there are several laboratories available to perform the testing. These advantages have, over time, resulted in meconium becoming the gold standard of newborn toxicology (11).

As with any testing protocol, there are several limitations to using meconium. Limitations include the lack of detection of prenatal exposure in early pregnancy. The detection window is bound by the time of the formation of meconium and the fact that most of the meconium production occurs in the last few weeks, thus diluting earlier use (11). The distribution of analytes in meconium is heterogeneous. Therefore, the ideal collection procedure includes all passages of meconium. The transition from meconium to milk stool can be difficult to discern in some cases. The collection procedure is a multi-step process, which requires multiple collections by multiple collectors over multiple shifts and sometimes over multiple days. Meconium collection can be a very timely and expensive process. Lastly, all laboratories do not have the capability to adequately execute testing on this very difficult specimen type. While there are laboratories available for meconium testing, the number of competent laboratories remains limited.

2.2.7. Newborn umbilical cord

Concheiro and Huestis (11) noted that due to the number of limitations to using meconium in an organization's newborn toxicology program, umbilical cord tissue segment testing was developed as an alternative specimen type to meconium. Testing newborn umbilical cord for substances of abuse has been gaining traction in the newborn toxicology environment over the past 15 years. The development of umbilical cord testing was a direct response to an unacceptable number of meconium specimens rejected or canceled due to low sample volume (30, 31).

Umbilical cord as a specimen for newborn toxicology has several advantages (30–34). There is an abundance of specimen available for each birth, making umbilical cord collection truly universal. **Table 1** provides a summary of examples in the literature demonstrating the extent of sample volume compliance when using meconium. The specimen collection and transfer to the laboratory occurs immediately following birth, which improves turnaround times. Analytes appear evenly distributed throughout the entire length of the cord. Analytes in meconium appear heterogeneously distributed, requires collection of the entire passage, and requires mechanical mixing (34, 39). Umbilical cord collection is a simple single-step procedure whereas meconium requires multiple collectors making multiple collections over multiple shifts and/or days.

TABLE 1 Examples in the literature that demonstrate the extent of sample volume compliance using meconium for monitoring substances.

Year	Study	Enrolled	Unavailable	% Unavailable
1999	Arendt et al. (35)	218	61	27.9
2001	Lester et al. (14)	8,527	3,284	27.8
2003	Derauf et al. (36)	546	110	20.1
2005	Eylera et al. (37)	51	5	9.8
2010	Gray et al. (38)	102	14	13.7

A disadvantage of using umbilical cord is that the concentrations of detectable substances and their metabolites are low, which requires more expensive laboratory equipment to achieve cutoffs that provide adequate sensitivity (30, 31, 40). This makes the analysis more expensive than meconium, but when controlling for the expense of multiple collections, missed opportunities, and turnaround time, the overall expense of using umbilical cord is comparable with meconium.

3. Concepts to consider when designing a perinatal substance monitoring policy

3.1. Questionnaire vs. biological specimen

An important question to ask when developing a newborn toxicology policy for your organization is whether to use a questionnaire and/or biological specimen. Several examples exist in the literature that compare the effectiveness of various self-report questionnaires and various validated biological specimen analyses (41–47). Following a review of the existing literature, the authors compared the rates of self-reported prenatal substance exposure and the presence of corresponding biomarkers using a variety of specimen types (13). In each instance in the literature reviewed, self-reported substance exposure was under-reported when compared to biological specimen analysis (13). Behnke et al. (8) noted that no single monitoring method was perfectly sensitive and specific and therefore recommended coupling questionnaire and biological analysis to improve the probability of identifying perinatal substance exposure.

3.2. Which biological specimen to choose

Take care when selecting the biological specimen type to use in a perinatal substance exposure program. Detection of a substance in a maternal specimen provides evidence of maternal exposure but does not necessarily provide conclusive evidence of substance exposure to the neonate (11). The detection of a substance or its metabolite in a specimen originating from the neonate provides conclusive evidence of prenatal exposure to a substance. Additionally, the Supreme Court of the United States (48) opined that using a maternal specimen that could result in legal repercussions requires the consent of the mother. This rationale does not extend to the specimens obtained from the neonate. The Keeping Children and Families Safe Act (Public Law 108-36) imposed a requirement to report the detection of prenatal illicit drug exposure to the State. Under these conditions, best practices necessitate that these tests, when ordered due to reasonable suspicion, should satisfy basic forensic tenants such as the maintenance of chain of custody and confirmation of presumptive positive results. **Table 2** lists advantages and disadvantages for various specimen types used for monitoring prenatal substance exposure.

3.3. Analysis of biological specimens

An effective substance exposure monitoring program requires a sensitive and specific testing strategy. While some research and

TABLE 2 Advantages and disadvantages of various specimen types commonly used for monitoring prenatal substance exposure.

Specimen type	Advantages	Disadvantages
Maternal urine	Test is inexpensive Most understood Analysis is simple and may be performed in house	Short detection window Gender issues at collection Requires maternal consent
Maternal blood		Short detection window Invasive collection Requires maternal consesnt Testing is very expensive Difficult and challenging analysis
Maternal hair	Long detection window Moderate costs Noninvasive collection	Requires maternal consent Cosmetic treatment issues Difficult and challenging analysis
Newborn Urine	Low cost Analysis is simple and may be performed in house	Cumbersome collection Easy to miss first void Very short detection window Insufficient quantity of specimen
Newborn hair	Long detection window Moderate costs	Insufficient quantity of specimen Difficult and challenging analysis
Meconium	Long detection window Moderate costs	Quantity is not sufficient for many babies May passed *in utero* due to fetal stress Requires multiple collections May require days to pass enough specimen for testing Analytes are not distributed evenly Difficult and challenging analysis
Umbilical Cord	Long detection window Moderate costs Plenty of specimen for every baby Specimen is available immediately following birth Collection is a single step procedure Analytes are distributed evenly throughout the length of the cord	Difficult and challenging analysis Requires newer more sensitive laboratory instruments

clinical environments rely on a single immunoassay or single mass spectrometric protocol, which is adequate under research and/or clinical conditions. Newborn toxicology cases routinely transition from a clinical situation to a forensic situation (49). Policy makers who design workflows that rely on results generated without using commonly accepted forensic standard protocols (maintenance of chain of custody and confirmation of presumptive positive specimens) to reduce costs are acting in a scientifically irresponsible manner.

3.4. Screening or initial testing

Several techniques exist to monitor newborn specimens to preliminarily detect prenatal substance exposure. The most common initial tests utilize the sensitivity, speed, and cost effectiveness of a variety of immunoassay techniques, such as enzyme linked immunosorbent assay (ELISA), enzyme multiplied immunoassay test (EMIT®), cloned enzyme donor immunoassay (CEDIA), Diagnostics Reagents Inc immunoassay (DRI®), or homogenous enzyme immunoassay (HEIA™) (50–52). These methods provide a quick and economical way to identify negative specimens with adequate sensitivity, which in turn allows the laboratory to focus its attention on the presumptive positive specimens.

Several methods exist in the literature and commerce that utilize a mass spectrometric initial test protocol. Most common are liquid chromatography tandem mass spectrometry (LCMSMS) and liquid chromatography time of flight mass spectrometry (LCTOFMS) (11, 39, 53). These techniques allow for a higher degree of specificity over immunoassay at the expense of time and/or cost. However, the laboratory should confirm presumptive positive results obtained from these methods using a second protocol before reporting results to the State.

3.5. Confirmation testing

Once the laboratory obtains a presumptive positive test result by an adequate initial test, a confirmation test follows to confirm the presence of the specific analyte identified with the initial test. Currently, mass spectrometric techniques are the gold standard for this purpose due to the technique's high degree of sensitivity and specificity. Confirmation testing should use a second portion of the original specimen, regardless of the method used for initial testing. This is a best practice to rule out frame shift errors.

3.6. Importance of confirmation testing

Gray and Huestis (15) said, "Confirmation of positive screening results is essential." Confirmation testing serves two primary purposes. First, the process of confirming an initial presumptive positive test by analyzing a second aliquot (a portion of a specimen used for analysis) mitigates the possibility of a frame shift error or sample switching in the initial testing process. Following a frame shift error during the initial testing process, the confirmation results will not agree with the initial test, thereby alerting the testing personnel of a potential error. Second, the use of two different analytical methodologies or procedures to arrive at the same result dramatically increases the analytical specificity of the entire process. This concept is even more important when considering that newborn biological tests represent a once in a lifetime opportunity to protect and enrich the life of the neonate. The use of a screen and confirm strategy while maintaining a documented chain of custody ensures the integrity of the identity of the specimen and ensures the accuracy of the result, thereby protecting the maternal-child dyad from erroneous results. These are the cornerstone principles of producing a forensically defensible result.

3.7. External oversight

External oversight of laboratory operations is an important best practice in our field, but all external oversight providers are not the same. There are multiple options of external oversight to choose from (such as CLIA, CAP, COLA), and the laboratory may select the oversight provider that best fits its geographic and/or regulatory needs. However, there are a select few options that provide oversight from the context of producing a forensically defensible result [such as CAP-FDT, NYDOH-Forensic Toxicology, ISO17025; (54)].

Clinical laboratories knowingly or unknowingly operating in a forensic environment without appropriate forensic oversight can expose all stakeholders involved to unexpected levels of risk (55). The Ontario Ministry of the Attorney General (55) reported how a well-respected laboratory staffed and managed by a highly competent team from a research and clinical perspective created a situation that required years of litigation and review of thousands of cases over multiple decades. Relevant external oversight would prevent this unfortunate outcome. It is important that newborn toxicology policymakers understand these differences and choose their testing laboratory accordingly.

4. Interpretation of biological specimen test results

Following the receipt of a biological specimen test result, you require an interpretation. Is the reported outcome the result expected? Is there a reasonable explanation for the result? Is a reasonable explanation lacking? These, among others, are very important questions that perinatal professionals address routinely.

4.1. Does a negative result infer abstinence?

A negative result is not conclusive evidence of abstinence. There are many reasons why a particular outcome is negative, especially considering the complex biology of a maternal-fetal system. The most common scenario in the experience of this authoris the test ordered does not include the specific substance in question. Standardization of newborn toxicology testing is

currently lacking and each laboratory performing newborn toxicology testing have unique testing panels and cutoffs. The ordering and/or result interpretation professional should be knowledgeable of the substances included in the test ordered. Additionally, a negative result may be due to the use of the substance beyond the detection window of the specimen type or the donor consumed an insufficient amount of the substance to generate a positive result.

4.2. What are the detection windows?

The amount of time represented for a biological specimen result is the detection window or window of detection. Each specimen type has a commonly agreed upon detection window (17, 30, 31, 50). The windows of detection for each specimen type appear previously, and these detection windows appear in **Table 3** for convenient comparison.

4.3. Is there a relationship between the reported concentration and the amount of substance consumed?

Several variables influence the observed concentration of any analyte in a reservoir specimen type, a specimen type where analytes may accumulate over time such as umbilical cord, meconium, hair, or urine. Currently, the scientific literature does not support using the reported concentrations to predict the amount of substance ingested, time of ingestion, or the frequency of ingestion (11, 56) even under tightly controlled research conditions (57).

TABLE 3 Commonly accepted windows of detection by specimen type.

Specimen type	Detection window	Comment
Maternal urine	2–5 days	For most drugs, most used
Maternal blood	1–2 days	Uncommon for this purpose due to short detection window and high expense
Maternal hair	Up to approximately 12 weeks	Using 1.5 inches of hair Hair color and cosmetic treatment are variables May detect environmental exposure
Newborn Urine	1–2 days	First void is best practice Very dilute
Newborn hair	8 weeks	Detection starts when hair starts forming Many babies do not have enough hair
Meconium	Up to approximately 20 weeks	Difficult multi step collection process Issues with sample amount compliance
Umbilical Cord	12 weeks	Developed to mirror meconium Universal specimen type

4.4. Are medications provided to the mother or newborn detectable in newborn specimens?

Perinatal professionals should review the results to determine if the positive result aligns with the medical record. Detection of medications provided to the mother prior to birth may occur in newborn specimen types, including medications provided during labor and delivery (58). Medications given to the neonate postnatally may also appear in specimens collected following birth, such as meconium or newborn urine.

4.5. Was chain of custody documented, and was confirmation testing performed?

US physicians must notify state child protective services of prenatal exposure to illegal substances. Knowledge of the consequences of a positive test result creates a dilemma with the performance of reasonable suspicion testing. Under these circumstances testing procedures should include documented chain of custody and automatic confirmation testing of presumptive positives.

4.6. What if a donor refutes a positive test result?

Occasionally, a test result is unexpected, does not align with the case, and/or the mother refutes the result. It is a common practice of accredited forensic laboratories to retain positive specimens in an appropriate storage condition (depending on the type of specimen) for an extended period (typically one year) while maintaining chain of custody of the specimen. The purpose of this policy is to allow for the option of retesting the specimen, at the original laboratory or another designated laboratory, to verify the accuracy of the original reported results. This policy provides a safety net of protection for all stakeholders involved.

5. Conclusion

Maternal use, misuse, and abuse of substances is a very complicated problem that may initiate lifelong negative consequences for the neonate. Huestis and Choo (56) raised the concern years ago that we need to do more for infants exposed to opioids *in utero* regarding follow-up and appropriate interventions, if needed. It is our responsibility as perinatal healthcare professionals to be aware of the latest developments in the field of toxicology so that we can do the best for the maternal/infant dyad and enrich the lives of those living through the Opioid Epidemic.

Author contribution

JJ conceived and composed this manuscript.

Acknowledgments

I would like to thank Loretta Finnegan for the encouragement to prepare this manuscript. Additionally, I would like to thank Guida Brown for reviewing and editing the paper.

Conflict of interest

JJ is employed by United States Drug Testing Laboratories, a national commercial reference laboratory, that is in the business of selling some of the services mentioned in this manuscript. This relationship did not influence the design or composition of this manuscript.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Ko JY, D'Angelo DV, Haight SC, Morrow B, Cox S, von Essen BS, et al. Vital signs: prescription opioid pain reliever use during pregnancy—34 US jurisdictions, 2019. *Morb Mortal Wkly Rep.* (2020) 69(28):897. doi: 10.15585/mmwr.mm6928a1

2. Sutter MB, Leeman L, Hsi A. Neonatal opioid withdrawal syndrome. *Obstet Gynecol Clin.* (2014) 41(2):317–34. doi: 10.1016/j.ogc.2014.02.010

3. Whiteman VE, Salemi JL, Mogos MF, Cain MA, Aliyu MH, Salihu HM. Maternal opioid drug use during pregnancy and its impact on perinatal morbidity, mortality, and the costs of medical care in the United States. *J Pregnancy.* (2014) 2014:1–8. doi: 10.1155/2014/906723

4. Chaffin M, Kelleher K, Hollenberg J. Onset of physical abuse and neglect: psychiatric, substance abuse, and social risk factors from prospective community data. *Child Abuse Negl.* (1996) 20(3):191–203. doi: 10.1016/S0145-2134(95)00144-1

5. Center on Addiction and Substance Abuse (CASA). *No safe haven: Children of substance abusing parents.* New York: Columbia University (1999).

6. U.S. Department of Health and Human Services (DHHS). Office of Disease Prevention and Health Promotion. HealthyPeople 2030: maternal, infant, and child health. MICH-11.1 Increase abstinence from illicit drugs among pregnant women. Available at: https://health.gov/healthypeople/objectives-and-data/browse-objectives/pregnancy-and-childbirth/increase-abstinence-illicit-drugs-among-pregnant-women-mich-11 (Retrieved October 08, 2022).

7. Center for Behavioral Health Statistics and Quality (CBHSQ). *2020 National survey on drug use and health: Detailed tables.* MD, USA: Substance Abuse and Mental Health Services Administration (2017). Available at: https://www.samhsa.gov/data/report/2020-nsduh-detailed-tables (Retrieved September 30, 2022)

8. Behnke M, Smith VC, Levy S, Ammerman S, Gonzalez P, Ryan S, et al. Prenatal substance abuse: short-and long-term effects on the exposed fetus. *Pediatrics.* (2013) 131(3):e1009–24. doi: 10.1542/peds.2012-3931

9. Blanco-Castañeda R, Galaviz-Hernández C, Souto PC, Lima VV, Giachini FR, Escudero C, et al. The role of xenobiotic-metabolizing enzymes in the placenta: a growing research field. *Expert Rev Clin Pharmacol.* (2020) 13(3):247–63. doi: 10.1080/17512433.2020.1733412

10. Ecker J, Abuhamad A, Hill W, Bailit J, Bateman BT, Berghella V, et al. Substance use disorders in pregnancy: clinical, ethical, and research imperatives of the opioid epidemic: a report of a joint workshop of the society for maternal-fetal medicine, American college of obstetricians and gynecologists, and American society of addiction medicine. *Am J Obstet Gynecol.* (2019) 221(1):B5–B28. doi: 10.1016/j.ajog.2019.03.022

11. Concheiro M, Huestis MA. Drug exposure during pregnancy: analytical methods and toxicological findings. *Bioanalysis.* (2018) 10(8):587–606. doi: 10.4155/bio-2017-0260

12. Chang G. Maternal substance use: consequences, identification, and interventions. *Alcohol Res.* (2020) 40(2):1–10. doi: 10.35946/arcr.v40.2.06

13. Chiandetti A, Hernandez G, Mercadal-Hally M, Alvarez A, Andreu-Fernandez V, Navarro-Tapia E, et al. Prevalence of prenatal exposure to substances of abuse: questionnaire versus biomarkers. *Reprod Health.* (2017) 14(1):1–2. doi: 10.1186/s12978-017-0385-3

14. Lester BM, ElSohly M, Wright LL, Smeriglio VL, Verter J, Bauer CR, et al. The maternal lifestyle study: drug use by meconium toxicology and maternal self-report. *Pediatrics.* (2001) 107(2):309–17. doi: 10.1542/peds.107.2.309

15. Gray T, Huestis M. Bioanalytical procedures for monitoring in utero drug exposure. *Anal Bioanal Chem.* (2007) 388(7):1455–65. doi: 10.1007/s00216-007-1228-9

16. Finanger T, Spigset O, Gråwe RW, Andreassen TN, Løkken TN, Aamo TO, et al. Phosphatidylethanol as blood biomarker of alcohol consumption in early pregnancy: an observational study in 4,067 pregnant women. *Alcohol Clin Exp Res.* (2021) 45(4):886–92. doi: 10.1111/acer.14577

17. Concheiro M, Lendoiro E, de Castro A, Gónzalez-Colmenero E, Concheiro-Guisan A, Peñas-Silva P, et al. Bioanalysis for cocaine, opiates, methadone, and amphetamines exposure detection during pregnancy. *Drug Test Anal.* (2017) 9(6):898–904. doi: 10.1002/dta.2087

18. Takayama N, Tanaka S, Kizu R, Hayakawa K. High-performance liquid chromatography study on effects of permanent wave, dye and decolorant treatments on methamphetamine and amphetamine in hair. *Biomed Chromatogr.* (1999) 13(4):257–61. doi: 10.1002/(SICI)1099-0801(199906)13:4<257::AID-BMC830>3.0.CO;2-V

19. Stout P. Hair testing for drugs—challenges for interpretation. *Forensic Sci Rev.* (2007) 19(2):69–84. PMID: 26247284.

20. Kwong TC, Ryan RM. Detection of intrauterine illicit drug exposure by newborn drug testing. *Clin Chem.* (1997) 43(1):235–42. doi: 10.1093/clinchem/43.1.235

21. Ursitti F, Klein J, Koren G. Clinical utilization of the neonatal hair test for cocaine: a four-year experience in Toronto. *Neonatology.* (1997) 72(6):345–51. doi: 10.1159/000244504

22. Bar-Oz B, Klein J, Karaskov T, Koren G. Comparison of meconium and neonatal hair analysis for detection of gestational exposure to drugs of abuse. *Arch Dis Child Fetal Neonatal Ed.* (2003) 88(2):F98–F100. doi: 10.1136/fn.88.2.F98

23. Vinner E, Vignau J, Thibault D, Codaccioni X, Brassart C, Humbert L, et al. Neonatal hair analysis contribution to establishing a gestational drug exposure profile and predicting a withdrawal syndrome. *Ther Drug Monit.* (2003) 25(4):421–32. doi: 10.1097/00007691-200308000-00002

24. Garcia-Bournissen F, Rokach B, Karaskov T, Koren G. Methamphetamine detection in maternal and neonatal hair: implications for fetal safety. *Arch Dis Child Fetal Neonatal Ed.* (2007) 92(5):351–5. doi: 10.1136/adc.2006.100156

25. Ostrea EM Jr, Parks PM, Brady MJ. Rapid isolation and detection of drugs in meconium of infants of drug-dependent mothers. *Clin Chem.* (1988) 34(11):2372–3. doi: 10.1093/clinchem/34.11.2372a

26. Ostrea EM Jr, Brady MJ, Parks PM, Asensio DC, Naluz A. Drug screening of meconium in infants of drug-dependent mothers: an alternative to urine testing. *J Pediatr.* (1989) 115(3):474–7. doi: 10.1016/S0022-3476(89)80860-1

27. Moore C, Negrusz A, Lewis D. Determination of drugs of abuse in meconium. *J Chromatogr B Biomed Appl.* (1998) 713(1):137–46. doi: 10.1016/S0378-4347(97)00479-9

28. Le NL, Reiter A, Tomlinson K, Jones J, Moore C. The detection of oxycodone in meconium specimens. *J Anal Toxicol.* (2005) 29(1):54–7. doi: 10.1093/jat/29.1.54

29. Concheiro-Guisan A, Concheiro M. Bioanalysis during pregnancy: recent advances and novel sampling strategies. *Bioanalysis.* (2014) 6(23):3133–53. doi: 10.4155/bio.14.278

30. Montgomery D, Plate C, Alder SC, Jones M, Jones J, Christensen RD. Testing for fetal exposure to illicit drugs using umbilical cord tissue vs meconium. *J Perinatol.* (2006) 26(1):11–4. doi: 10.1038/sj.jp.7211416

31. Montgomery DP, Plate CA, Jones M, Jones J, Rios R, Lambert DK, et al. Using umbilical cord tissue to detect fetal exposure to illicit drugs: a multicentered study in Utah and New Jersey. *J Perinatol.* (2008) 28(11):750–3. doi: 10.1038/jp.2008.97

32. Jones J, Rios R, Jones M, Lewis D, Plate C. Determination of amphetamine and methamphetamine in umbilical cord using liquid chromatography–tandem mass spectrometry. *J Chromatogr B.* (2009) 877(29):3701–6. doi: 10.1016/j.jchromb.2009.09.021

33. Jones J, Magri R, Rios R, Jones M, Plate C, Lewis D. The detection of caffeine and cotinine in umbilical cord tissue using liquid chromatography–tandem mass spectrometry. *Anal Methods.* (2011) 3(6):1310–5. doi: 10.1039/c0ay00625d

34. Jones JT, Jones M, Jones B, Sulaiman K, Plate C, Lewis D. Detection of codeine, morphine, 6-monoacetylmorphine, and meconin in human umbilical cord tissue: method validation and evidence of in utero heroin exposure. *Ther Drug Monit.* (2015) 37(1):45. doi: 10.1097/FTD.0000000000000104

35. Arendt RE, Singer LT, Minnes S, Salvator A. Accuracy in detecting prenatal drug exposure. *J Drug Issues*. (1999) 29:203–14. doi: 10.1177/002204269902900203

36. Derauf C, Katz AR, Easa D. Agreement between maternal self-reported ethanol intake and tobacco use during pregnancy and meconium assays for fatty acid ethyl esters and cotinine. *Am J Epidemiol*. (2003) 158(7):705–9. doi: 10.1093/aje/kwg215

37. Eyler FD, Behnke M, Wobie K, Garvan CW, Tebbett I. Relative ability of biologic specimens and interviews to detect prenatal cocaine use. *Neurotoxicol Teratol*. (2005) 27 (4):677–87. doi: 10.1016/j.ntt.2005.04.001

38. Gray TR, Eiden RD, Leonard KE, Connors G, Shisler S, Huestis MA. Nicotine and metabolites in meconium as evidence of maternal cigarette smoking during pregnancy and predictors of neonatal growth deficits. *Nicotine Tob Res*. (2010) 12(6):658–64. doi: 10.1093/ntr/ntq068

39. Marin SJ, Christensen RD, Baer VL, Clark CJ, McMillin GA. Nicotine and metabolites in paired umbilical cord tissue and meconium specimens. *Ther Drug Monit*. (2011) 33(1):80–5. doi: 10.1097/FTD.0b013e3182055f14

40. Moore CM, Brown S, Negrusz A, Tebbett I, Meyer W, Jain L. Determination of cocaine and its major metabolite, benzoylecgonine, in amniotic fluid, umbilical cord blood, umbilical cord tissue, and neonatal urine: a case study. *J Anal Toxicol*. (1993) 17(1):62. doi: 10.1093/jat/17.1.62

41. Bessa MA, Mitsuhiro SS, Chalem E, Barros MM, Guinsburg R, Laranjeira R. Underreporting of use of cocaine and marijuana during the third trimester of gestation among pregnant adolescents. *Addict Behav*. (2010) 35(3):266–9. doi: 10.1016/j.addbeh.2009.10.007

42. García-Serra J, Ramis J, Simó S, Joya X, Pichini S, Vall O, et al. Alternative biological materials to detect prenatal exposure to drugs of abuse in the third trimester of pregnancy. *An Pediatr (Barc)*. (2012) 77(5):323–8. doi: 10.1016/j.anpedi.2012.02.019

43. Lendoiro E, González-Colmenero E, Concheiro-Guisán A, de Castro A, Cruz A, López-Rivadulla M, et al. Maternal hair analysis for the detection of illicit drugs, medicines, and alcohol exposure during pregnancy. *Ther Drug Monit*. (2013) 35 (3):296–304. doi: 10.1097/FTD.0b013e318288453f

44. Hutson JR, Magri R, Gareri JN, Koren G. The incidence of prenatal alcohol exposure in Montevideo Uruguay as determined by meconium analysis. *Ther Drug Monit*. (2010) 32(3):311–7. doi: 10.1097/FTD.0b013e3181dda52a

45. Friguls B, Joya X, Garcia-Serra J, Gómez-Culebras M, Pichini S, Martinez S, et al. Assessment of exposure to drugs of abuse during pregnancy by hair analysis in a Mediterranean island. *Addiction*. (2012) 107(8):1471–9. doi: 10.1111/j.1360-0443.2012.03828.x

46. García-Algar O, Scaravelli G, Pacifici R, Pichini S. Prenatal exposure to drugs of abuse using meconium analysis in a low socioeconomic population in Barcelona. *An Pediatr (Barc)*. (2008) 70(2):151–8. doi: 10.1016/j.anpedi.2008.08.008

47. Joya X, Gomez-Culebras M, Callejón A, Friguls B, Puig C, Ortigosa S, et al. Cocaine use during pregnancy assessed by hair analysis in a canary islands cohort. *BMC Pregnancy Childbirth*. (2012) 12(1):1–8. doi: 10.1186/1471-2393-12-2

48. Ferguson v. Charleston, 532 US 67 - Supreme Court 2001.

49. Gray T. Meconium drug testing. In: B Levine, S Kerrigan, editors. *Principles of forensic toxicology*. 5th ed. Cham, Switzerland: Springer (2020). p. 657–63.

50. Elsohly MA, Stanford D, Murphy T, Lester B, Wright L, Smeriglio V, et al. Immunoassay and GC-MS procedures for the analysis of drugs of abuse in meconium. *J Anal Toxicol*. (1999) 23:436–45. doi: 10.1093/jat/23.6.436

51. Novikov N, Melanson SE, Ransohoff JR, Petrides AK. Rates of fentanyl positivity in neonatal urine following maternal analgesia during labor and delivery. *J Appl Lab Med*. (2020) 5(4):686–94. doi: 10.1093/jalm/jfaa027

52. Jones J, Coy D, Mitacek R, Thompson S, Maxwell S. Neonatal cord tox panel and maternal fentanyl exposure: a retrospective chart review. *Am J Anal Chem*. (2021) 12:324–31. doi: 10.4236/ajac.2021.129020

53. Marin SJ, Metcalf A, Krasowski MD, Linert BS, Clark CJ, Strathmann FG, et al. Detection of neonatal drug exposure using umbilical cord tissue and liquid chromatography time-of-flight mass spectrometry. *Ther Drug Monit*. (2014) 36 (1):119–24. doi: 10.1097/FTD.0b013e3182a0d18c

54. Bissell MG. Regulatory issues in accreditation of toxicology laboratories. *Clin Lab Med*. (2012) 32(3):525–42. doi: 10.1016/j.cll.2012.06.007

55. Ontario Ministry of the Attorney General. The Honorable Susan B. Lang: Report of the Motherisk Hair Analysis Independent Review (2015). Available at: http://m-hair.ca/docs/default-source/default-document-library/motherisk_enbfb30b45b7f266cc881aff0000960f99.pdf?sfvrsn=2 (Retrieved October 09, 2022).

56. Huestis MA, Choo RE. Drug abuse's Smallest victims: in utero drug exposure. *Forensic Sci Int*. (2002) 128(1–2):20–30. doi: 10.1016/S0379-0738(02)00160-3

57. Kacinko SL, Jones HE, Johnson RE, Choo RE, Huestis MA. Correlations of maternal buprenorphine dose, buprenorphine, and metabolite concentrations in meconium with neonatal outcomes. *Clin Pharmacol Ther*. (2008) 84(5):604–12. doi: 10.1038/clpt.2008.156

58. Alexander A, Abbas L, Jones M, Jones J, Lewis D, Negrusz A. Discordant umbilical cord drug testing results in monozygotic twins. *J Anal Toxicol*. (2018) 42(5):e47–9. doi: 10.1093/jat/bky009

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 23 February 2023
DOI 10.3389/fped.2023.1139378

Check for updates

OPEN ACCESS

EDITED BY
Henrietta S Bada,
University of Kentucky, United States

REVIEWED BY
Balaji Govindaswami,
Valley Medical Center Foundation, United States
Thitinart Sithisarn,
University of Kentucky, United States

*CORRESPONDENCE
Lauren L. Jantzie
✉ LJantzie@jhmi.edu

SPECIALTY SECTION
This article was submitted to Neonatology, a section of the journal Frontiers in Pediatrics

RECEIVED 06 January 2023
ACCEPTED 03 February 2023
PUBLISHED 23 February 2023

CITATION
Chin EM, Kitase Y, Madurai NK, Robinson S and Jantzie LL (2023) *In utero* methadone exposure permanently alters anatomical and functional connectivity: A preclinical evaluation.
Front. Pediatr. 11:1139378.
doi: 10.3389/fped.2023.1139378

COPYRIGHT
© 2023 Chin, Kitase, Madurai, Robinson and Jantzie. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

In utero methadone exposure permanently alters anatomical and functional connectivity: A preclinical evaluation

Eric M. Chin[1,2,3], Yuma Kitase[4], Nethra K. Madurai[4], Shenandoah Robinson[1,2,5] and Lauren L. Jantzie[1,2,3,4,5]*

[1]Department of Neurodevelopmental Medicine, Phelps Center for Cerebral Palsy and Neurodevelopmental Medicine, Kennedy Krieger Institute, Baltimore, MD, United States, [2]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, United States, [3]Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, United States, [4]Department of Pediatrics, Division of Neonatal-Perinatal Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, United States, [5]Department of Neurosurgery, Division of Pediatric Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, MD, United States

The opioid epidemic is an ongoing public health crisis, and children born following prenatal opioid exposure (POE) have increased risk of long-term cognitive and behavioral sequelae. Clinical studies have identified reduced gray matter volume and abnormal white matter microstructure in children with POE but impacts on whole-brain functional brain connectivity (FC) have not been reported. To define effects of POE on whole brain FC and white matter injury in adult animals, we performed quantitative whole-brain structural and functional MRI. We used an established rat model of POE in which we have previously reported impaired executive function in adult rats analogous to persistent neurocognitive symptoms described in humans with POE. Pregnant Sprague-Dawley rat dams received continuous methadone (12 mg/kg/day) vs. saline infusion for 28 days via osmotic mini-pumps, exposing rats to pre- and postnatal opioid until weaning. At young adult age (P60), POE and saline exposed offspring underwent *in vivo* MRI included diffusion tensor imaging and functional MRI (fMRI). Results indicate that fractional anisotropy (FA) was decreased in adult animals with POE [$n = 11$] compared to animals that received saline [$n = 9$] in major white matter tracts, including the corpus callosum ($p < 0.001$) and external capsule ($p < 0.01$). This change in FA was concomitant with reduced axial diffusivity in the external capsule ($p < 0.01$) and increased radial diffusivity in the corpus callosum ($p < 0.01$). fMRI analyses reveal brainwide FC was diffusely lower in POE ($p < 10^{-6}$; 10% of variance explained by group). Decreased connectivity in cortical-cortical and cortico-basal ganglia circuitry was particularly prominent with large effect sizes (Glass's $\Delta > 1$). Taken together, these data confirm POE reduces brainwide functional connectivity as well as microstructural integrity of major white matter tracts. Altered neural circuitry, dysregulated network refinement, and diffuse network dysfunction have been implicated in executive function deficits that are common in children with POE. FC may serve as a translatable biomarker in children with POE.

KEYWORDS

prenatal opioid exposure, methadone, functional connectivity, white matter microstructure, neurodevelopment

Introduction

The opioid epidemic is a public health crisis (1, 2). The National Institutes of Health (NIH) has deemed opioid misuse a national health emergency (3, 4), and efforts to address the opioid crisis are major priorities of the US congress (5, 6), March of Dimes Foundation (5, 7), and World Health Organization (8). Centers for Disease Control and Prevention (CDC) estimate the total economic burden of opioid misuse to be 78.5 billion USD annually, underscoring the enormous impact on health, social and financial well-being (3, 9, 10). Pregnant women and children are often overlooked in public health efforts to address the opioid crisis. Indeed, the incidence of substance misuse during pregnancy and its negative impact on postnatal outcomes is a critical threat to pediatric and adult health (11). Thus, there is an immediate need to define the full spectrum of adverse outcomes associated with prenatal opioid exposure (POE) (1).

The incidence of substance misuse during pregnancy and its negative impacts on postnatal outcomes requires intense research efforts (11). The increased prevalence of opioid use disorder (OUD) in pregnant people is paralleled by a staggering increase in neonatal opioid withdrawal syndrome (NOWS) (12–15). NOWS is a well-recognized clinical syndrome associated with POE. It has risen 5-fold in the past decade. Specifically, in the USA NOWS occurs in ∼5.8 infants in every 1000-hospital births, accounting for an estimated 1.5 billion dollars in hospital charges, the majority of which is incurred by Medicaid, in addition to the cumulative individual, familial and societal burdens (1, 13, 16–18). Maryland has one of the highest rates of OUD recorded at infant delivery and these numbers have more than quadrupled from 1999 to 2014 similar to national statistics (19).

While NOWS is a well-defined clinical syndrome, the potential for long-term damage to the developing brain due to opioid medications remains a serious and poorly understood concern. Recently, there is greater appreciation that the adverse effects of POE on neurodevelopment extend far beyond the symptoms of NOWS. Not all infants with POE who are at risk for brain injury exhibit withdrawal symptoms (20–22). In line with clinical practice guidelines, OUD is typically treated with methadone or buprenorphine during pregnancy as a safer alternative to abstinence or withdrawal. However, the safety of opioid maintenance treatment during pregnancy, including the use of methadone and buprenorphine to manage OUD, has been defined by studies with limited evaluation of postnatal sequelae, with no randomized control trials that included imaging or long-term follow-up on the exposed children (5, 23–28).

Here, we build on a growing body of literature examining chronic changes to brain structure and function caused by POE (20, 29–37). We hypothesized that methadone would be toxic to developing neural cells resulting in structural and functional brain injury. We expected that *in utero* methadone exposure would cause disruption of white matter microstructure and deficits in functional connectivity—manifestations of sustained neural network dysfunction. Using state-of-the-art preclinical magnetic resonance imaging (MRI), including diffusion tensor imaging (DTI) and functional connectivity using functional MRI (FC/fMRI), we examined neural networks and major white matter tracts essential to cognition.

Methods

Animals

Sprague-Dawley rat dams and litters were maintained in a temperature and humidity-controlled facility with food and water available *ad libitum*. A 12-hour dark/light cycle was maintained for all animals with lights on at 0800 h. All experiments were performed in strict accordance with protocols approved by the institutional Animal Care and Use Committee (ACUC) at the Johns Hopkins University. Protocols were developed and performed consistent with National Research Council and ARRIVE guidelines (38). Litter size was similar between methadone-exposed and saline-exposed litters, with no differences in maternal weights. As previously published (39–41), pup weights were significantly lower in methadone-exposed litters as compared to saline-exposed litters. For each experiment described, the data represents true n (individual rats). Each rat fetus has its own placenta and thus, represents an individual maternal-placental-fetal unit. Accordingly, 1 fetus/pup is considered a singular experimental unit consistent with published norms. However, for every experiment and outcome measure, we used offspring from at least 4 different dams and litters per condition to control for the potential of litter effects. There was no difference in maternal care, including on nest and off nest activities observed between groups. Male and female offspring were used in every outcome measure and in approximately equal numbers where possible.

Methadone exposure

Per previously published methods, on embryonic day 16 (E16), osmotic mini pumps (ALZET, Cupertino, California) were implanted subcutaneously in the nape of the neck of pregnant dams for 28 days of continuous methadone (12 mg/kg/day infused at 0.25 µl/h flow rate) or sterile saline infusion (**Figure 1**) (39–41). Methadone is a synthetic, long-acting, µ-opioid receptor agonist that readily crosses the placenta and blood-brain barrier. Specifically, following induction and maintenance of anesthesia with inhaled isoflurane, dams underwent minipump placement with a 1.5 cm transverse skin incision followed by careful blunt dissection of the subcutaneous space. Osmotic pumps were prefilled and primed prior to insertion. Dams were carefully monitored after closure with 2–3 sutures following the procedure for full recovery. Rat pups were born at E22/postnatal day 0 (P0) following completion of gestation and remained with their dams. Pups continued to receive methadone or saline through the maternal milk supply until weaning on P21 (39–41).

10.3389/fped.2023.1139378

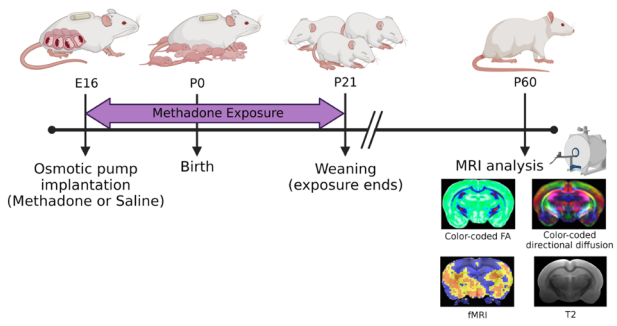


FIGURE 1
Experimental paradigm. This timeline highlights key study timepoints (pump implantation, birth, weaning, and *in vivo* brain imaging in young adulthood).

Imaging

In vivo imaging was performed on P60, (young adult age equivalent) using an 11.7 T scanner (Bruker BioSpec, Billerica, MA; **Figure 2**). Rats were sedated with dexmedetomidine for multisequence acquisition using a volumetric head coil. Our imaging protocol included a high-resolution fat-suppressed T_2-weighted anatomical sequence (0.27 mm isotropic resolution; 2 averages), BOLD-weighted fMRI [0.4 mm isotropic with TR = 1000 ms × 451 volumes, TE minimized (4.5 ms)], and high-resolution diffusion imaging (0.4 mm isotropic × 30 directions at b = 1,000 and 5 b_0 volumes)—all with whole-brain coverage.

Microstructure analysis (DTI)

We performed a quantitative DTI analysis of white matter microstructure alterations in POE. We selected white matter regions of interest (ROI) *a priori* that have been implicated in functional outcome and cognition (corpus callosum and external capsule). As we have performed previously (39, 42–47), ROIs were traced by an observer masked to experimental conditions and analyzed using Bruker's Paravision 6.1 imaging software (Billerica, MA). In brief, fractional anisotropy (FA), axial diffusivity (λ_1), and radial diffusivity $\left(\frac{\boldsymbol{\lambda}_2 + \boldsymbol{\lambda}_3}{2}\right)$ scalar maps

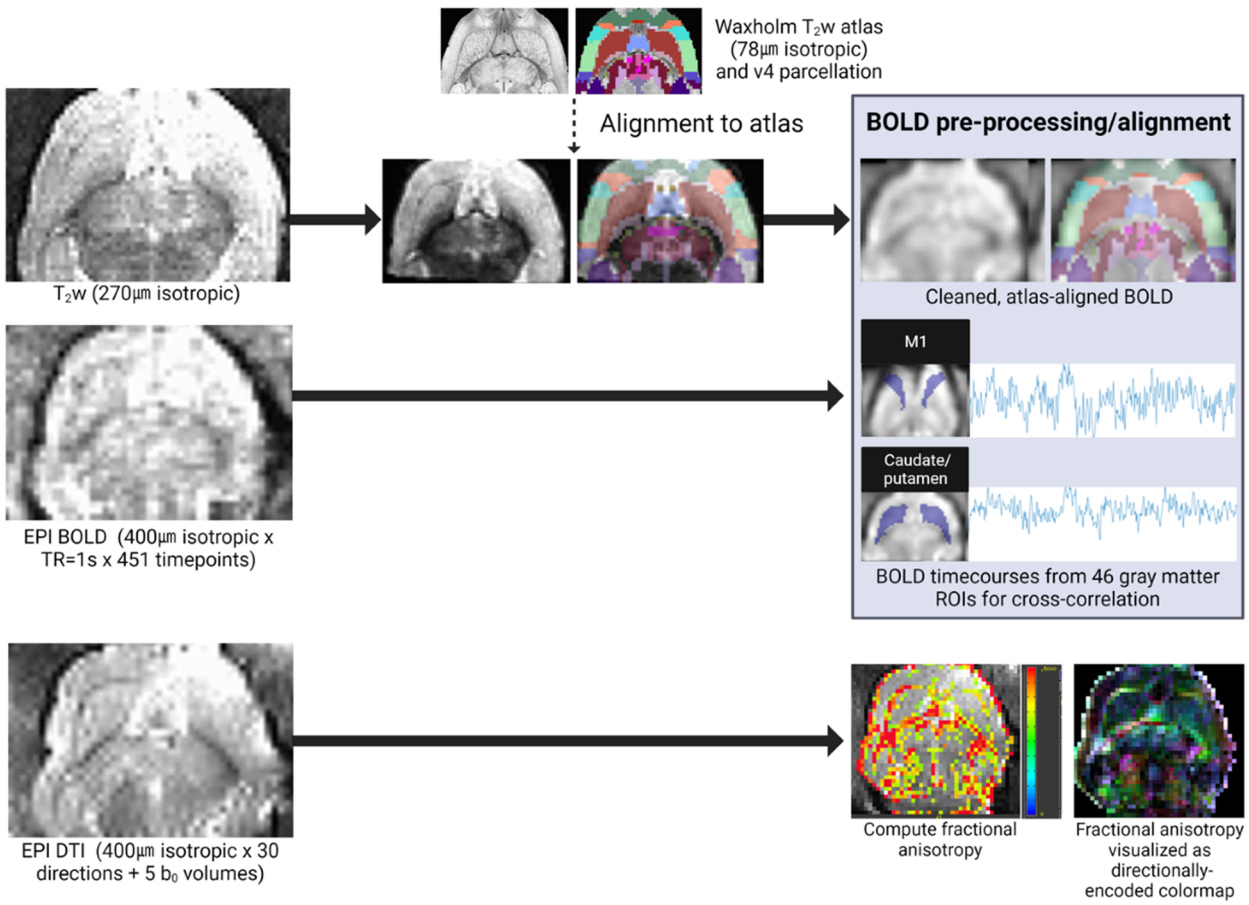


FIGURE 2
Quantitative MRI analysis pipeline. *In vivo* imaging included a T_2-weighted anatomical sequence (for alignment to the Waxholm reference atlas), BOLD-weighted fMRI, and DTI. Individual fMRI scans were pre-processed and aligned to the reference atlas for extraction of ROI-specific BOLD timecourses for cross-correlation in functional connectivity analyses. Individual DTI scans were manually segmented (extracting corpus callosum and external capsule ROIs), and these white matter ROI masks were used to compute diffusion scalars (e.g., FA pictured here).

were computed, and means were calculated individually for each ROI. For bilateral neuroanatomical ROIs, scalar means were acquired on each side and averaged per ROI. Two scans (both in the Saline group) were excluded from analysis—one due to poor field of view coverage and one due to severe motion-related artifact.

Functional MRI (fMRI) analysis

Resting state functional imaging data were pre-processed using AFNI version 20.1.06 (Bethesda, MD). T_2-weighted anatomical images were pre-processed (skullstripped using the AFNI @NoisySkullStrip function) and intensity-normalized (3dUnifize function). Non-linear warp transformations to the Waxholm Atlas T_2-weighted reference image were computed for T_2-weighted anatomical and BOLD-weighted fMRI images simultaneously (@AnimalWarper function, feature_size = 0.05 mm) (48). This transformation, as well as pre-processing, were applied to BOLD-weighted images using the afni_proc.py function. We employed stringent *a priori* artifact correction to mitigate anticipated artifacts including artifactual spatial distortion (mitigated using non-linear alignment as above), cardiorespiratory artifact, and effects of head motion. In particular, additional pre-processing steps used within afni_proc.py removed pre-steady state volumes (first 2 TRs), applied slice timing correction, applied despiking, aligned BOLD volumes to each other, applied a Gaussian blur (0.8 mm full width at half maximum), applied outlier censoring (rejecting BOLD volumes during which more than 5% of brain voxels were outliers), low-pass filtering (0.08 Hz cutoff) to mitigate cardiac/respiratory artifact, and regression of nuisance variables (6 axes of head motion as well as their first time derivatives). We also utilized customized quality control procedures to only include scans with adequate BOLD-atlas alignment and with gray matter temporal signal-to-noise consistently above 100 (more typically exceeding 200). One scan (Saline group) was excluded from analysis due to poor field of view coverage.

Gray matter regions of interest (ROIs) were selected *a priori* from the version 4 Waxholm Atlas (accessed via https://www.nitrc.org/projects/whs-sd-atlas). Cortical, and subcortical gray matter ROIs were selected that (1) were expected to lie within the imaging field of view; (2) were related to sensory, motor, pain, affective, or cognitive functioning; (3) and were at least 15 voxels in size when resampled into the 0.4 mm isotropic imaging matrix used in this study. In total, 46 ROIs were examined in terms of region-to-region functional connectivity (see Supplemental Data Sheet for details). Functional connectivity was computed on an individual scan level as the Fisher Z-transformed Pearson correlation coefficient of ROIs' voxelwise mean BOLD signal timecourses.

Statistical analysis

Diffusion data are represented as mean ± the standard error of the mean (SEM). Data was tested for normality using the Shapiro-Wilk test. When data for both groups was normal (Shapiro-Wilk $p > 0.05$), statistical differences were established with two-tailed Student's *t*-tests. When either demonstrably deviated from normality (Shapiro-Wilk $p < 0.05$; Saline RD), we conservatively employed the non-parametric Mann-Whitney test. In either case, $p < 0.05$ in a two-tailed test was considered statistically significant.

In fMRI analyses, we directly tested our hypothesis of diffuse, global FC changes across the brain by examining patterns of group x edge differences using a Type III ANOVA—attempting to distinguish (1) connectivity patterns that are common across all scans (main effect of edge), (2) brain-wide differences in connectivity magnitude between study groups (main effect of group), and (3) differences between groups in specific network connections (interaction of edge x group).

ROI-to-ROI connections were also examined individually using a non-parametric rank sum test with multiple comparisons correction performed using the Benjamini-Hochberg procedure (false discovery rate = 0.05) due to the large number of imaging features compared (FC for each of 46*45/2 = 1,035 ROI-to-ROI connections). In addition to binarized hypothesis testing, we additionally examined group differences in terms of standardized effect size (Glass's Δ assessing differences between group means in units of the standard deviation of FC_{Saline}) to descriptively define patterns of altered FC.

GraphPad Prism 9.3.1 software and MATLAB version 2022a (MathWorks, Natick, MA) were used to perform statistical analysis.

Results

Microstructural analyses

Fractional anisotropy (FA) was decreased in POE compared to saline controls (**Figure 3**), including in both the corpus callosum

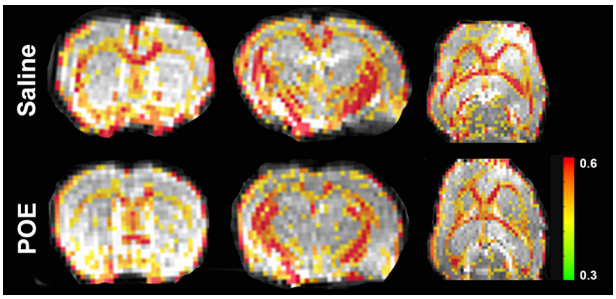


FIGURE 3
White matter microstructure alterations in POE: fractional anisotropy maps. These are sections of whole-brain fractional anisotropy maps in one representative Saline group scan (***top row***) and in one representative POE scan (***bottom row***). Two coronal sections (***first two columns***) and an axial section (***last column***) are included here. In each panel, the grayscale background is a raw b = 0 image; the superimposed colored voxels indicate fractional anisotropy (FA) for white matter voxels (voxels with FA > 0.3). The color of the white matter voxel indicates the FA value (from high [0.6+; red] to low [0.3; green]). Note that high-FA regions of large white matter tracts overall appear to be wider (spanning a greater diameter within each tract) and extend further along the length of each tract.

(Saline: 0.491 ± 0.008 vs. POE: 0.451 ± 0.005; $p < 0.001$) and in the external capsule (Saline: 0.381 ± 0.008 vs. POE: 0.350 ± 0.006; $p < 0.01$; **Figures 4A,B**). High-FA regions of large white matter tracts overall appeared to be wider (spanning a greater diameter within each tract) and to extend further along the length of each tract (**Figure 3**).

As FA is a measure of microstructural flow selectivity (near one when axial diffusivity [AD] >> radial diffusivity [RD]; near zero when AD ≈ RD), decreased AD or increased RD can both contribute to differences in FA and be associated with axonal injury and impaired myelination. AD was significantly decreased in the external capsule (Saline: $1.1 \times 10^{-3} \pm 4.8 \times 10^{-5}$ vs. POE: $0.9 \times 10^{-3} \pm 1.2 \times 10^{-5}$; $p < 0.01$) and trended lower in the corpus callosum (**Figures 4C,D**). RD was increased in the corpus callosum (Saline: $5.2 \times 10^{-4} \pm 1.2 \times 10^{-5}$ vs. POE: $5.7 \times 10^{-4} \pm 9.5 \times 10^{-6}$; $p < 0.01$) and trended higher in the external capsule (Saline: $5.7 \times 10^{-4} \pm 1.2 \times 10^{-5}$ vs. POE: $5.9 \times 10^{-4} \pm 1.9 \times 10^{-5}$; $p = 0.2$; **Figures 4E,F**).

Functional connectivity

In both groups, FC profiles consisted almost entirely of positive (rather than negative) correlations. In both groups, "strong" (high FC) connections occurred in expected well-described resting-state networks (e.g., within sensorimotor cortical networks and between thalamic nuclei; **Figures 5A,B**). The topology of connectivity (the pattern of which network connections were strong vs. weak) was generally consistent between rats (ANOVA effect of edge: [$p < 10^{-6}$; 25.7% of variance explained]), and topology did not grossly vary between groups [no significant group x edge interactions ($p = 0.56$; 2.2% of variance explained)]. In summary, established resting state networks were robustly recapitulated in both study groups.

Between-group comparisons revealed a global reduction in connectivity consistent with multi-network dysfunction and abnormal neural circuitry in POE rats. FC was reduced ($FC_{POE} < FC_{Saline}$) in most network edges examined. Large reductions ($\Delta < -0.8$; **Figure 5C**) were particularly common in cortico-cortical and thalamo-basal ganglia connections. FC reductions preferentially impacted strong connections ($\Delta FC = FC_{POE} - FC_{Saline} \approx -0.1$ for connections with $FC_{Saline} > 0.2$ but ΔFC approaching zero for connections with $FC_{Saline} < 0.2$; **Figure 5D**). Group differences in functional connectivity in specific network edges did not survive multiple comparisons correction. However, in the group x edge ANOVA, brainwide functional connectivity was reduced in the opioid exposed group (effect of group: $p < 10^{-6}$; 10.3% of variance explained). In summary, FC was diffusely decreased in POE across cortical and deep gray networks.

Discussion

While mechanisms of NOWS are well understood, mechanisms of the neurodevelopmental and long-term consequences of POE are still being explored. This is essential given the individual and societal consequences of a growing population of children with lifelong cognitive and behavioral issues stemming from POE. This study supports the growing body of literature that POE has long-term structural and functional neurological sequelae, including lasting brain injury. Specifically, we found that POE resulted in (1) diffuse decreases in large-tract white matter anisotropy and (2) diffuse, widespread decreases in functional connectivity between gray matter regions in adult rats. Previously, using the same model of POE, we identified a robust systemic inflammatory response syndrome and immune system dysfunction during the neonatal period concomitant with microstructural white matter injury and cognitive deficits in adulthood (39). POE led to immune cell priming in the immediate perinatal period with significant baseline elevation in secretion of pro-inflammatory cytokines and chemokines, as well as an exaggerated inflammatory response from PBMCs after stimulation with LPS (40, 41). This effect lasted in adulthood, and included shifts in cerebral immune cell populations, defined specifically by increased neutrophils and regulatory T-cells, occurring months after prenatal opioid exposure (40). The present data extend these findings by confirming structural and functional MRI changes through adulthood, emphasizing the neurodevelopmental care and follow-up that children exposed to opioids need beyond the NICU or formal medical and hospital setting.

Microstructural alterations

We found decreased fractional anisotropy in large-tract white matter ROIs examined—in keeping with decreases in white matter FA described in human studies of POE to date [in the internal capsule and internal longitudinal fasciculus in term infants (12, 32), and in central inferior and posterior white matter tracts in school-aged children, respectively] (49, 50). These cross-sectional human subjects studies have been unable to attribute these alterations to POE itself as opposed to associated biopsychosocial factors; our results suggests that POE is itself sufficient to decrease white matter FA (37). Underlying architectural differences responsible for differences in diffusion metrics remain unknown; decreased FA may be caused, for instance, by larger axon diameters, by a lower axon packing density, or by increased membrane permeability (whether due to decreased myelination or otherwise) (51). Trends towards decreased axial diffusivity and increased radial diffusivity in POE in this study provide some clues: as diffusivity in b = 1,000 imaging is thought to be driven mainly by extra-axonal water flow, increased radial diffusivity may suggest decreased myelin volume, decreased axonal density, or a loss of extracellular matrix (51). We previously identified white matter volume loss and axonal injury in this model in *ex vivo* pathology that is consistent with these long-term changes in diffusion (39). Taken together with the profound inflammation that is present during this developmental time frame, the effects on the elaborate neurodevelopmental program guiding oligodendrocyte maturation, myelination and neural circuit formation cannot be overemphasized (52, 53).

10.3389/fped.2023.1139378

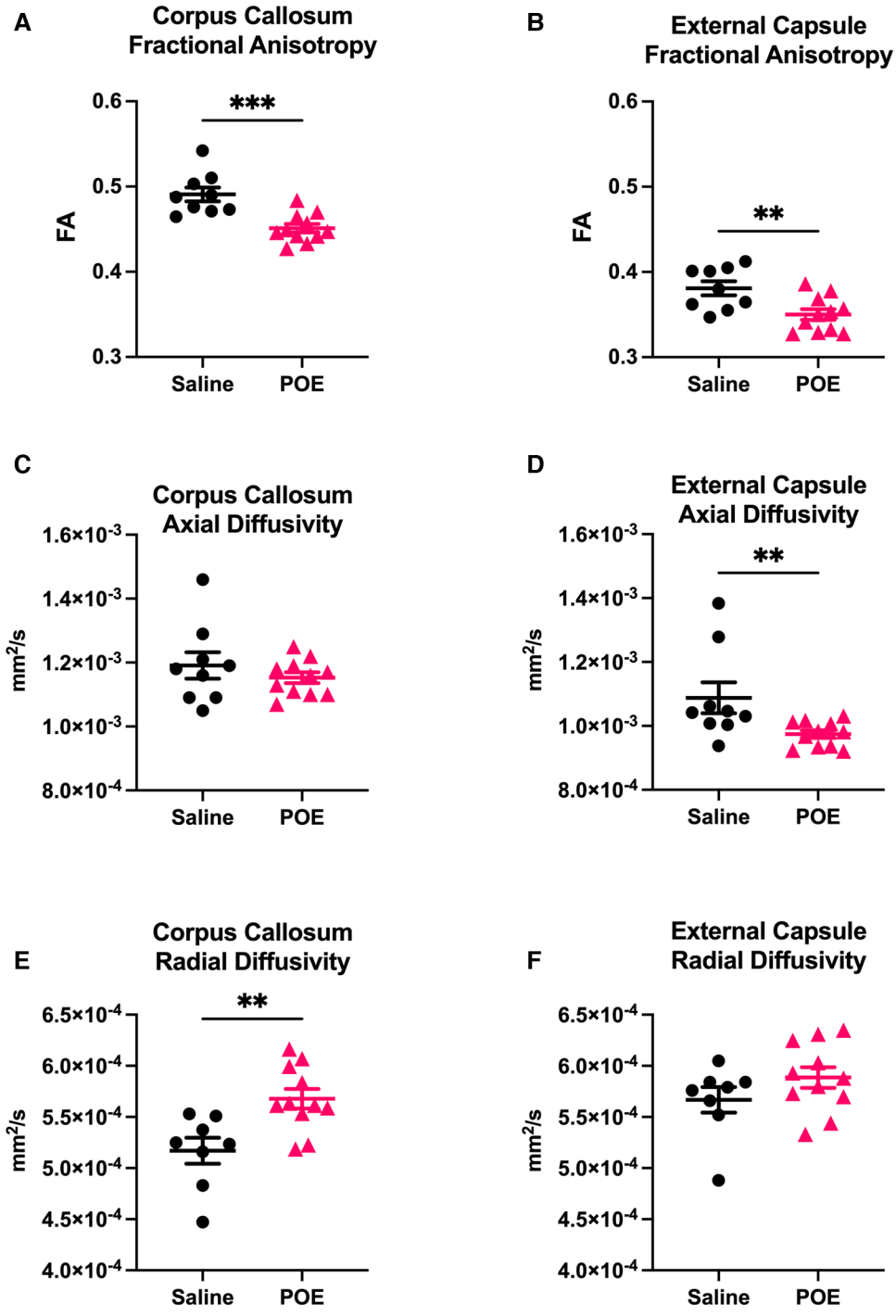


FIGURE 4
White matter microstructure alterations in POE: groupwise comparison of diffusion tensor metrics. Diffusion tensor metrics assess permeability to water flow (diffusivity) along (axial) vs. perpendicular to (radial) white matter tracts. Metrics were examined in two regions of interest (ROIs): corpus callosum (*left column:* A,C,E) and external capsule (*right column:* B,D,F). In each plot, individual values (black circles [Saline] vs. gray triangles [POE]) are plotted as well as group statistics (mean ± SEM). Fractional anisotropy (FA; A,B) can be considered a measure of microstructural flow selectivity (near one when axial diffusivity [AD] >> radial diffusivity [RD]; near zero when AD ≈ RD). Note that FA is decreased in POE in both ROIs. This appears to be attributable to decreased AD and increased RD in both ROIs, though differences are most statistically significant for AD in external capsule and for RD in corpus callosum.

Decreased functional connectivity

Our primary fMRI finding was a diffuse decrease in FC in POE. Decreased FC is often interpreted as a decrease in bidirectional information flow between gray matter regions, and such a decrease could be expected in the setting of diffuse white matter alterations. Potential alternative/additional causes of apparent decreases in FC should also be considered—including

10.3389/fped.2023.1139378

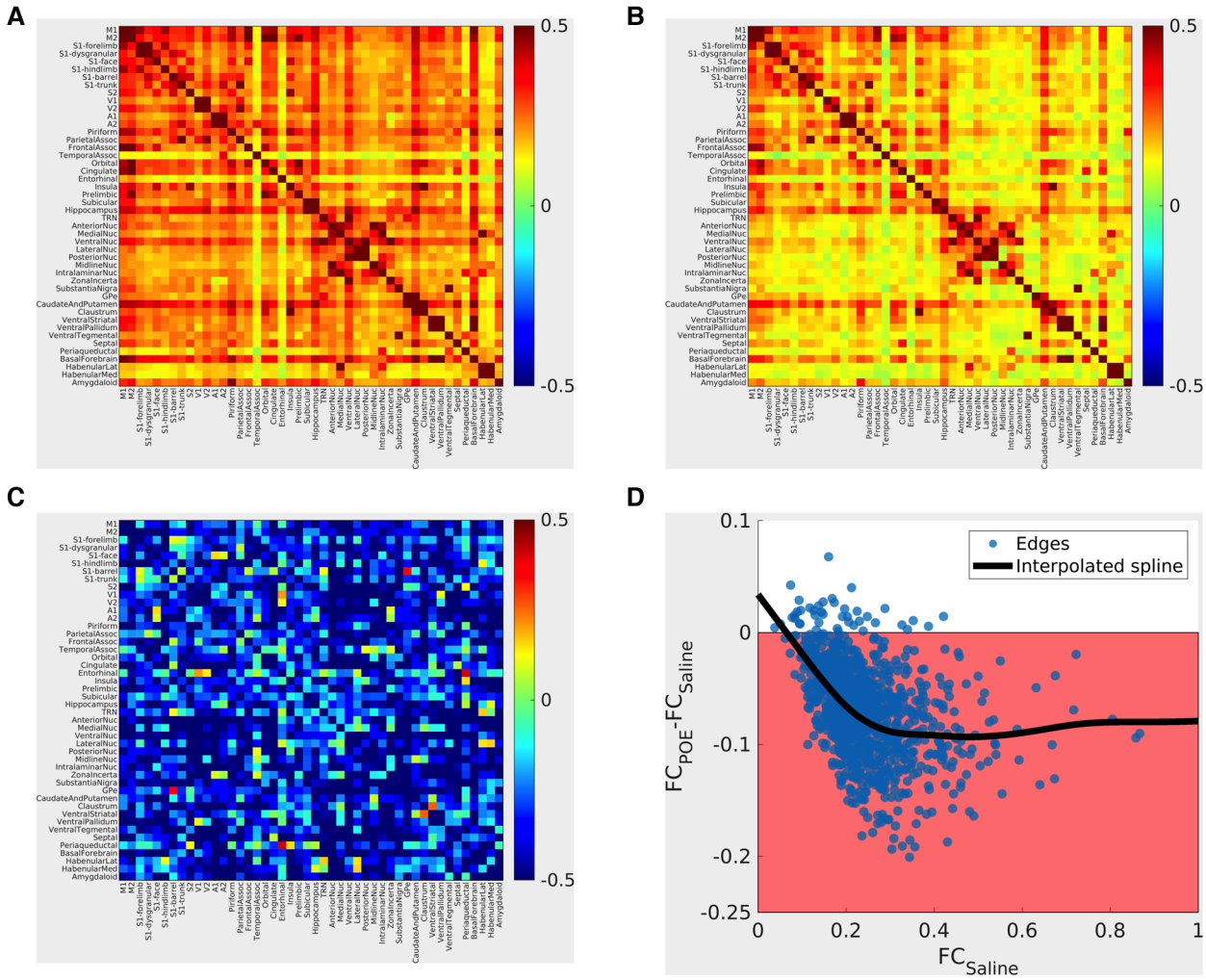


FIGURE 5
Functional connectivity alterations in POE. *Top panels: Group mean cross-correlation (functional connectivity) matrices*. Heatmaps (A: saline group; B: methadone group) summarize functional connectivity profiles seen in each group—each row and each column correspond to a gray matter ROI, and the color of the voxel at the intersection of the row/column indicates the functional connectivity seen between the two ROIs (warm colors = positive correlation; cool colors = negative correlation). "Strong" (high FC) connections seen nearly all consisted of positive correlations and that "strong" connections were seen in both groups, for example, within sensorimotor cortical networks and between thalamic nuclei. ***Bottom left panel C: Between-group differences*** are pictured in terms of standardized effect size (Glass's Δ; differences in group means in units of Saline standard deviation). Highly positive values (warm colors) indicate $FC_{POE} > FC_{Saline}$, and highly negative values (cool colors) indicate $FC_{POE} < FC_{Saline}$. Absolute values greater than 0.8 are considered "large" effect sizes. Note that edges with large effect sizes are predominantly negative ($FC_{POE} < FC_{Saline}$) with clusters including cortico-cortical and cortico-basal ganglia edges. ***Bottom right panel D: Between-group differences vs. FC_{Saline}.*** Each point indicates one ROI-to-ROI connection; *x*-values indicate FC_{Saline}, and *y*-values indicate FC_{POE}-FC_{Saline}. The shaded region indicates $FC_{POE} < FC_{Saline}$. The bold line indicates a smoothed curve to visualize overall trends (MATLAB smoothingspline, SmoothingParam = 0.995). Note again that nearly all edges exhibit $FC_{POE} < FC_{Saline}$ and that differences are particularly prominent for "strong" (high FC_{Saline}) connections.

displacement of functional processing nodes (altered topography) or differences in network constituents (54). The preservation of "neurotypical" topography suggests that atlas-based parcellation remains grossly accurate (e.g., that primary motor cortex is similarly located in both groups), but more sophisticated techniques such as representational similarity analysis would be needed to exclude more subtle topographical or topological differences in network structure (55).

Studies of infants and children with a history of POE have not converged upon a characteristic "signature" of altered functional connectivity in this population (37). As such, it is difficult to compare our findings directly to extant literature. Again, however, this preclinical study may help differentiate effects of POE itself from effects of associated biopsychosocial factors.

Clinical implications

Neurocognitive sequelae of POE appear to impact a number of cognitive domains—ultimately impacting psychomotor and behavioral outcomes (56–61). Especially in older children, impairments in general cognition, psychomotor development, language development, fine motor skills, hand-eye coordination, attention, and executive function have all been raised as

significant concerns (5, 29, 35, 62–69). Children born to opioid-dependent pregnant people have a greater likelihood of being impaired in two or more domains at school entry compared to non-opioid exposed children, and they carry their risk for educational delay throughout their school years (5, 35, 66–69). Impacts on attention and executive function have been particularly prominent. Children with POE are at greater risk for impaired executive function and have difficulties with information processing, and children with POE are at higher risk of developing ADHD (25, 35, 57, 58, 70).

This relatively non-specific pattern of developmental cognitive challenges is common across many neurologic conditions and can result from various brain injury patterns. Deficits in attention and executive function are common in white matter disorders ranging from neurodevelopmental disorders (e.g., spastic cerebral palsy) to acquired brain injury (e.g., traumatic brain injury or multiple sclerosis) (71–73). In each of these disorders, multi-domain cognitive performance (including prominent deficits in attention and executive functioning) has been linked to white matter DTI metrics. The data presented here increases concern that the neurocognitive sequelae of POE may similarly be mediated by diffuse network dysfunction.

This paper adds to a growing body of clinical and preclinical evidence suggesting that neurocognitive sequelae of POE are associated with quantifiable abnormalities in brain structure and in functional connectivity profiles (3, 5, 12, 14, 23, 28, 32, 36). Neonates exposed to methadone or buprenorphine have smaller brains, microcephaly, reduced basal ganglia and cerebellar volumes, reduced cortical thickness, and impaired white matter tract development (23, 32, 49, 50, 74–77). They have microstructural brain injury seen on MRI and impaired neurodevelopment (30, 78, 79). Decreased volumes (whole brain, cortical volume/thickness, and deep gray nucleus) and the white matter DTI profile observed here (decreased FA, decreased AD, and increased RD) have in particular been associated with general cognitive functioning in the POE population (30, 33, 50, 78, 79). However, as highlighted above, further mechanistic evaluation of the effects of methadone and buprenorphine use on the developing brain and long-term outcome studies are desperately needed.

Advances in molecular neuroscience reveal the importance of the multifaceted interplay of the central and peripheral immune systems in regulating brain development and the impacts on dynamic and developing neural circuitry. Indeed, POE occurs at a critical timepoint in development that disrupts the delicate homeostatic pathways essential for proper maturation of neural and neural-immune communication and function (39–41). Recently published data suggest opioid exposure commencing *in utero* propagates inflammation and that POE shares many features of a profound neuroinflammatory disease concomitant with white matter loss and axonal injury (39–41, 80), and immune activation has implications for maladaptive opioid-induced neuroplasticity. Indeed, TLR4 binds microenvironmental toxins, such as LPS and opioids, in both fetal and maternal compartments (81). Methadone can readily cross the placenta and blood-brain barrier and can lead to direct stimulation of inflammatory pathways via TLR4-mediated signaling (82–84). By shifting these pathways towards a pro-inflammatory state, opioids alter the developing immune system, and this alteration is sustained (39, 80, 85). However, how opioids interact with TLR4 in the developing CNS and on immature neural cells is unknown.

From a broader public health perspective, clinical practice guidelines suggest that treating OUD with methadone or buprenorphine is safer than abstinence or withdrawal during pregnancy (65, 86–89). The evidence reviewed above, however, suggests that long-term neurocognitive sequelae are not fully mitigated by replacement strategies and that there is potential for untold consequences on neural cell maturation, circuit formation and plasticity. Beyond mechanistic research, we are hopeful that further preclinical work extending this study may be of use in developing translatable opioid-sparing protocols during pregnancy and in the perinatal period to further prevent neurocognitive sequelae. DTI and FC studies performed in larger cohorts of children, as they mature, would also be beneficial.

Limitations

This was a single study performed using a single model (one strain of one species with one exposure/dosage). While parallels to changes in brain structure and neurocognitive phenotypes seen in humans following POE are reassuring, it cannot be assumed that brain injury mechanisms are identical to those in human POE or that mechanisms are the same across dosing/dose timing regimens. Opioid exposure in this model occurs from E16 through P21 and may not reflect the effects of opioid exposure early in pregnancy (E0 to E15).

While we included an equal number of males and females in this investigation, our study was not powered to evaluate differences in connectivity based on sex. Further investigations into sex dependent differences, including changes in body size throughout the lifespan with opioid exposure and brain connectivity are important for identifying novel mechanisms of injury at the circuit level, for identifying at-risk individuals, and for evaluating responsiveness to novel therapeutic approaches including neuroimmunomodulation.

In vivo imaging protocols used in this study carry potential confounds from artifacts (e.g., motion, cardiac/respiratory pulsation, effects of sedation). We have attempted to mitigate the effects of these artifacts to the degree currently achievable using best practices, but confounding effects remain possible.

Conclusions

In sum, these studies connect POE to impaired neural maturation, aberrant white matter microstructure, weakened network connectivity, and fragmented neural networks in adulthood. These data emphasize the need for long-term neurodevelopmental follow-up in children with POE. In addition, a critical need exists for novel and precise diagnostic and prognostic imaging and biobehavioral biomarkers, and

elucidation of novel druggable targets for neurorepair in this vulnerable patient population. Moving forward, it is essential to understand how *in utero* insults constrain brain structure and function in adulthood, and what targeted interventions will be required to improve long-term outcomes in the countless children born exposed to opioids each year.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The animal study was reviewed and approved by the Johns Hopkins University Animal Care and Use Committee.

Author contributions

Conceptualization and design, LLJ, EMC, SR; methodology, LLJ. EMC, SR; Investigation, NM, YK, LLJ, EMC.; formal analysis, NM, YK, EMC, LLJ, SR.; writing—original draft preparation, EMC, LLJ.; writing—review and editing, all authors; supervision, LLJ; project administration, LLJ; funding acquisition, LLJ; Correspondence and Material Requests, LLJ. All authors contributed to the article and approved the submitted version.

Funding

The authors are grateful for the generous funding provided by the National Institutes of Health/National Institute of Drug Abuse 1U18DA052402 to LLJ and SR, the National Institutes of Health R01HL139492 to LLJ, the Blaustein Pain Research Fund to LLJ, the Johns Hopkins Children's Innovation fund to LLJ, the Institutional Training Grant for Clinician Scientists in Pediatric Critical Cardiopulmonary Disease (T32HL125239) to NM, and the Johns Hopkins Neurosurgery Pain Research Institute Scholars Program to EMC.

Acknowledgments

The authors are grateful for the contribution provided by Lena Wood and Ayush Bajaj.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2023.1139378/full#supplementary-material.

References

1. Honein MA, Boyle C, Redfield RR. Public health surveillance of prenatal opioid exposure in mothers and infants. *Pediatrics*. (2019) 143(3). doi: 10.1542/peds.2018-3801

2. Committee On Obstetric Practice ASoAM. Opioid Use and Opioid Use Disorder in Pregnancy The American College of Obstetricians and Gynecologists 2017;ACOG Committee Opinion(711): (August 2017).

3. Alipio JB, Brockett AT, Fox ME, Tennyson SS, deBettencourt CA, El-Metwally D, et al. Enduring consequences of perinatal fentanyl exposure in mice. *Addict Biol*. (2021) 26(2):e12895. doi: 10.1111/adb.12895

4. Vivolo-Kantor AM, Seth P, Gladden RM, Mattson CL, Baldwin GT, Kite-Powell A, et al. Vital signs: trends in emergency department visits for suspected opioid overdoses—united States, July 2016-September 2017. *MMWR Morb Mortal Wkly Rep*. (2018) 67(9):279–85. doi: 10.15585/mmwr.mm6709e1

5. Oei JL, Melhuish E, Uebel H, Azzam N, Breen C, Burns L, et al. Neonatal abstinence syndrome and high school performance. *Pediatrics*. (2017) 139(2). doi: 10.1542/peds.2016-2651

6. United States Congress. Protecting Our Infants Act of 2015. S799 2015; 114th Congress (2015–2016).

7. Howse J. March of Dimes Foundation letter of support. March 18, 2015 2015; Available at: www.marchofdimes.org/materials/HR-1462-March-of-Dimes-LetterofSupport-March-18-2015.pdf

8. World Health Organization. Guidelines for the identification and management of substance use and substance use disorders in pregnancy. Available at: http://appswhoint/iris/bitstream/10665/107130/1/9789241548731_engpdf 2016

9. Florence C, Luo F, Rice K. The economic burden of opioid use disorder and fatal opioid overdose in the United States, 2017. *Drug Alcohol Depend*. (2021) 218:108350. doi: 10.1016/j.drugalcdep.2020.108350

10. Florence CS, Zhou C, Luo F, Xu L. The economic burden of prescription opioid overdose, abuse, and dependence in the United States, 2013. *Med Care*. (2016) 54 (10):901–6. doi: 10.1097/MLR.0000000000000625

11. Ogunyankin F. Opioid exposure in newborns: lessons learned from fetal alcohol spectrum disorder. *J Public Health Policy*. (2020) 41(4):529–34. doi: 10.1057/s41271-020-00239-w

12. Monnelly VJ, Hamilton R, Chappell FM, Mactier H, Boardman JP. Childhood neurodevelopment after prescription of maintenance methadone for opioid dependency in pregnancy: a systematic review and meta-analysis. *Dev Med Child Neurol*. (2019) 61(7):750–60. doi: 10.1111/dmcn.14117

13. Patrick SW, Davis MM, Lehmann CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: united States 2009 to 2012. *J Perinatol*. (2015) 35(8):650–5. doi: 10.1038/jp.2015.36

14. Schlagal CR, Dunn TJ, Xu P, Felsing DE, Merritt CR, Manja S, et al. Maternal opioid exposure culminates in perturbed murine neurodevelopment and hyperactive

phenotype in adolescence. *Neuroscience*. (2021) 463:272–87. doi: 10.1016/j.neuroscience.2021.03.014

15. Coyle MG, Brogly SB, Ahmed MS, Patrick SW, Jones HE. Neonatal abstinence syndrome. *Nat Rev Dis Primers*. (2018) 4(1):47. doi: 10.1038/s41572-018-0045-0

16. Patrick SW, Schiff DM. Committee on substance USE, prevention. A public health response to opioid use in pregnancy. *Pediatrics*. (2017) 139(3):e20164070. doi: 10.1542/peds.2016-4070

17. Schiff DM, Patrick SW. Treatment of opioid use disorder during pregnancy and cases of neonatal abstinence syndrome. *JAMA Pediatr*. (2017) 171(7):707. doi: 10.1001/jamapediatrics.2017.0854

18. Brandt L, Finnegan LP. Neonatal abstinence syndrome: where are we, and where do we go from here? *Curr Opin Psychiatry*. (2017) 30(4):268–74. doi: 10.1097/YCO.0000000000000334

19. Haight SC, Ko JY, Tong VT, Bohm MK, Callaghan WM. Opioid use disorder documented at delivery hospitalization—united States, 1999–2014. *MMWR Morb Mortal Wkly Rep*. (2018) 67(31):845–9. doi: 10.15585/mmwr.mm6731a1

20. Sirnes E, Oltedal L, Bartsch H, Eide GE, Elgen IB, Aukland SM. Brain morphology in school-aged children with prenatal opioid exposure: a structural MRI study. *Early Hum Dev*. (2017) 106-107:33–9. doi: 10.1016/j.earlhumdev.2017.01.009

21. Nekhayeva IA, Nanovskaya TN, Deshmukh SV, Zharikova OL, Hankins GD, Ahmed MS. Bidirectional transfer of methadone across human placenta. *Biochem Pharmacol*. (2005) 69(1):187–97. doi: 10.1016/j.bcp.2004.09.008

22. Gerdin E, Rane A, Lindberg B. Transplacental transfer of morphine in man. *J Perinat Med*. (1990) 18(4):305–12. https://www.ncbi.nlm.nih.gov/pubmed/2262875 doi: 10.1515/jpme.1990.18.4.305

23. Boardman JP, Mactier H, Devlin LA. Opioids and the developing brain: time to rethink perinatal care for infants of opioid-dependent mothers. *Arch Dis Child Fetal Neonatal Ed*. (2022) 107(1):98–104. doi: 10.1136/archdischild-2020-320102

24. Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med*. (2010) 363(24):2320–31. doi: 10.1056/NEJMoa1005359

25. Sundelin Wahlsten V, Sarman I. Neurobehavioural development of preschool-age children born to addicted mothers given opiate maintenance treatment with buprenorphine during pregnancy. *Acta Paediatr*. (2013) 102(5):544–9. doi: 10.1111/apa.12210

26. Corsi DJ, Hsu H, Fell DB, Wen SW, Walker M. Association of maternal opioid use in pregnancy with adverse perinatal outcomes in Ontario, Canada, from 2012 to 2018. *JAMA Netw Open*. (2020) 3(7):e208256. doi: 10.1001/jamanetworkopen.2020.8256

27. Azuine RE, Ji Y, Chang HY, Kim Y, Ji H, DiBari J, et al. Prenatal risk factors and perinatal and postnatal outcomes associated with maternal opioid exposure in an urban, low-income, multiethnic US population. *JAMA Netw Open*. (2019) 2(6):e196405. doi: 10.1001/jamanetworkopen.2019.6405

28. Oei JL. Adult consequences of prenatal drug exposure. *Intern Med J*. (2018) 48(1):25–31. doi: 10.1111/imj.13658

29. Yen E, Davis JM. The immediate and long-term effects of prenatal opioid exposure. *Front Pediatr*. (2022) 10:1039055. doi: 10.3389/fped.2022.1039055

30. Yen E, Madan N, Tarui T, Kaneko-Tarui T, Breeze JL, Davis JM, et al. Sex-specific inflammatory and white matter effects of prenatal opioid exposure: a pilot study. *Pediatr Res*. (2022). doi: 10.1038/s41390-022-02357-5. [Epub ahead of print]

31. Caritis SN, Panigrahy A. Opioids affect the fetal brain: reframing the detoxification debate. *Am J Obstet Gynecol*. (2019) 221(6):602–8. doi: 10.1016/j.ajog.2019.07.022

32. Monnelly VJ, Anblagan D, Quigley A, Cabez MB, Cooper ES, Mactier H, et al. Prenatal methadone exposure is associated with altered neonatal brain development. *Neuroimage Clin*. (2018) 18:9–14. doi: 10.1016/j.nicl.2017.12.033

33. Nygaard E, Slinning K, Moe V, Due-Tonnessen P, Fjell A, Walhovd KB. Neuroanatomical characteristics of youths with prenatal opioid and poly-drug exposure. *Neurotoxicol Teratol*. (2018) 68:13–26. doi: 10.1016/j.ntt.2018.04.004

34. Radhakrishnan R, Elsaid NMH, Sadhasivam S, Reher TA, Hines AC, Yoder KK, et al. Resting state functional MRI in infants with prenatal opioid exposure-a pilot study. *Neuroradiology*. (2021) 63(4):585–91. doi: 10.1007/s00234-020-02552-3

35. Sirnes E, Griffiths ST, Aukland SM, Eide GE, Elgen IB, Gundersen H. Functional MRI in prenatally opioid-exposed children during a working memory-selective attention task. *Neurotoxicol Teratol*. (2018) 66:46–54. doi: 10.1016/j.ntt.2018.01.010

36. Grecco GG, Mork BE, Huang JY, Metzger CE, Haggerty DL, Reeves KC, et al. Prenatal methadone exposure disrupts behavioral development and alters motor neuron intrinsic properties and local circuitry. *Elife*. (2021) 10:e66230. doi: 10.7554/eLife.66230

37. Radhakrishnan R, Grecco G, Stolze K, Atwood B, Jennings SG, Lien IZ, et al. Neuroimaging in infants with prenatal opioid exposure: current evidence, recent developments and targets for future research. *J Neuroradiol*. (2021) 48(2):112–20. doi: 10.1016/j.neurad.2020.09.009

38. Kilkenny C, Browne WJ, Cuthill IC, Emerson M, Altman DG. Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. *PLoS Biol*. (2010) 8(6):e1000412. doi: 10.1371/journal.pbio.1000412

39. Jantzie LL, Maxwell JR, Newville JC, Yellowhair TR, Kitase Y, Madurai N, Ramachandra S, Bakhireva LN, Northington FJ, Gerner G, Tekes A, Milio LA, Brigman JL, Robinson S, Allan A. Prenatal opioid exposure: the next neonatal neuroinflammatory disease. *Brain Behav Immun*. (2020) 84:45–58. doi: 10.1016/j.bbi.2019.11.007

40. Madurai N, Kitase Y, Hamimi S, Kirk S, Sevensky R, Ramachandra S, et al. Methadone alters the peripheral inflammatory and central immune landscape following prenatal exposure in rats. *Adv Drug Alco Res*. (2022) 2:10792. doi: 10.3389/adar.2022.10792

41. Newville J, Maxwell J, Kitase Y, Robinson S, Jantzie L. Perinatal opioid exposure primes the peripheral immune system towards hyperreactivity. *Front Pediatr*. (2020) (8):272. doi: 10.3389/fped.2020.00272

42. Jantzie LL, Getsy P, Denson JL, Firl DJ, Wilson CG, Robinson S. Prenatal hypoxia-ischemia induces potassium chloride cotransporter 2 loss and abnormalities in inhibitory tone. *Front Cell Neurosci*. (2015) 3(9):347. doi: 10.3389/fncel.2015.00347

43. Robinson S, Conteh FS, Oppong AY, Yellowhair TR, Newville JC, Demerdash NE, et al. Extended combined neonatal treatment with erythropoietin plus melatonin prevents posthemorrhagic hydrocephalus of prematurity in rats. *Front Cell Neurosci*. (2018) 12:322. doi: 10.3389/fncel.2018.00322

44. Robinson S, Corbett CJ, Winer JL, Chan LAS, Maxwell JR, Anstine CV, et al. Neonatal erythropoietin mitigates impaired gait, social interaction and diffusion tensor imaging abnormalities in a rat model of prenatal brain injury. *Exp Neurol*. (2017) 302:1–13. doi: 10.1016/j.expneurol.2017.12.010

45. Robinson S, Winer JL, Berkner J, Chan LA, Denson JL, Maxwell JR, et al. Imaging and serum biomarkers reflecting the functional efficacy of extended erythropoietin treatment in rats following infantile traumatic brain injury. *J Neurosurg Pediatr*. (2016) 17(6):739–55. doi: 10.3171/2015.10.PEDS15554

46. Robinson S, Winer JL, Chan LAS, Oppong AY, Yellowhair TR, Maxwell JR, et al. Extended erythropoietin treatment prevents chronic executive functional and microstructural deficits following early severe traumatic brain injury in rats. *Front Neurol*. (2018) 9:451. doi: 10.3389/fneur.2018.00451

47. Yellowhair TR, Noor S, Maxwell JR, Anstine CV, Oppong AY, Robinson S, et al. Preclinical chorioamnionitis dysregulates CXCL1/CXCR2 signaling throughout the placental-fetal-brain axis. *Exp Neurol*. (2018) 301(Pt B):110–9. doi: 10.1016/j.expneurol.2017.11.002 (in eng)

48. Papp EA, Leergaard TB, Calabrese E, Johnson GA, Bjaalie JG. Waxholm space atlas of the sprague dawley rat brain. *Neuroimage*. (2014) 97:374–86. doi: 10.1016/j.neuroimage.2014.04.001

49. Walhovd KB, Watts R, Amlien I, Woodward LJ. Neural tract development of infants born to methadone-maintained mothers. *Pediatr Neurol*. (2012) 47(1):1–6. doi: 10.1016/j.pediatrneurol.2012.04.008

50. Walhovd KB, Westlye LT, Moe V, Slinning K, Due-Tonnessen P, Bjornerud A, van der Kouwe A, Dale AM, Fjell AM. White matter characteristics and cognition in prenatally opiate- and polysubstance-exposed children: a diffusion tensor imaging study. *AJNR Am J Neuroradiol*. (2010) 31(5):894–900. doi: 10.3174/ajnr.A1957

51. Jones DK, Knosche TR, Turner R. White matter integrity, fiber count, and other fallacies: the do's And don'ts of diffusion MRI. *Neuroimage*. (2013) 73:239–54. doi: 10.1016/j.neuroimage.2012.06.081

52. Vestal-Laborde AA, Eschenroeder AC, Bigbee JW, Robinson SE, Sato-Bigbee C. The opioid system and brain development: effects of methadone on the oligodendrocyte lineage and the early stages of myelination. *Dev Neurosci*. (2014) 36(5):409–21. doi: 10.1159/000365074

53. Sanchez ES, Bigbee JW, Fobbs W, Robinson SE, Sato-Bigbee C. Opioid addiction and pregnancy: perinatal exposure to buprenorphine affects myelination in the developing brain. *Glia*. (2008) 56(9):1017–27. doi: 10.1002/glia.20675

54. Gordon E, Nelson S. Three types of individual variation in brain networks revealed by single-subject functional connectivity analyses. *Curr Opin Behav Sci*. (2021) 40:79–86. doi: 10.1016/j.cobeha.2021.02.014

55. Kriegeskorte N, Mur M, Bandettini P. Representational similarity analysis—connecting the branches of systems neuroscience. *Front Syst Neurosci*. (2008) 2:4. doi: 10.3389/neuro.06.004.2008

56. Conradt E, Flannery T, Aschner JL, Annett RD, Croen LA, Duarte CS, et al. Prenatal opioid exposure: neurodevelopmental consequences and future research priorities. *Pediatrics*. (2019) 144(3):e20190128. doi: 10.1542/peds.2019-0128

57. Guo X, Spencer JW, Suess PE, Hickey JE, Better WE, Herning RI. Cognitive brain potential alterations in boys exposed to opiates: in utero and lifestyle comparisons. *Addict Behav*. (1994) 19(4):429–41. doi: 10.1016/0306-4603(94)90065-5

58. Konijnenberg C, Melinder A. Visual selective attention is impaired in children prenatally exposed to opioid agonist medication. *Eur Addict Res*. (2015) 21(2):63–70. doi: 10.1159/000366018

59. Konijnenberg C, Sarfi M, Melinder A. Mother-child interaction and cognitive development in children prenatally exposed to methadone or buprenorphine. *Early Hum Dev*. (2016) 101:91–7. doi: 10.1016/j.earlhumdev.2016.08.013

60. Kaltenbach K, O'Grady KE, Heil SH, Salisbury AL, Coyle MG, Fischer G, et al. Prenatal exposure to methadone or buprenorphine: early childhood developmental outcomes. *Drug Alcohol Depend*. (2018) 185:40–9. doi: 10.1016/j.drugalcdep.2017.11.030

61. Kongstorp M, Bogen IL, Stiris T, Andersen JM. Prenatal exposure to methadone or buprenorphine impairs cognitive performance in young adult rats. *Drug Alcohol Depend*. (2020) 212:108008. doi: 10.1016/j.drugalcdep.2020.108008

62. Arter S, Lambert J, Brokman A, Fall N. Diagnoses during the first three years of life for children with prenatal opioid exposure and neonatal abstinence syndrome using a large maternal infant data hub. *J Pediatr Nurs*. (2021) 61:34–9. doi: 10.1016/j.pedn.2021.03.011

63. Welton S, Blakelock B, Madden S, Kelly L. Effects of opioid use in pregnancy on pediatric development and behaviour in children older than age 2: systematic review. *Can Fam Physician*. (2019) 65(12):e544–51. https://www.ncbi.nlm.nih.gov/pubmed/31831504

64. Krans EE. Neonatal outcomes after use of buprenorphine during pregnancy. *N Engl J Med*. (2022) 387(22):2085–6. doi: 10.1056/NEJMe2212967

65. Bailey BA, Shah DS, Boynewicz KL, Justice NA, Wood DL. Impact of in utero opioid exposure on newborn outcomes: beyond neonatal opioid withdrawal syndrome. *J Matern Fetal Neonatal Med*. (2022) 35(25):9383–90. doi: 10.1080/14767058.2022.2035713

66. Patrick SW, Dudley J, Martin PR, Harrell FE, Warren MD, Hartmann KE, et al. Prescription opioid epidemic and infant outcomes. *Pediatrics*. (2015) 135(5):842–50. doi: 10.1542/peds.2014-3299

67. Lee SJ, Woodward LJ, Henderson JMT. Educational achievement at age 9.5 years of children born to mothers maintained on methadone during pregnancy. *PLoS One*. (2019) 14(10):e0223685. doi: 10.1371/journal.pone.0223685

68. Yeoh SL, Eastwood J, Wright IM, Morton R, Melhuish E, Ward M, et al. Cognitive and motor outcomes of children with prenatal opioid exposure: a systematic review and meta-analysis. *JAMA Netw Open*. (2019) 2(7):e197025. doi: 10.1001/jamanetworkopen.2019.7025

69. Lee SJ, Pritchard VE, Austin NC, Henderson JMT, Woodward LJ. Health and neurodevelopment of children born to opioid-dependent mothers at school entry. *J Dev Behav Pediatr*. (2020) 41(1):48–57. doi: 10.1097/DBP.0000000000000711

70. Schwartz AN, Reyes LM, Meschke LL, Kintziger KW. Prenatal opioid exposure and ADHD childhood symptoms: a meta-analysis. *Children*. (2021) 8(2):106. doi: 10.3390/children8020106

71. Rai Y, Chaturvedi S, Paliwal VK, Goyal P, Chourasia A, Singh Rathore RK, Yadav A, Pandey CM, Lalla RS, Garg RK, Gupta RK. DTI Correlates of cognition in term children with spastic diplegic cerebral palsy. *Eur J Paediatr Neurol*. (2013) 17(3):294–301. doi: 10.1016/j.ejpn.2012.11.005

72. Wallace EJ, Mathias JL, Ward L. The relationship between diffusion tensor imaging findings and cognitive outcomes following adult traumatic brain injury: a meta-analysis. *Neurosci Biobehav Rev*. (2018) 92:93–103. doi: 10.1016/j.neubiorev.2018.05.023

73. Yu HJ, Christodoulou C, Bhise V, Greenblatt D, Patel Y, Serafin D, et al. Multiple white matter tract abnormalities underlie cognitive impairment in RRMS. *Neuroimage*. (2012) 59(4):3713–22. doi: 10.1016/j.neuroimage.2011.10.053

74. Broussard CS, Rasmussen SA, Reefhuis J, Friedman JM, Jann MW, Riehle-Colarusso T, et al. Maternal treatment with opioid analgesics and risk for birth defects. *Am J Obstet Gynecol*. (2011) 204(4):314 e1–11. doi: 10.1016/j.ajog.2010.12.039

75. Hunt RW, Tzioumi D, Collins E, Jeffery HE. Adverse neurodevelopmental outcome of infants exposed to opiate in-utero. *Early Hum Dev*. (2008) 84(1):29–35. doi: 10.1016/j.earlhumdev.2007.01.013

76. Merhar SL, Kline JE, Braimah A, Kline-Fath BM, Tkach JA, Altaye M, He L, Parikh NA. Prenatal opioid exposure is associated with smaller brain volumes in multiple regions. *Pediatr Res*. (2021) 90(2):397–402. doi: 10.1038/s41390-020-01265-w

77. Merhar SL, Parikh NA, Braimah A, Poindexter BB, Tkach J, Kline-Fath B. White matter injury and structural anomalies in infants with prenatal opioid exposure. *AJNR Am J Neuroradiol*. (2019) 40(12):2161–5. doi: 10.3174/ajnr.A6282

78. Peterson BS, Rosen T, Dingman S, Toth ZR, Sawardekar S, Hao X, et al. Associations of maternal prenatal drug abuse with measures of newborn brain structure, tissue organization, and metabolite concentrations. *JAMA Pediatr*. (2020) 174(9):831–42. doi: 10.1001/jamapediatrics.2020.1622

79. Sikka P, Madan N, Yen E. Early white matter tract changes in neonates with prenatal opioid exposure: a pilot study. *J Perinatol*. (2022):doi: 10.1038/s41372-022-01427-0. [Epub ahead of print]

80. Vasan V, Kitase Y, Newville JC, Robinson S, Gerner G, Burton VJ, et al. Neonatal opioid exposure: public health crisis and novel neuroinflammatory disease. *Neural Regen Res*. (2021) 16(3):430–2. doi: 10.4103/1673-5374.293136

81. Chin PY, Dorian CL, Hutchinson MR, Olson DM, Rice KC, Moldenhauer LM, Robertson SA. Novel toll-like receptor-4 antagonist (+)-naloxone protects mice from inflammation-induced preterm birth. *Sci Rep*. (2016) 6:36112. doi: 10.1038/srep36112

82. Hutchinson MR, Northcutt AL, Hiranita T, Wang X, Lewis SS, Thomas J, et al. Opioid activation of toll-like receptor 4 contributes to drug reinforcement. *J Neurosci*. (2012) 32(33):11187–200. doi: 10.1523/JNEUROSCI.0684-12.2012

83. Jurga AM, Rojewska E, Piotrowska A, Makuch W, Pilat D, Przewlocka B, et al. Blockade of toll-like receptors (TLR2, TLR4) attenuates pain and potentiates buprenorphine analgesia in a rat neuropathic pain model. *Neural Plast*. (2016) 2016:5238730. doi: 10.1155/2016/5238730

84. Lewis SS, Loram LC, Hutchinson MR, Li CM, Zhang Y, Maier SF, et al. (+)-naloxone, an opioid-inactive toll-like receptor 4 signaling inhibitor, reverses multiple models of chronic neuropathic pain in rats. *J Pain*. (2012) 13(5):498–506. doi: 10.1016/j.jpain.2012.02.005

85. Allen MC, Moog NK, Buss C, Yen E, Gustafsson HC, Sullivan EL, et al. Co-occurrence of preconception maternal childhood adversity and opioid use during pregnancy: implications for offspring brain development. *Neurotoxicol Teratol*. (2021) 88:107033. doi: 10.1016/j.ntt.2021.107033

86. Jones HE, Johnson RE, Jasinski DR, O'Grady KE, Chisholm CA, Choo RE, et al. Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome. *Drug Alcohol Depend*. (2005) 79(1):1–10. doi: 10.1016/j.drugalcdep.2004.11.013

87. Jansson LM, Velez M, McConnell K, Spencer N, Tuten M, Jones HE, et al. Maternal buprenorphine treatment and fetal neurobehavioral development. *Am J Obstet Gynecol*. (2017) 216(5):529 e1–e8. doi: 10.1016/j.ajog.2017.01.040

88. Kraft WK, Adeniyi-Jones SC, Chervoneva I, Greenspan JS, Abatemarco D, Kaltenbach K, et al. Buprenorphine for the treatment of the neonatal abstinence syndrome. *N Engl J Med*. (2017) 376(24):2341–8. doi: 10.1056/NEJMoa1614835

89. Suarez EA, Huybrechts KF, Straub L, Hernandez-Diaz S, Jones HE, Connery HS, et al. Buprenorphine versus methadone for opioid use disorder in pregnancy. *N Engl J Med*. (2022) 387(22):2033–44. doi: 10.1056/NEJMoa2203318

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 27 March 2023
DOI 10.3389/fped.2023.1020716

Check for updates

OPEN ACCESS

EDITED BY
Loretta Finnegan,
Finnegan Consulting LLC, United States

REVIEWED BY
Rachana Singh,
Tufts University, United States
Pavla Pokorna,
Charles University, Czechia

*CORRESPONDENCE
Hubert O. Ballard
✉ hubie.ballard@uky.edu

SPECIALTY SECTION
This article was submitted to Neonatology, a section of the journal Frontiers in Pediatrics

RECEIVED 16 August 2022
ACCEPTED 23 February 2023
PUBLISHED 27 March 2023

CITATION
Walther H, Schadler A, Garlitz K, Bauer JA, Kohler L, Waldsmith E and Ballard HO (2023) Impact of *in utero* drug exposure on neonates requiring ECMO: A retrospective cohort study. Front. Pediatr. 11:1020716. doi: 10.3389/fped.2023.1020716

COPYRIGHT
© 2023 Walther, Schadler, Garlitz, Bauer, Kohler, Waldsmith and Ballard. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Impact of *in utero* drug exposure on neonates requiring ECMO: A retrospective cohort study

Hallie Walther[1], Aric Schadler[2], Karen Garlitz[2,3], John A. Bauer[2], Lindsay Kohler[3], Erika Waldsmith[3] and Hubert O. Ballard[2]*

[1]College of Medicine, University of Kentucky, Lexington, KY, United States, [2]Department of Pediatrics, Kentucky Children's Hospital, College of Medicine, University of Kentucky, Lexington, KY, United States, [3]College of Pharmacy, University of Kentucky, Lexington, KY, United States

The incidence of *in utero* drug exposure (IUDE) and neonatal extracorporeal membrane oxygenation (ECMO) utilization have both increased over the past decade. However, there are no studies to date that examine the impact that IUDE has on neonates requiring ECMO. In this retrospective cohort study, we compared the clinic course and outcomes of neonates who were placed on ECMO with IUDE vs. neonates without IUDE. Analysis included data extracted from medical records from all neonatal ECMO runs between January 2014 and January 2021 at the University of Kentucky Children's Hospital. A total of 56 neonatal patients were placed on ECMO during this time period and there were a total of 57 ECMO runs. Nearly one-third of neonates (16) had documented IUDE. There were no differences in gestational age, length of ECMO run, survival to discharge, or number of major complications while on ECMO in the neonates with IUDE compared to those without. In contrast, greater use of sedative and analgesic adjuvant medications during ECMO was required for IUDE-ECMO cases ($p < 0.01$). Trending results indicated that post-ECMO feeding complications and total hospitalization length were also greater in the IUDE-ECMO group. These findings illustrate the complex influence of prenatal drug exposures on neonatal patient care and warrant the development of clinical care strategies optimized for this unique patient group.

KEYWORDS

neonatal abstinence syndrome, extracorporeal membrane oxygenation (ECMO), neonate, *in utero* drug exposure, retrospective cohort analysis

Introduction

Extracorporeal membrane oxygenation (ECMO) is an advanced life-support modality used for the treatment of respiratory and cardiac failure in critically ill neonates who are not responsive to conventional therapies. The use of ECMO in neonates has increased over the past decade and was utilized 6,656 times in this patient group between 2015 and 2020 in the United States (1). Clinical outcomes for neonatal ECMO can be excellent and are often substantially better than older age pediatric patients or adults (1). A critical clinical component of successful neonatal ECMO therapy involves monitoring and maintaining a proper level of patient comfort and sedation. This typically requires continuous infusions of one or more sedative and analgesic medications (2–4) and continuous monitoring of patient status. Sedation of neonates on ECMO is complicated by numerous factors, including the pharmacokinetic variability related to gestational age and the relative circuit volume, the sequestration of drugs in the ECMO circuit, the development of tolerance to sedative medications, and ECMO-related physiologic and

metabolic alterations (5–16). The duration and severity of diseases in neonates requiring ECMO often requires a prolonged course and high doses of sedative and analgesic drugs, as well as nearly continuous assessment of sedation status and dose adjustments (3, 4, 8, 10).

A recently emerging challenge in the sedation of neonates on ECMO is related to the increasing incidence of intrauterine drug exposure (IUDE). In recent years, IUDE has risen dramatically, corresponding with the rise of the opioid epidemic (17–19). This has been especially true for the region our institution serves (the state of Kentucky and central Appalachian region of the United States). A national survey of neonatal intensive care units (NICUs) found that IUDE leading to neonatal abstinence syndrome (NAS) accounted for 4% of all NICU hospital days nationwide, with some centers reporting that over 20% of NICU days were attributed to the care of infants with NAS (17). It is, therefore, likely that the frequency of infants with IUDE who require ECMO has also increased. The impact of IUDE in neonates who are critically ill is not well-documented, but this is a likely factor complicating their hospital course. Despite the increasing number of neonates with IUDE, and the importance of sedation management in neonatal ECMO, there have been no reports describing the impact of prenatal drug exposures in this special clinical setting.

Sedation management in neonates on ECMO is challenging in all infants but is further complicated in the setting of IUDE. Exposure to drugs *in utero* can lead to tolerance to sedative medications routinely used in the NICU (20). Additionally, the withdrawal symptoms that patients with IUDE experience may necessitate increased doses of these medications to maintain neonates' comfort. To our knowledge, no studies have examined the use of sedatives in this population. Adequate sedation is essential during neonatal ECMO to avoid pain and discomfort, but oversedation and prolonged duration of sedation will make the post-ECMO course more complicated (2, 10, 21, 22). Therefore, it is crucial to gain a better understanding of how to maintain sedation goals in this population.

In this study, we sought to characterize the clinical course of neonatal patients with documented IUDE who require ECMO focusing on (1) patient outcomes, (2) sedation requirements, and (3) nutritional requirements. Comparisons were made to ECMO patients from the same institution and timeframe who did not have IUDE.

Methods

Participants

We performed a retrospective chart review of all neonatal patients placed on ECMO between January 2014 and January 2021 at the University of Kentucky Children's Hospital. A total of 56 neonates were identified; one patient was placed on ECMO twice, resulting in a total of 57 ECMO runs. No patients who received neonatal ECMO during this time period were excluded from the study. Approval for this study was obtained through the University of Kentucky Institutional Review Board (IRB).

Study design

This study was designed as a retrospective cohort. Using data extracted from medical records, we compared the clinical course of neonates that had IUDE prior to ECMO requirement vs. those only requiring ECMO at our institution. Cases involving IUDE were identified by one or more of the following: an abnormal urine drug screen during the last trimester of pregnancy identified *via* maternal medical record, enrollment of the mother in an institutional prenatal medication-assisted treatment (MAT) program, or description of drug exposure in the neonatal delivery note and/or NICU patient medical record. Due to the severity of illness and degree of patient instrumentation, we were not practically able to use clinical scoring assessments to identify NAS. Data from each neonate were analyzed for birth weight, gestational age, mode of delivery, sex, diagnosis, complications during ECMO, duration of ECMO, survival to discharge, length of stay, time until full feeds, and sedation requirements. Data on sedation included medication type, number of medications, and dosage. Total oral morphine equivalents (OME) were calculated in order to standardize the dosing comparison of the various narcotics that were utilized among patients (23). ECMO complications were reported based on ESLO guidelines. Time until full P.O. feeds was calculated by determining the date where the neonate took 100% of their feeds by mouth. If an infant received a G-tube, their total length of stay was used as their time to full P.O. feeds.

Sedation protocol

Induction and maintenance of sedation in all neonatal ECMO cases were performed identically using institutional standard clinical practice guidelines. Per NICU protocol, depth of sedation was determined hourly using the Richmond Agitation-Sedation Scale (RASS) (24) and adequate sedation was defined as a RASS score of 0 to −2 with the patient being awake, but not agitated or uncomfortable; patient status was verified hourly and dose adjustments were determined by the bedside team (including a physician, a pharmacist, and nursing specialists). During cannulation, neonates were given bolus injections of fentanyl and midazolam. Following cannulation, patients were started on a morphine drip at 10–20 μg/kg/h and midazolam drip at 0.1 mg/kg/h. Fentanyl, dexmedetomidine, phenobarbital, lorazepam, diazepam, hydromorphone, clonidine, and ketamine were each available as analgesic adjuvants. Methadone and buprenorphine were available for the treatment of withdrawal. Once stabilized on ECMO, patients underwent daily sedation holidays to prevent the development of tolerance to sedative and analgesic medications. Following sedation holidays, drips were restarted at 10% less than their prior dose. The use of

paralytic agents was minimized in order to allow for hourly neurological examination.

Statistical methods

Initial review of the collected data set showed that nearly all variables were skewed and non-normally distributed. For these reasons, we used nonparametric statistical testing between groups. Descriptive statistics were reported as median (interquartile range) for continuous variables and count (percentage) for categorical data. Categorical data about the demographic and clinical characteristics were analyzed using Pearson's chi-squared or Fisher's exact test as appropriate. Continuous variables were analyzed utilizing nonparametric methods with independent-samples difference of medians test. An alpha level of 0.05 was used to identify significance. All statistical analysis was performed using IBM SPSS Statistics version 28.

Results

ECMO patient population and baseline characteristics

Table 1 identifies the patient characteristics for neonates who received ECMO following IUDE vs. those without IUDE. During the period studied, approximately one-third of the neonatal ECMO cases at our institution had IUDE (16 of 56, 28%). The most common conditions indicating the need for ECMO in both groups were persistent pulmonary hypertension, shock, and meconium aspiration syndrome. Neonates with IUDE were more likely to have meconium aspiration syndrome than neonates without IUDE (43.8% vs. 17.5%, $p = 0.04$). The majority of neonates with and without IUDE were placed on veno-venous (VV) ECMO. Gestational age and frequency of vaginal birth were not different between groups. The birth weight of the neonates in the IUDE group tended to be lower than those without IUDE (2,868.5 g vs. 3,314.5 g, $p = 0.14$), with a greater fraction of patients less than 2 kg in the IUDE group. There was also no difference in total ECMO run time between groups.

TABLE 1 Characteristics of neonates requiring ECMO.

	ECMO only control ($n = 40$)	IUDE-ECMO ($n = 16$)	*p*-value
Patient characteristics			
Gestational age (weeks), median (IQR)	38.1 (36.6–40.0)	38.2 (35.9–39.2)	0.90
Birth weight (g), median (IQR)	3,314 (2767–3686)	2,868 (2308–3450)	0.14
Vaginal delivery, *n* (%)	20 (50)	8 (50)	1.00
Indication(s) for ECMO, *n* (%)			
PPHN	36 (92)	16 (100)	0.25
Shock	5 (31)	14 (35)	0.79
Meconium aspiration	7 (17)	7 (43)	0.04
ECMO type, *n* (%)			
VA	14 (35)	6 (37)	0.86
VV	26 (65)	10 (62)	0.82
Time to cannulation, median (IQR)			
Hours to cannulation	50.8 (32.2–85.6)	51.5 (23.9–79.3)	0.47
ECMO procedure time			
Total hours on ECMO	117.1 (85.5–150.3)	89.1 (78.89–164.0)	0.38

ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; IUDE, *in utero* drug exposure; MAS, meconium aspiration syndrome; P.O., by mouth; PPHN, persistent pulmonary hypertension of the newborn; VA, veno-arterial; VV, veno-venous.

Sedation management during ECMO

Table 2 shows the sedation and analgesic dosing requirements for the two patient groups during their ECMO runs. Despite the use of an identical standard clinical protocol for sedation management, several differences were observed between groups. Neonates with IUDE required a median of five adjuvant sedative and/or analgesic medications and neonates without IUDE required a median of three adjuvants ($p < 0.01$). IUDE in ECMO patients was associated with a more than three-fold median total

TABLE 2 Sedation and analgesic requirements during ECMO.

	ECMO only control ($n = 40$)	IUDE-ECMO ($n = 16$)	*p*-value
	Median (IQR)	Median (IQR)	
Agent and dose requirement (mg/kg)			
Morphine			
Drip	19.9 (11.9–36.4)	34.4 (15.0–100.5)	0.14
Bolus	3.5 (2.2–8.5)	7.0 (3.0–13.8)	0.38
Oral	0.5 (0–6.6)	0 (0–8.4)	0.77
Fentanyl			
Drip	0 (0–0)	0 (0–0)	0.68
Bolus	10.7 (0.0–25.0)	23.5 (2.5–51.4)	0.14
Hydromorphone drip			
Drip	0 (0–0)	0 (0–0)	0.03
Bolus	0 (0–0)	0 (0–0)	0.14
Methadone	0 (0–0)	0 (0–8.0)	0.01
Diazepam	0 (0–0)	0 (0–13.5)	0.08
Midazolam			
Drip	8.9 (0.6–24.0)	15.0 (0.7–77.0)	0.77
Bolus	3.7 (1.2–6.3)	4.9 (1.5–13.0)	0.77
Phenobarbital bolus	0 (0–1.0)	0 (0–2.3)	0.89
Dexmedetomidine drip	0 (0–8.9)	49.5 (0–170.5)	0.08
Composite measures			
Total oral morphine equivalents	77.1 (47.2–167.0)	245.7 (89.7–639.3)	0.14
Total no. of adjuvants	3 (2–4)	5 (3.25–7.7)	<0.01
Total morphine equivalents per hour of ECMO runtime	0.7 (0.4–1.3)	1.49 (0.7–4.2)	<0.01

ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; IUDE, *in utero* drug exposure.

10.3389/fped.2023.1020716

dose of oral morphine equivalents over the course of their ECMO run compared to neonates without IUDE (246 vs. 77.1 mg/kg), although this was marginally significant. When the total morphine equivalents used for each patient were normalized to the actual ECMO run time, there was a striking difference between groups: IUDE cases required two-fold greater morphine equivalents per hour of ECMO (0.7 vs. 1.49 mg/kg/h, $p < 0.01$).

Clinical outcomes following ECMO

Table 3 shows comparisons of clinical outcomes following ECMO for the two groups (IUDE vs. no IUDE). No difference was seen in survival to discharge in the neonates with IUDE vs. those without IUDE (75.0% vs. 90.0%, $p = 0.18$). Neonates with IUDE required the same amount of time on oxygen (28.0 vs. 20.0, $p = 0.49$) and ventilatory support (17.0 vs. 14.5, $p = 0.38$) than neonates without IUDE. However, trending results show that neonates with IUDE did require a longer length of stay than those without IUDE (41.0 vs. 31.5 days, $p = 0.10$).

Nutrition

There was no difference observed in the percentage of neonates with and without IUDE who reached full P.O. feeds by the time of discharge (69.4% vs. 58.3%, $p = 0.48$) (Table 2). Of these infants, it took a median length of 40 days for neonates with IUDE to reach full P.O. feeds compared to 19 days in neonates without IUDE ($p = 0.24$) (Table 3). There was also no difference seen in the amount who required a G-tube (25.0% vs. 16.7%, $p = 0.67$) (Table 2).

TABLE 3 Clinical outcomes following ECMO.

	ECMO only control ($n = 40$)	IUDE-ECMO ($n = 16$)	p-value
Clinical outcome, *n* (%)			
Survival to discharge	36 (90.0)	12 (75.0)	0.21
ECMO complications			
Intracranial hemorrhage	9 (22)	2 (12)	0.48
Sepsis	3 (7)	1 (6)	1.00
Days on oxygen, median (IQR)	20 (14.3–30.5)	28 (14.0–57.0)	0.49
Days on ventilator, median (IQR)	14.5 (11.0–19.0)	17 (12.0–28.75)	0.38
Length of stay, median (IQR)	31.5 (22.3–48.8)	41 (26.3–74.5)	0.10
Post-ECMO feeding complications			
Days until full P.O. feeds, median (IQR)[a]	19 (14.0–42.0)	40 (14.5–84.3)	0.24
Full P.O. feeds by discharge, *n* (%)[a]	25 (69.4)	7 (58.3)	0.48
Gastric tube, *n* (%)[a]	6 (16.7)	3 (25.0)	0.67

ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; IUDE, *in utero* drug exposure.
[a]Only infants who survived until discharge were included in this analysis.

Discussion

Despite a steady rise in numbers of prenatally drug-exposed infants along with an established clinical value and excellent outcomes for neonates receiving ECMO, little is known about the overlay of these two aspects of neonatal intensive care. In this retrospective cohort study, we examined the role that IUDE plays in the treatment and outcomes of neonates requiring ECMO in order to improve sedation and medical management in this vulnerable population. We observed that neonates with and without IUDE did not differ in rates of survival to discharge or the number or type of morbidities. However, neonates with IUDE + ECMO do require more adjuvant therapies for sedation during ECMO. Trending data indicate that neonates with IUDE required greater than 300% higher doses of oral morphine equivalents, may experience more feeding difficulty than those without IUDE, and have a longer length of stay.

Previous studies on neonates who require ECMO show the development of tolerance and the consequent need for increased sedation over the course of their hospital stay (4, 10, 25). This is consistent with our findings that showed all neonates, regardless of the presence of IUDE, required an increase in the amount of sedation and analgesic medication throughout their hospitalization. This was particularly true for neonates with IUDE. The increased sedation requirements for neonates with IUDE is likely due to the increased pain and discomfort experienced secondary to drug withdrawal as well as the development of tolerance to sedative medications *in utero*. In addition, the rapid clearance of maternal drugs from the ECMO circuit may have resulted in earlier and more severe symptoms of withdrawal in neonates with IUDE. Our findings are consistent with studies in adult populations that found the need for higher doses of sedation in patients with previous exposure to opioids or sedative medications (26–28).

Opioid treatment in neonates has been associated with a delay in attainment of full oral feeds (29, 30). This is consistent with our trending results that indicate that neonates with IUDE may take twice as long to reach full oral feeds compared to those without IUDE. The time it takes neonates to reach full oral feeds is a major determinant of length of stay (31, 32). These studies suggest that feeding ability plays a crucial role in determining the length of hospital stay in neonates who require ECMO. Given the role feeding ability plays in length of stay, the delay seen in reaching full oral feeds in neonates with IUDE might explain their increased length of stay compared to neonates without IUDE.

As a result of the findings from this investigation, Kentucky Children's Hospital has developed new clinical practice guidelines (CPG) for the sedation of neonates with IUDE requiring ECMO. These updated guidelines address the increased need for sedative and analgesic medications in neonates with IUDE who are put on ECMO. The CPG include the following: (1) no sedation holidays; (2) use of methadone as the primary medication to control withdraw symptoms; (3) start methadone treatment at 0.3 mg every 12 h, dose can be increased daily by 0.05 mg to a maximum dose of 0.2 mg/kg/dose; (4) consider adding clonidine,

phenobarbital, or diazepam as adjuvants therapies; and (5) wean morphine and increase methadone once the neonate is captured. The updated CPG was not used on any neonates in this study. Prospective, multicenter studies should be performed to evaluate the efficacy of the new CPG in controlling the comfort level of neonates with IUDE who require ECMO.

The findings of this study are subject to limitations, which include the small sample size and retrospective study design limited types of analyses we were able to perform. This led to results that were clinically significant but in some cases did not reach the level of statistical significance. Examples of this discrepancy are seen as the number of days it took neonates to reach full oral feeds and the total OME required for pain control and sedation. Additionally, we did not have information on the frequency, timing, or type of drugs that the neonates were exposed to *in utero*. It is possible that these factors impacted the severity of withdraw in the neonates and their response to drugs given in the NICU. For practical reasons, we were also unable to diagnose neonates with IUDE with NAS or capture clinical characteristics of this condition using a standardized scoring system given the critical nature of their illness. We note that our institution is the only level 4 NICU offering ECMO life support to children throughout our region, an area that has been one of the hardest hit from the opiate abuse epidemic (e.g., Central and Eastern Kentucky and Mid-Appalachian US). For these reasons, our patient experiences thus far may be leading other sites, and future studies should include collaborations with other centers to increase the cohort size and to refine and improve clinical guidelines for this unique patient group.

This retrospective study is the first to analyze the impact that IUDE has on the treatment of neonates requiring ECMO life support. We found that neonates with IUDE who require ECMO had no change in survival to discharge or ECMO complications than neonates without IUDE requiring ECMO. However, IUDE was associated with increased need for sedation and analgesic requirements, longer length of hospitalization, and overall more complex care. Our observations suggest that refined strategies and clinical guidelines for this special patient group may be warranted, as well as prospective studies to develop optimized clinical care for improvements in clinical course and outcomes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

All authors contributed to the idea generation and execution, data collection and analysis, and manuscript preparation. All authors contributed to the article and approved the submitted version.

Funding

The Department of Pediatrics at the University of Kentucky has paid the cost of publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. ECMO Registry of the Extracorporeal Life Support Organization (ELSO). Ann Arbor, Michigan (2020). Available at: https://www.elso.org/registry/internationalsummaryandreports/reports.aspx#UnitedStatesOctober2020.

2. Anand KJ, Barton BA, McIntosh N, Lagercrantz H, Pelausa E, Young TE, et al. Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN trial. Neonatal outcome and prolonged analgesia in neonates. *Arch Pediatr Adolesc Med.* (1999) 153(4):331–8. doi: 10.1001/archpedi.153.4.331

3. Shekar K, Roberts JA, Mullany DV, Corley A, Fisquet S, Bull TN, et al. Increased sedation requirements in patients receiving extracorporeal membrane oxygenation for respiratory and cardiorespiratory failure. *Anaesth Intensive Care.* (2012) 40(4):648–55. doi: 10.1177/0310057X1204000411

4. Schneider JB, Sweberg T, Asaro LA, Kirby A, Wypij D, Thiagarajan RR, et al. Sedation management in children supported on extracorporeal membrane oxygenation for acute respiratory failure. *Crit Care Med.* (2017) 45(10):e1001–10. doi: 10.1097/CCM.0000000000002540

5. Buck ML. Pharmacokinetic changes during extracorporeal membrane oxygenation: implications for drug therapy of neonates. *Clin Pharmacokinet.* (2003) 42(5):403–17. doi: 10.2165/00003088-200342050-00001

6. Shekar K, Fraser JF, Smith MT, Roberts JA. Pharmacokinetic changes in patients receiving extracorporeal membrane oxygenation. *J Crit Care.* (2012) 27(6):741.e9–e18. doi: 10.1016/j.jcrc.2012.02.013

7. Wildschut ED, Hanekamp MN, Vet NJ, Houmes RJ, Ahsman MJ, Mathot RA, et al. Feasibility of sedation and analgesia interruption following cannulation in neonates on extracorporeal membrane oxygenation. *Intensive Care Med.* (2010) 36 (9):1587–91. doi: 10.1007/s00134-010-1931-4

8. Dagan O, Klein J, Bohn D, Koren G. Effects of extracorporeal membrane oxygenation on morphine pharmacokinetics in infants. *Crit Care Med.* (1994) 22 (7):1099–101. doi: 10.1097/00003246-199407000-00008

9. Ahsman MJ, Hanekamp M, Wildschut ED, Tibboel D, Mathot RA. Population pharmacokinetics of midazolam and its metabolites during venoarterial extracorporeal membrane oxygenation in neonates. *Clin Pharmacokinet.* (2010) 49 (6):407–19. doi: 10.2165/11319970-000000000-00000

10. Arnold JH, Truog RD, Orav EJ, Scavone JM, Hershenson MB. Tolerance and dependence in neonates sedated with fentanyl during extracorporeal membrane oxygenation. *Anesthesiology.* (1990) 73(6):1136–40. doi: 10.1097/00000542-199012000-00011

11. Tobias JD. Tolerance, withdrawal, and physical dependency after long-term sedation and analgesia of children in the pediatric intensive care unit. *Crit Care Med*. (2000) 28(6):2122–32. doi: 10.1097/00003246-200006000-00079

12. Mulla H, McCormack P, Lawson G, Firmin RK, Upton DR. Pharmacokinetics of midazolam in neonates undergoing extracorporeal membrane oxygenation. *Anesthesiology*. (2003) 99(2):275–82. doi: 10.1097/00000542-200308000-00008

13. Nasr VG, Meserve J, Pereira LM, Faraoni D, Brediger S, Goobie S, et al. Sedative and analgesic drug sequestration after a single bolus injection in an ex vivo extracorporeal membrane oxygenation infant circuit. *ASAIO J*. (2019) 65(2):187–91. doi: 10.1097/MAT.0000000000000793

14. Shekar K, Roberts JA, McDonald CI, Fisquet S, Barnett AG, Mullany DV, et al. Sequestration of drugs in the circuit may lead to therapeutic failure during extracorporeal membrane oxygenation. *Crit Care*. (2012) 16(5):R194. doi: 10.1186/cc11679

15. Wildschut ED, Ahsman MJ, Allegaert K, Mathot RA, Tibboel D. Determinants of drug absorption in different ECMO circuits. *Intensive Care Med*. (2010) 36 (12):2109–16. doi: 10.1007/s00134-010-2041-z

16. Mehta NM, Halwick DR, Dodson BL, Thompson JE, Arnold JH. Potential drug sequestration during extracorporeal membrane oxygenation: results from an ex vivo experiment. *Intensive Care Med*. (2007) 33(6):1018–24. doi: 10.1007/s00134-007-0606-2

17. Tolia VN, Patrick SW, Bennett MM, Murthy K, Sousa J, Smith PB, et al. Increasing incidence of the neonatal abstinence syndrome in U.S. neonatal ICUs. *N Engl J Med*. (2015) 372(22):2118–26. doi: 10.1056/NEJMsa1500439

18. Winkelman TNA, Villapiano N, Kozhimannil KB, Davis MM, Patrick SW. Incidence and costs of neonatal abstinence syndrome among infants with Medicaid: 2004–2014. *Pediatrics*. (2018) 141(4):e20173520. doi: 10.1542/peds.2017-3520

19. Strahan AE, Guy GP Jr., Bohm M, Frey M, Ko JY. Neonatal abstinence syndrome incidence and health care costs in the United States, 2016. *JAMA Pediatr*. (2020) 174(2):200–2. doi: 10.1001/jamapediatrics.2019.4791

20. Hudak ML, Tan RC. Neonatal drug withdrawal. *Pediatrics*. (2012) 129(2): e540–60. doi: 10.1542/peds.2011-3212

21. Davidson A, Flick RP. Neurodevelopmental implications of the use of sedation and analgesia in neonates. *Clin Perinatol*. (2013) 40(3):559–73. doi: 10.1016/j.clp.2013.05.009

22. Ista E, van Dijk M, Gamel C, Tibboel D, de Hoog M. Withdrawal symptoms in children after long-term administration of sedatives and/or analgesics: a literature review. "assessment remains troublesome". *Intensive Care Med*. (2007) 33 (8):1396–406. doi: 10.1007/s00134-007-0696-x

23. Nielsen S, Degenhardt L, Hoban B, Gisev N. A synthesis of oral morphine equivalents (OME) for opioid utilisation studies. *Pharmacoepidemiol Drug Saf*. (2016) 25(6):733–7. doi: 10.1002/pds.3945

24. Kerson AG, DeMaria R, Mauer E, Joyce C, Gerber LM, Greenwald BM, et al. Validity of the Richmond Agitation-Sedation Scale (RASS) in critically ill children. *J Intensive Care*. (2016) 4:65. doi: 10.1186/s40560-016-0189-5

25. Rosen DA, Rosen KR. Midazolam for sedation in the paediatric intensive care unit. *Intensive Care Med*. (1991) 17(Suppl 1):S15–9. doi: 10.1007/BF01731149

26. Treu CN, Groth CM, Patel JH. The use of continuous ketamine for analgesia and sedation in critically ill patients with opioid abuse: a case series. *J Crit Care Med (Targu Mures)*. (2017) 3(4):148–52. doi: 10.1515/jccm-2017-0026

27. Vadivelu N, Mitra S, Kaye AD, Urman RD. Perioperative analgesia and challenges in the drug-addicted and drug-dependent patient. *Best Pract Res Clin Anaesthesiol*. (2014) 28(1):91–101. doi: 10.1016/j.bpa.2014.02.003

28. Rapp SE, Ready BL, Nessly ML. Acute pain management in patients with prior opioid consumption: a case-controlled retrospective review. *Pain*. (1995) 61 (2):195–201. doi: 10.1016/0304-3959(94)00168-E

29. Menon G, Boyle EM, Bergqvist LL, McIntosh N, Barton BA, Anand KJ. Morphine analgesia and gastrointestinal morbidity in preterm infants: secondary results from the NEOPAIN trial. *Arch Dis Child Fetal Neonatal Ed*. (2008) 93(5): F362–7. doi: 10.1136/adc.2007.119297

30. Bellù R, de Waal KA, Zanini R. Opioids for neonates receiving mechanical ventilation. *Cochrane Database Syst Rev*. (2005) (1):Cd004212. doi: 10.1002/14651858.CD004212.pub2

31. Jadcherla SR, Berseth CL. Antroduodenal motility and feeding outcome among neonatal extracorporeal membrane oxygenation survivors. *J Pediatr Gastroenterol Nutr*. (2005) 41(3):347–50. doi: 10.1097/01.mpg.0000174331.00711.6d

32. Jackson BN, Kelly BN, McCann CM, Purdy SC. Predictors of the time to attain full oral feeding in late preterm infants. *Acta Paediatr*. (2016) 105(1):e1–6. doi: 10.1111/apa.13227

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 18 April 2023
DOI 10.3389/fped.2023.1118634

Check for updates

OPEN ACCESS

EDITED BY
Eugene Dempsey,
University College Cork, Ireland

REVIEWED BY
Balaji Govindaswami,
Valley Medical Center Foundation,
United States
Pavla Pokorna,
Charles University, Czechia

*CORRESPONDENCE
Ruth Hamilton
✉ ruth.hamilton@glasgow.ac.uk

SPECIALTY SECTION
This article was submitted to Neonatology, a section of the journal Frontiers in Pediatrics

RECEIVED 07 December 2022
ACCEPTED 22 March 2023
PUBLISHED 18 April 2023

CITATION
Spowart KM, Reilly K, Mactier H and Hamilton R (2023) Executive functioning, behavioural, emotional, and cognitive difficulties in school-aged children prenatally exposed to methadone.
Front. Pediatr. 11:1118634.
doi: 10.3389/fped.2023.1118634

COPYRIGHT
© 2023 Spowart, Reilly, Mactier and Hamilton. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Executive functioning, behavioural, emotional, and cognitive difficulties in school-aged children prenatally exposed to methadone

Katherine M. Spowart[1], Kasey Reilly[1], Helen Mactier[2,3] and Ruth Hamilton[3,4]*

[1]Specialist Children's Services, NHS Greater Glasgow and Clyde, Glasgow, United Kingdom, [2]Princess Royal Maternity, NHS Greater Glasgow and Clyde, Glasgow, United Kingdom, [3]College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, United Kingdom, [4]Department of Clinical Physics and Bioengineering, Royal Hospital for Children, NHS Greater Glasgow and Clyde, Glasgow, United Kingdom

Aim: The aim of this study was to examine executive function and emotional and behavioural difficulties of children aged between 8 and 10 years who had been prenatally exposed to methadone, compared to non-exposed peers.
Methods: Prospective study: third follow-up of an original cohort of 153 children born to methadone-maintained opioid-dependent mothers 2008–2010: previous investigations were at 1–3 days and at 6–7 months of age. Carers completed the Strength and Difficulties Questionnaire (SDQ) and the Behaviour Rating Inventory of Executive Function, Second Edition (BRIEF®2). Results were compared between exposed and non-exposed groups.
Results: Carers of 33 of 144 traceable children completed the measures. SDQ responses showed no group differences on subscales of emotional symptoms, conduct problems, or peer relationship problems. A marginally higher proportion of exposed children had a high or very high hyperactivity subscale score. Exposed children scored significantly higher on BRIEF®2 behavioural, emotional, and cognitive regulation indices, and on the global executive composite. After controlling for potentially confounding higher reported maternal tobacco use in the exposed group *via* regression modelling, the effect of methadone exposure reduced.
Interpretation: This study supports evidence that methadone exposure *in utero* is associated with adverse neurodevelopmental outcomes in childhood. Challenges in studying this population include difficulties with long-term follow-up and controlling for potentially confounding factors. Further investigation of the safety of methadone and other opioids in pregnancy must include consideration of maternal tobacco use.

KEYWORDS

prenatal methadone exposure, cognition, behaviour, long-term outcomes, prenatal tobacco exposure

1. Introduction

Opioid use in pregnancy has been widely reported to cause significant harm to children, evident both in the neonatal period and in later childhood (1, 2). In the neonatal period, children may suffer from neonatal abstinence syndrome/neonatal opioid withdrawal syndrome (NAS/NOWS) with prolonged hospital admission and/or maternal/infant

separation and necessity for pharmaceutical treatment. The development of overt NAS/NOWS is not a prerequisite for adverse childhood outcome(s) (1), but the association of illicit opioid use with multiple obstetric complications may further impact longer-term outcomes (2, 3). Methadone is commonly used to manage opioid misuse in pregnancy with current guidelines stating that this practice is safe other than the risk of NAS/NOWS (4, 5). This advice does not concur with increasing evidence that prenatal opioid exposure is associated with increased risk of adverse neurodevelopmental outcomes, specifically impaired infant cognition and psychomotor performance, impaired early childhood internalising and externalising behaviour, and attention problems (6–9). Difficulties with executive functioning, vision (8), language, and regulation (9) are also reported.

Neurodevelopmental outcomes in later childhood and adolescence are less well understood although it would be predicted that lower cognitive performance in children aged over 2 years would carry a risk of longer-term difficulties (10). Indeed, in a longitudinal study of children prenatally exposed to opioids, group differences in cognition, attention, and behaviour had widened by 8 years of age (11, 12). Lower cognitive function compared to non-opioid-exposed controls has been described in 17- to 21-year-old youths although their performance was within normal limits (13). Unfortunately, studies in this field are limited methodologically because of the challenges of identifying polydrug and other licit [including tobacco (14) and alcohol] exposures, and the potentially confounding effects of these additional drug exposures as well as adverse pregnancy or neonatal illness, ill-health associated with poor socioeconomic status, and suboptimal childhood environment.

A prospective cohort study of infants born to methadone-maintained opioid-dependent (MMOD) mothers established polydrug exposures *via* both maternal and infant toxicology and recruited a comparison group matched for major confounding factors. The study was designed to investigate visual outcomes and found impaired neonatal visual evoked potentials (15) and significant visual problems at 6 months (16) and at 8–10 years. A subgroup of the cohort attended at 8–10 years for detailed visual investigation and both neurodevelopmental and behavioural enquiry. The aim of this study arm was to compare results of neurodevelopmental/behavioural carer-completed questionnaires at 8–10 years between exposed and comparison children.

2. Methods

2.1. Participants

Participants comprised 33 of 144 (98 exposed, 46 comparison) traceable children followed up at ages of 8–10 years. Exposed children ($n = 21$) were born to MMOD mothers and comparison (non-exposed) children ($n = 12$) were born contemporaneously (2008–2010) at the same maternity hospital. All were born after 36 weeks' gestation; none had congenital ocular abnormality or significant neonatal illness. Prenatal drug exposure of infants born to MMOD mothers was established *via* maternal urine, infant urine and meconium, maternal casenote review, and confidential interview (15). A subgroup of comparison infants had meconium drug analysis. For both exposed and non-exposed newborns, a subset of meconium samples was analysed for prenatal alcohol exposure (PAE), with a fatty acid ethyl ester (FAEEs) concentration ≥10,000 ng/g considered to represent significant PAE (17). Comparison infants were matched at recruitment for completed week of gestation, birthweight (±250 g) and socioeconomic status [Carstairs deprivation index using postcode of residence (±1)] (18) and partially matched for maternal tobacco use. Selection bias was likely to be low due to the high consent rate (98%) at recruitment (19). Characteristics of the 33 children are detailed in **Table 1**. The 33 attending children closely matched the non-attending traceable children ($n = 111$) for birth characteristics and drug exposure.

Exposed children were considered to have developed NAS/NOWS if they received pharmaceutical treatment according to the well-established hospital protocol. Oral morphine replacement was commenced (60 μg/kg × 6 per day) and weaned (usually by 10 μg/kg/day as symptoms diminished) when two consecutive 12-h scores >5 on a modified Lipsitz scale (20) were recorded in conjunction with poor feeding/weight gain. Second line phenobarbital was added when morphine treatment was unsuccessful (minority of babies). The median length of morphine treatment was 10 days; phenobarbital, if required, was generally weaned and discontinued by 6 weeks of age. All children had been prenatally exposed to methadone; most were exposed to additional drugs (**Figure 1**). Casenotes were reviewed for any attendance at hospital eye services, care arrangements (birth parent, adopted, or kinship or foster care), supported learning, or diagnosis of autistic spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and/or foetal alcohol spectrum disorder (FASD). Casenote review was performed by researchers masked to exposure status with limited bias potential as data collected were previously documented, objective findings.

2.2. Assessments

A paediatric research nurse documented care and education status, height, weight, and occipitofrontal head circumference (OFC). Detailed visual assessments were undertaken with predetermined fail criteria (acuity poorer than 0.2 logMAR not attributable to refractive error; any manifest strabismus or any nystagmus; inability to overcome any base-out prisms; or a Frisby stereothreshold >110 arcsec). A researcher applied two child behaviour questionnaires to accompanying adults, assisting where necessary and encouraging completion of all questions.

The Strengths and Difficulties Questionnaire (SDQ) (21) is a 25-item emotional and behavioural screening questionnaire with five subscales: emotional problems, conduct problems, hyperactivity and peer problems where high scores indicate more problems, and a prosocial subscale where high scores indicate fewer problems. Each item is scored on a Likert scale (not

TABLE 1 Characteristics of exposed and comparison children.

Maternal, birth, and neonatal characteristics	Exposed children ($n = 21$)	Comparison children ($n = 12$)	Difference (95% CI)	Test, p-value
Sex, (n) % male	(10) 48%	(3) 25%	23% (−12% to 48%)	FE, $p = 0.18$
Gestation, week[a]	39.4 (37.8–40.4)	39.9 (38.4–41.0)	−0.6 (−1.9 to 0.4)	MW, $p = 0.28$
Birthweight, g[b]	2,878 (448)	3,114 (550)	−236 (−626 to 154)	t-test, $p = 0.22$
Birth occipitofrontal head circumference, cm[b]	33.3 (1·8)	34.1 (1.7)	−0.8 (−2.1 to 0.5)	t-test, $p = 0.23$
Maternal tobacco use, (n) %	(21) 100%	(8) 67%	33% (3% to 33%)	χ^2, $p = 0.012$
Reported cigarettes per day[a]	10 (10–15)	10 (0–10)	5 (0 to 10)	MW, $p = 0.043$
Known prenatal alcohol exposure, (n) %	6/15, 40%	1/5[c], 20%	20% (−23% to 63%)	FE, $p = 0.4$
Maternal body mass index[a]	23 (21–25)	25 (22–33.75)	−3 (−8 to 0)	MW, $p = 0.08$
Maternal Carstairs deprivation index[a]	7 (4.5–7)	6.5 (5–7)	0 (−1 to 1)	MW, $p = 0.9$
NAS/NOWS, (n) %	(14) 67%	—	—	—
Drug exposure, (n) %				
Methadone	(21) 100%	0/7 tested		
Prescribed dose at delivery (mg/day)[a]	55 (40–80)	—		
Opiates	(19) 90%	0/7 tested		
Benzodiazepines	(16) 76%	1/7 tested		
Cannabis	(13) 62%	1/7 tested		
Amphetamine	(3) 14%	1/7 tested		
Cocaine	(4) 19%	0/7 tested		
Follow-up demographics and outcomes				
Age, years[b]	9.3 (0.7)	9.3 (0.7)	0.1 (−0.6 to 0.4)	t-test, $p = 0.7$
Birth mother deceased, (n) %	(3) 14%	(0) 0%	14% (−12% to 35%)	FE, $p = 0.24$
Adopted or in foster/kinship care, (n) %	(10) 48%	(3) 25%	23% (−12% to 48%)	FE, $p = 0.18$
Learning support at school, (n) %	(5/18) 28%	(1) 8%	19 (−12 to 44)	χ^2, $p = 0.20$
Height, cm[b]	135 (7.1)	135 (5.4)	0.3 (−5 to 4)	t-test, $p = 0.9$
Weight, kg[b]	31.6 (7.5)	34.3 (8.1)	−2.6 (−8.6 to 3.3)	t-test, $p = 0.37$
Head circumference, cm[b]	53.0 (2.0)	53.3 (1.1)	−0.3 (−1.4 to 0.8)	t-test, $p = 0.6$
Visual outcome "fail," (n) %	(14) 67%	(2) 17%	50% (8% to 71%)	FE, $p = 0.01$

CI, confidence interval; FE, Fisher's exact test; MW, Mann–Whitney test; NAS/NOWS, neonatal abstinence syndrome/neonatal opioid withdrawal syndrome requiring pharmaceutical treatment; PAE, prenatal alcohol exposure.

[a]Median (interquartile range).

[b]Mean (standard deviation).

[c]Due to data loss, PAE status is known only for one comparison child: denominator is unknown but assumed to be $n = 5$ based on neonatal data proportions.

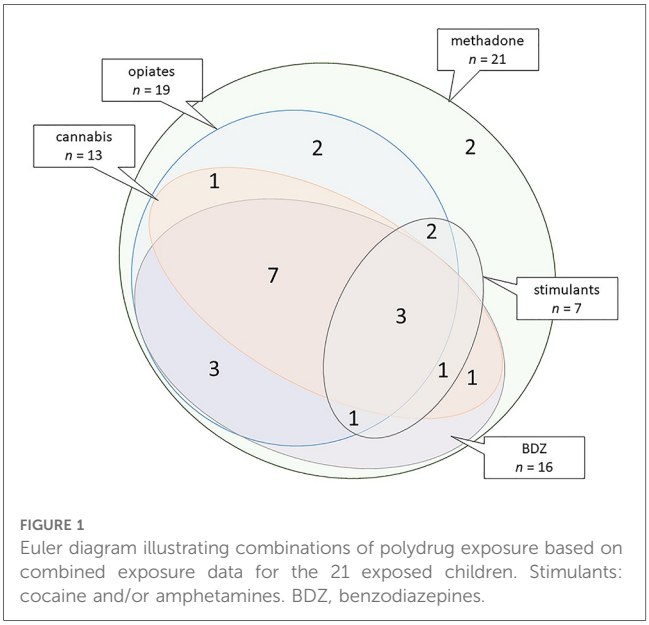


FIGURE 1
Euler diagram illustrating combinations of polydrug exposure based on combined exposure data for the 21 exposed children. Stimulants: cocaine and/or amphetamines. BDZ, benzodiazepines.

true = 0; somewhat true = 1, certainly true = 2) with possible subscales scores of 0–10. The total difficulties score is the sum of scores for the first four subscales (possible values 0–40). Scores are categorised as follows: close to average, slightly raised, high, or very high using "parent-completed" scores relative to a large UK reference population (22). The SDQ has high reliability, validity (23), and good concurrent validity (24, 25).

The Behaviour Rating Inventory of Executive Function, 2nd edition (BRIEF®2) (26) is a clinical rating scale of executive function comprising three regulation indices and a global executive composite (GEC). The behavioural regulation index (BRI) measures the child's ability to regulate and monitor their behaviour effectively and consists of "inhibit" and "self-monitor" scales. The emotion regulation index (ERI) measures the child's ability to regulate their emotional responses and to adjust to changes in environment, people, plans or demands, and consists of "shift" and "emotional" scales. The cognitive regulation index (CRI) measures the child's ability to control and manage cognitive processes and to problem solve, and consists of

"initiation," "working memory," "planning," "task-monitor," and "organisation of materials" scales. The GEC is a summed score of all nine scales. The three indices and the GEC are expressed as *T*-scores. Scores are categorised as follows: mildly elevated (60–64 inclusive), potentially clinically elevated (65–69 inclusive), or clinically elevated (≥70). The test design incorporates checks for inconsistency (respondent answered similar items in an inconsistent manner), infrequency (respondent endorsed unlikely events), and negativity (respondent answered in an unusually negative manner) with criteria for exclusion.

Questionnaires were independently scored by two researchers (RH and KMS) and interpreted and analysed by researchers (KMS and KR) qualified to do so. Researchers were masked to exposure status to limit bias potential. Assessments took place at the paediatric Clinical Research Facility, Queen Elizabeth University Hospital campus, Glasgow, United Kingdom, between January 2018 and February 2020. Any child causing medical or social concern not already being addressed was notified to relevant services after discussion with their carer. Families were offered reimbursement of expenses and the child was given a £20 voucher. Written informed consent was given by the child's legal guardian; children gave written informed assent. The study was approved by West of Scotland Research Ethics Committee 3 (17/WS/0093).

2.3. Data analysis

SDQ scores were compared between exposed and comparison children using Mann–Whitney *U* tests; proportions of children with scores classified as "high/low" or "very high/low" were compared using Fisher's exact test. BRIEF®2 scores were compared between exposed and comparison children using *t*-tests without the assumption of equal variance; proportions of children with scores classified as "potentially clinical elevated" or "clinically elevated" were compared using Fisher's exact tests. To assess potential confounders, factors differing meaningfully between exposed and comparison children were treated as predictor variables in regression models of BRIEF®2 scores. SDQ total difficulties and BRIEF®2 GEC scores were compared using linear correlation to investigate whether an elevated score on one questionnaire was associated with an elevated score on the other. Findings were compared qualitatively with neurodevelopmental assessment undertaken at 6 months of age using the Griffiths Mental Development Scales (27). Findings for exposed children were compared for those who had and had not required treatment for NAS/NOWS (SDQ scores, Mann–Whitney *U* tests; BRIEF®2 scores, unpaired *t*-tests without assumption of equal variance). The relation between prescribed maternal methadone dose at delivery and questionnaire scores was investigated using scatter plots. Analyses were performed using SPSS® Statistics v24.0 (IBM Corp., Armonk, NY, United States), Minitab® v20.3 (Minitab LLC, PA, United States), and MedCalc® v20.014 (MedCalc Software Ltd, Ostend, Belgium).

3. Results

Exposed and comparison children did not differ in neonatal characteristics except for maternal tobacco use: all MMOD mothers but only two-thirds of comparison mothers smoked tobacco cigarettes (Table 1). Groups did not differ in childhood characteristics except for a greater fail rate on vision assessment for exposed children (Table 1). Individual child characteristics are shown in Table 2.

3.1. SDQ

All SDQ screening questionnaires ($n = 33$) were completed adequately. Details of accompanying adult who completed the SDQ (e.g., birth mother, grandparent, etc.) are given in Table 2. Exposed children and comparison children scored similarly on all subscales and total difficulties scores. Similar proportions of exposed and comparison children had "high" or "very high" scores in three subscales and in total difficulties. A marginally greater proportion of exposed children had "high" or "very high" scores on the hyperactivity subscale (more children with hyperactive behaviour, Table 3).

3.2. BRIEF®2

Six BRIEF®2 questionnaires were excluded from analysis (two exposed and four comparison children). Three were excluded for inconsistency (respondents: one birth father, one grandparent, and one adoptive mother), two for infrequency (respondents: one birth mother and one birth father). and one for negativity (respondent: grandparent). Data were, therefore, available for 19 exposed children and 8 comparison children. Exposed children scored significantly higher than comparison children on all three regulation indices (behavioural, emotional, and cognitive) and on their total score (GEC) (Table 4). Five of the 19 (26%) exposed children had a clinically elevated GEC. No comparison child had any clinically elevated or potentially clinically elevated index. Three exposed children (#004, #147, and #057) had all three indices clinically elevated, one child (#044) had clinically elevated BRI and CRI, and one child (#105) had clinically elevated ERI and potentially clinically elevated CRI (Tables 2, 4). Of these five children, one had a diagnosis of ADHD and ASD, one was being investigated for ADHD, one was being investigated for ASD, and one was known to have motor and speech difficulties. Statistically significant differences in the proportions of children with potentially clinically elevated and/or clinically elevated indices were not found: large confidence intervals (CIs) indicate a small sample size effect, with only eight comparison children contributing to BRIEF®2 data (Table 4). Regression modelling showed that the effect size (higher BRIEF®2 scores for exposed children) reduced for all indices and for GEC after controlling for maternal tobacco use: methadone exposure no longer predicted higher BRIEF®2 GEC scores after controlling for

TABLE 2 Individual subject social, medical, and neurodevelopmental findings (case note review and history) and provision of learning support.

#	Exposed or comparison	Treated NAS	Sex	Age	Birth mother alive	Looked after status	Accompanying adult	Medical issues	Neurodevelopmental issues	Learning support at school	SDQ total difficulties score	BRIEF®2 GEC *T*-score	Griffiths general quotient
4	Exposed	Y	M	11.0	Yes	BP	Mother		ADHD (treated); ASD	No	30	86	97
6	Exposed	Y	F	10.6	Yes	BP	Father			No	8	56	88
7	Exposed	Y	M	9.2	Yes	BP	Mother			No	8	51	95
11	Exposed	Y	F	9.2	Yes	A	Mother			No	10	48	88
18	Exposed	Y	F	9.0	Yes	KC	Grandmother			No	15	54	82
21	Exposed	Y	F	9.1	Yes	BP	Mother			not known	7	56	99
25	Exposed		M	9.0	Yes	A	Mother			No	9	52	98
30	Exposed	Y	M	9.9	Yes	A	Mother	Asthma	ADHD	No	12	55	101
38	Exposed		F	10.2	Yes	BP	Mother			No	6	45	
43	Exposed	Y	F	10.7	Yes	KC	Grandmother	Headaches		No	15	61	97
44	Exposed		M	8.8	No	KC	Grandmother	Eczema	Being investigated for ADHD	not known	19	75	92
57	Exposed	Y	M	8.8	Yes	A/KC	Aunt = adoptive mother	Asthma	Being investigated for ASD	not known	28	80	104
74	Exposed	Y	F	9.5	Yes	BP	Father			No	17	58	93
77	exposed	Y	F	9.5	Yes	BP	Mother	Asthma, headaches		No	8	54	102
105	Exposed		M	8.9	Yes	BP	Mother	Hypermobility		No	14	72	93
109	Exposed	Y	F	8.8	No	BP	Father		ASD/ADHD concern	Yes	9	Inconsistent	99
112	Exposed	Y	F	9.1	No	KC	Grandfather			Yes	18	Negativity	100
141	Exposed		M	8.7	Yes	A	Mother	Dermatographia		No	6	47	92
143	Exposed	Y	F	8.7	Yes	BP	Mother			No	7	56	94
147	Exposed		M	8.8	Yes	BP	Father	Motor difficulties, language delay		Visual impairment teacher; child psychologist	30	81	97
153	Exposed		M	8.7	Yes	A	Mother			Reading help	19	63	
5	Comparison		M	10.5	Yes	BP	Mother			No	9	51	
55	Comparison		F	10.3	Yes	KC	Grandmother	Diabetes, coeliac disease, constipation		No capacity to write	16	Inconsistent	98
79	Comparison		F	9.7	Yes	BP	Mother	Constipation		No	2	42	102
80	Comparison		F	9.7	Yes	BP	Mother			No	4	47	96
100	Comparison		F	8.8	Yes	BP	Mother	Meningitis, hearing impairment		No	9	52	
115	Comparison		M	8.8	Yes	A/KC	Aunt = adoptive mother			No	7	54	
116	Comparison		F	9.4	Yes	BP	Father	Heart murmur from birth, constipation		No	18	Infrequency	100
125	Comparison		F	9.0	Yes	BP	Stepmother			No	7	45	114
130	Comparison		M	8.7	Yes	A/KC	Aunt = adoptive mother		ASD	No	18	Inconsistent	107
136	Comparison		F	8.6	Yes	BP	Mother	Chronic constipation		No	14	56	100
139	Comparison		F	8.9	Yes	BP	Mother	Hip dysplasia, ankle fractures		No	6	48	115
146	Comparison		F	8.7	Yes	BP	Mother	Enlarged bladder, constipation		No	14	Infrequency	102

NAS, neonatal abstinence syndrome; M, male; F, female; BP, birth parent; A, adopted; KC, kinship care; ADHD, attention deficit hyperactivity disorder; ASD, autistic spectrum disorder; BRIEF®2, Behaviour Rating Inventory of Executive Function, 2nd edition; GEC, global executive composite; SDQ, strengths and difficulties questionnaire.

*SDQ total difficulties score classified as "high" or "very high."

**BRIEF®2 GEC score classified as "potentially clinically significant" or "clinically significant."

***Any Griffiths sub-quotient scored "low" or "very low."

10.3389/fped.2023.1118634

10.3389/fped.2023.1118634

maternal tobacco use (Table 5). Controlling for maternal tobacco use changed BRI effect size most markedly and had a minimal effect on ERI (Table 5).

3.3. SDQ and BRIEF®2 concordance

Considering the 27 children with both questionnaires completed satisfactorily (19 exposed and 7 comparison children), SDQ total difficulty scores and BRIEF®2 GEC scores were highly and positively correlated ($r = 0.92$, 95% CI 0.82–0.96, $p < 0.0005$, Figure 2). Treating classifications for each questionnaire as equivalent (SDQ high/very high ≡ BRIEF®2 potentially or clinically elevated; SDQ slightly elevated ≡ BRIEF®2 mildly elevated; SDQ close to average ≡ BRIEF®2 not elevated), 22/27 (81%) children had concordant classifications: 17 children were classified as normal on both, one child was mildly elevated/slightly raised on each, and four children were potentially or clinically elevated and high/very high on each (Figure 2). Of the five children with discordant classifications, one child had a BRIEF®2 score indicating more problems than their SDQ score, and four children had SDQ scores indicating more difficulties than their BRIEF®2 score.

TABLE 5 Regression parameters: association of methadone exposure with BRIEF®2 scores before (unadjusted) and after (adjusted) controlling for maternal tobacco use.

	Unadjusted effect size—score difference between exposed and comparison children (SE)	*p*-value	Adjusted effect size (SE)	Adjusted *p*-value
BRI	9.0 (4.1)	0.04	5.8 (4.8)	0.2
ERI	11.6 (4.7)	0.02	10.3 (5.7)	0.085
CRI	8.4 (3.7)	0.03	5.7 (4.4)	0.2
GEC	11.2 (4.5)	0.02	8.3 (5.4)	0.14

BRIEF®2, Behaviour Rating Inventory of Executive Function, 2nd edition; BRI, behaviour regulation index; ERI, emotional regulation index; CRI, cognitive regulation index; GEC, global executive composite.

TABLE 3 SDQ results.

	Median score, exposed children ($n = 21$)	Median score, comparison children ($n = 12$)	95% CI of difference; Mann–Whitney *U* test *p*-value	Proportion of exposed children classified with "high/low" or "very high/low"	Proportion of comparison children classified with "high/low" or "very high/low"	95% CI of difference; Fisher's exact test *p*-value
Emotional problems subscale	3	3	−1 to 3 $p = 0.47$	9/21	2/12	−7% to 50% $p = 0.12$
Conduct problems subscale	1	1	−1 to 2 $p = 0.50$	5/21	2/12	−24% to 32% $p = 0.5$
Hyperactivity subscale	5.0	4.5	−0 to 4 $p = 0.13$	6/21	0/12	0.2% to 50% $p = 0.049$
Peer relationships problems subscale	2.0	1.5	−1 to 2 $p = 0.43$	7/21	3/12	−24% to 35% $p = 0.5$
Total difficulties	12	9	−1 to 8 $p = 0.20$	7/21	2/12	−16% to 41% $p = 0.4$
Prosocial subscale	9	10	−2 to 0 $p = 0.34$	3/21	2/12	32% to −21% $p = 0.6$

CI, confidence interval; SDQ, Strength and Difficulties Questionnaire.
Total difficulties is the sum of scores from the first four subscales where a high score indicates more problems.

TABLE 4 BRIEF®2 results.

	Mean T-score, exposed children ($n = 19$)	Mean T-score, comparison children ($n = 8$)	95% CI of difference; Mann–Whitney *U* test *p*-value	Proportion of exposed children classified with "potentially" or "clinically significant"	Proportion of comparison children classified with "potentially" or "clinically significant"	95% CI of difference; Fisher exact test *p*-value
BRI	58	49	2 to 16 $p = 0.015$	4/19	0/8	−14% to 43% $p = 0.22$
ERI	61	49	5 to 18 $p = 0.002$	5/19	0/8	−9% to 49% $p = 0.14$
CRI	58	49	2.5 to 14 $p = 0.007$	5/19	0/8	−9% to 49% $p = 0.14$
GEC	61	49	4 to 18 $p = 0.002$	5/19	0/8	−9% to 49% $p = 0.14$

CI, confidence interval; BRIEF®2, Behaviour Rating Inventory of Executive Function, 2nd edition; BRI, behaviour regulation index; ERI, emotional regulation index; CRI, cognitive regulation index; GEC, global executive composite.
GEC is the sum of the three regulation indices where a high score indicates more problems.

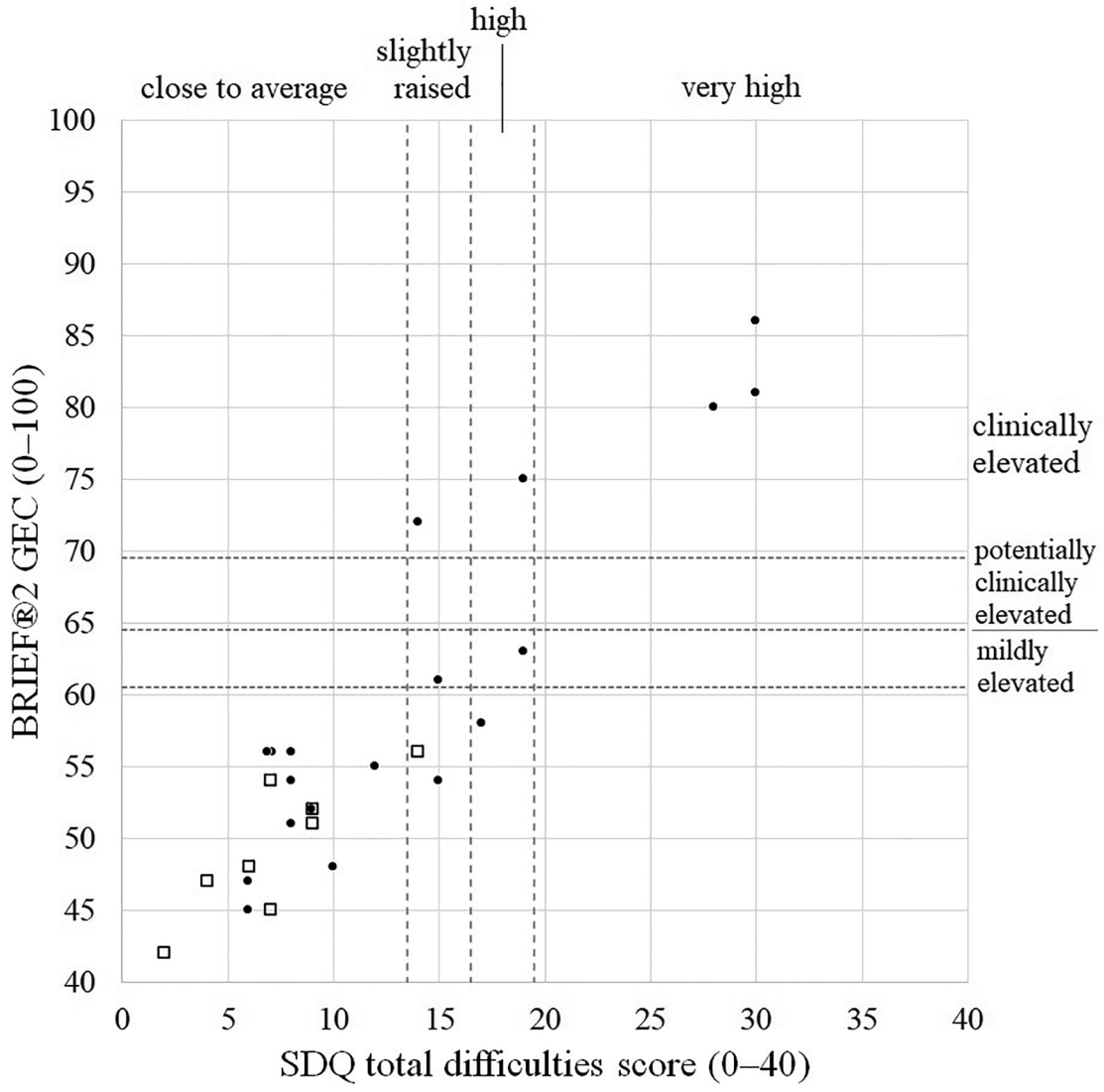


FIGURE 2
Scatterplot of BRIEF®2 GEC scores vs. SDQ total difficulties scores illustrating degree of concordance. Closed circles, exposed children; Open squares, comparison children. BRIEF®2, Behaviour Rating Inventory of Executive Function, 2nd edition; GEC, global executive composite; SDQ, Strength and Difficulties Questionnaire.

3.4. Comparison with infant Griffiths scores, NAS/NOWS, and maternal methadone dose

Twenty-eight of these 33 children had attended for investigation at age of 6 months and had completed the Griffiths MD neurodevelopmental assessment (Table 2). Only 2 of these 28 had problematic infant scores: child #011 had a low eye-hand sub-quotient in infancy, but normal results on SDQ and BRIEF®2 at 8–10 years; child #018 had a low performance and eye-hand sub-quotients in infancy and also had normal SDQ and BRIEF®2 scores. Conversely, nine children with either an abnormal SDQ total difficulties score or an abnormal BRIEF®2 GEC at age 8–10 years had normal Griffiths scores in infancy.

Considering only exposed children, neither SDQ scores (subscales, total difficulties score) nor BRIEF®2 scores (subscales, indices, GEC) differed between children who did ($n = 14$) or did not ($n = 7$) require treatment for NAS/NOWS. Scatter plots of questionnaire scores and maternal methadone dose at delivery were random by visual inspection, indicating no relation between these two factors.

4. Discussion

The main aim of this study was to expand current literature on the developmental impact of prenatal opioid exposure for older children. We found that, at mid-elementary school age, children prenatally exposed to methadone and/or other drugs were not significantly different from their non-exposed peers in terms of carer reports on the SDQ screening questionnaire. On the

BRIEF®2 measure, methadone-exposed children scored significantly higher than their non-exposed peer group on behaviour, emotional, and cognitive regulation indices as well as GEC, indicating that methadone-exposed children were significantly less able to cognitively regulate, control, and manage cognitive processes and problem solve in various contexts. After controlling for maternal tobacco use, however, methadone exposure was no longer a predictor of higher BRIEF®2 scores, with the BRI and CRI indices showing the largest adjustments. This may represent a type II error with this relatively small study as a large study of 92 methadone-exposed 2-year-old children and 108 unexposed control children found problems with motor function, cognitive development, and emotional/behaviour dysregulation persisted after controlling for confounding licit (including tobacco) and illicit drug use in pregnancy (9).

Prenatal tobacco exposure is known to be detrimental to brain development and function (14) with a long-term follow-up study linking tobacco exposure to reduced cognition (28). In a large US study of teenagers using teacher-reported BRIEF questionnaires, tobacco exposure was found to predict impaired behavioural regulation but not meta-cognition after controlling for multiple confounders including cocaine, alcohol, and cannabis (but not opioid exposure) (29). Our data support this finding by suggesting that tobacco exposure particularly exacerbates problems with behaviour regulation. Maternal smoking is significantly associated with childhood ADHD after adjusting for parental psychiatric history and socioeconomic status, but other confounders—such as opioid exposure—could not be included in the meta-analysis (30). It remains uncertain, therefore, whether tobacco and opioids act independently, exacerbate the other's teratogenic effect, or act as a marker for more extensive use. Studies investigating the safety of opioids in pregnancy must therefore control for maternal tobacco use (31).

Griffiths scores at 6 months were poorly predictive of 8–10 year outcomes. NAS/NOWS requiring treatment was not related to the presence or extent of any difficulties, suggesting that any prenatal exposure to opioids is a better risk factor for surveillance than a history of treated NAS/NOWS (1). The SDQ and BRIEF®2 tests correlated well across a wide range of scores, suggesting that non-significant SDQ findings may relate to the lower sensitivity of non-parametric testing used to compare SDQ scores between groups. The preponderance of children with difficulties highlighted by the SDQ but not by BRIEF®2 ($n = 4$) rather than vice versa ($n = 1$) is in keeping with the SDQ's design as a screening questionnaire.

Strengths of this study include being the first prospective cohort-based study describing longer-term neurodevelopmental effects of prenatal methadone exposure, uniquely comprehensive information on maternal substance misuse in pregnancy and a comparison group matched for gestation, birthweight, and postcode at delivery as a proxy for socioeconomic status. Limitations include the small sample size which reflects the difficulty of long-term follow-up of families with challenging and/or chaotic lives. The greater imprecision associated with small sample sizes may have masked any methadone effect after controlling for maternal tobacco use. Children in the exposed group had birthweights 236 g lighter on average and had smaller birth OFC by an average of 0.8 cm, in line with expected, corrected differences seen in methadone-exposed children (32), but not reaching significance likely due to the small sample size. A greater proportion of exposed children had poor vision: since vision tests were selected to be easily performed by younger children, visual findings are unlikely to be affected by behaviour or executive difficulties. It is possible that reported behaviour and/or executive difficulties were at least partly due to the presence of visual problems but because prenatal opioid exposure is associated with impaired vision (10), childhood vision outcome was not treated as a confounder. The comparison group had a higher proportion of females than the exposed group (6/8, 75%, vs. 9/19, 47%, with adequately completed BRIEF®2), which may have exaggerated positive findings in the exposed group as ADHD is more prevalent in males. Long-term outcomes for all children are confounded by multiple factors including impaired foetal growth, socioeconomic deprivation, and challenged parenting skills, each of which is more likely to affect those exposed prenatally to opioids, thereby limiting the strength of any association. However, multiple systematic analyses now point to an independent effect of prenatal opioid exposure on developmental outcomes (1, 6, 7, 10).

Opioid exposure *in utero*, specifically methadone, may at least partly explain adverse neurodevelopmental outcomes at mid-elementary school age, which are currently misunderstood or misdiagnosed, potentially as ASD or ADHD, by professionals. Unfortunately, potentially confounding effects of other illicit and licit drug exposures, challenged parenting and/or multiple placements (33), and socioeconomic deprivation are extremely difficult to control. Given national recommendations (4, 5) and the widespread use of methadone in the treatment of opioid use disorder in pregnancy, establishing whether this practice may contribute to long-term harm for children's developmental outcomes is essential.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by West of Scotland Research Ethics Committee 3 (17/WS/0093). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

RH and HM conceived the study. KMS, RH, and HM contributed significantly to the study design and all authors

contributed significantly to data collection or analysis. KR wrote the first version of the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was funded by a joint grant from Action Medical Research for Children, Horsham, UK, and the Chief Scientist Office, Edinburgh, UK (Ref GN2493) and supported by The RS Macdonald Charitable Trust.

Acknowledgments

We thank the children and their families; the research nursing and administrative team, Helen Bannister, Emily Blyth, Karen Duffy, Annmarie Jordan, Barry Milligan, Leeanne Milne, Ashleigh Neil, Elizabeth Waxman; and Janice Waterson-Wilson, research orthoptists, for help with clinical data collection and SDQ scoring.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Hall ES, McAllister JM, Wexelblatt SL. Developmental disorders and medical complications among infants with subclinical intrauterine opioid exposures. *Popul Health Manag.* (2019) 22:19–24. doi: 10.1089/pop.2018.0016

2. Minozzi S, Amato L, Jahanfar S, Bellisario C, Ferri M, Davoli M. Maintenance agonist treatments for opiate-dependent pregnant women. *Cochrane Database Syst Rev.* (2020) 2020. doi: 10.1002/14651858.CD006318.pub4

3. Patrick SW, Barfield WD, Poindexter BB, COMMITTEE ON FETUS AND NEWBORN, COMMITTEE ON SUBSTANCE USE AND PREVENTION; James Cummings. Neonatal opioid withdrawal syndrome. *Pediatrics.* (2020) 146: e2020029074. doi: 10.1542/peds.2020-029074

4. ASAM. The ASAM national practice guideline for the treatment of opioid use disorder: 2020 focused update. *J Addict Med.* (2020) 14:1–91. doi: 10.1097/ADM.0000000000000633

5. Clinical Guidelines on Drug Misuse and Dependence Update 2017 Independent Expert Working Group. Drug misuse and dependence: UK guidelines on clinical management (2017). Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/673978/clinical_guidelines_2017.pdf (Accessed June 10, 2021).

6. Baldacchino A, Arbuckle K, Petrie DJ, McCowan C. Erratum: neurobehavioral consequences of chronic intrauterine opioid exposure in infants and preschool children: a systematic review and meta-analysis. *BMC Psychiatry.* (2015) 15:134. doi: 10.1186/s12888-015-0438-5

7. Lee SJ, Bora S, Austin NC, Westerman A, Henderson JMT. Neurodevelopmental outcomes of children born to opioid-dependent mothers: a systematic review and meta-analysis. *Acad Pediatr.* (2020) 20:308–18. doi: 10.1016/j.acap.2019.11.005

8. Andersen JM, Høiseth G, Nygaard E. Prenatal exposure to methadone or buprenorphine and long-term outcomes: a meta-analysis. *Early Hum Dev.* (2020) 143:104997. doi: 10.1016/j.earlhumdev.2020.104997

9. Levine TA, Davie-Gray A, Kim HM, Lee SJ, Woodward LJ. Prenatal methadone exposure and child developmental outcomes in 2-year-old children. *Dev Med Child Neurol.* (2021) 63:1114–22. doi: 10.1111/dmcn.14808

10. Monnelly VJ, Hamilton R, Chappell FM, Mactier H, Boardman JP. Childhood neurodevelopment after prescription of maintenance methadone for opioid dependency in pregnancy: a systematic review and meta-analysis. *Dev Med Child Neurol.* (2019) 61:750–60. doi: 10.1111/dmcn.14117

11. Nygaard E, Moe V, Slinning K, Walhovd KB. Longitudinal cognitive development of children born to mothers with opioid and polysubstance use. *Pediatr Res.* (2015) 78:330–5. doi: 10.1038/pr.2015.95

12. Nygaard E, Slinning K, Moe V, Walhovd KB. Behavior and attention problems in eight-year-old children with prenatal opiate and poly-substance exposure: a longitudinal study. *PLoS One.* (2016) 11:e0158054. doi: 10.1371/journal.pone.0158054

13. Nygaard E, Slinning K, Moe V, Walhovd KB. Cognitive function of youths born to mothers with opioid and poly-substance abuse problems during pregnancy. *Child Neuropsychol.* (2017) 23:159–87. doi: 10.1080/09297049.2015.1092509

14. Hofhuis W. Adverse health effects of prenatal and postnatal tobacco smoke exposure on children. *Arch Dis Child.* (2003) 88:1086–90. doi: 10.1136/adc.88.12.1086

15. McGlone L, Mactier H, Hamilton R, Bradnam MS, Boulton R, Borland W. Visual evoked potentials in infants exposed to methadone in utero. *Arch Dis Child.* (2008) 93:784–6. doi: 10.1136/adc.2007.132985

16. McGlone L, Hamilton R, McCulloch DL, MacKinnon JR, Bradnam M, Mactier H. Visual outcome in infants born to drug-misusing mothers prescribed methadone in pregnancy. *Br J Ophthalmol.* (2014) 98:238–45. doi: 10.1136/bjophthalmol-2013-303967

17. Gareri J, Lynn H, Handley M, Rao C, Koren G. Prevalence of fetal ethanol exposure in a regional population-based sample by meconium analysis of fatty acid, ethyl esters. *Ther Drug Monit.* (2008) 30:239–45. doi: 10.1097/FTD.0b013e318167cfe5

18. McLoone P. Carstairs scores for Scottish postcode sectors from the 2001 census (2004). Available at: https://www.gla.ac.uk/researchinstitutes/healthwellbeing/research/mrccsosocialandpublichealthsciencesunit/programmes/inequalities/healthinequalities/determinantsofhealthandhealthinequalitiesinscotland/carstairsscores/ (Accessed October 25, 2021).

19. Mactier H, McGlone L. Comment on: infants of opioid-dependent mothers: neurodevelopment at six months reply. *Early Hum Dev.* (2015) 91:245–245. doi: 10.1016/j.earlhumdev.2015.01.006

20. Lipsitz P. Proposed narcotic withdrawal score for use with newborn-infants—pragmatic evaluation of its efficacy. *Clin Pediatr.* (1975) 14:592–4. doi: 10.1177/000992287501400613

21. Goodman R. The strengths and difficulties questionnaire: a research note. *J Child Psychol Psychiatry.* (1997) 38:581–6. doi: 10.1111/j.1469-7610.1997.tb01545.x

22. Goodman A, Goodman R. Strengths and difficulties questionnaire as a dimensional measure of child mental health. *J Am Acad Child Adolesc Psychiatry.* (2009) 48:400–3. doi: 10.1097/CHI.0b013e3181985068

23. Yao S, Zhang C, Zhu X, Jing X, McWhinnie CM, Abela JRZ. Measuring adolescent psychopathology: psychometric properties of the self-report strengths and difficulties questionnaire in a sample of Chinese adolescents. *J Adolesc Health.* (2009) 45:55–62. doi: 10.1016/j.jadohealth.2008.11.006

24. Muris P, Meesters C, van den Berg F. The strengths and difficulties questionnaire (SDQ). *Eur Child Adolesc Psychiatry.* (2003) 12:1–8. doi: 10.1007/s00787-003-0298-2

25. Goodman R, Ford T, Simmons H, Gatward R, Meltzer H. Using the strengths and difficulties questionnaire (SDQ) to screen for child psychiatric disorders in a community sample. *Br J Psychiatry.* (2000) 177:534–9. doi: 10.1192/bjp.177.6.534

26. Gioia GA, Isquith PK, Guy SC, Kenworthy L. TEST REVIEW behavior rating inventory of executive function. *Child Neuropsychol.* (2000) 6:235–8. doi: 10.1076/chin.6.3.235.3152

27. McGlone L, Mactier H. Infants of opioid-dependent mothers: neurodevelopment at six months. *Early Hum Dev*. (2015) 91:19–21. doi: 10.1016/j.earlhumdev.2014.10.006

28. Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 13- to 16-year-olds prenatally exposed to cigarettes and marihuana. *Neurotoxicol Teratol*. (2003) 25:427–36. doi: 10.1016/S0892-0362(03)00029-1

29. Rose-Jacobs R, Richardson MA, Buchanan-Howland K, Chen CA, Cabral H, Heeren TC. Intrauterine exposure to tobacco and executive functioning in high school. *Drug Alcohol Depend*. (2017) 176:169–75. doi: 10.1016/j.drugalcdep.2017.02.022

30. Dong T, Hu W, Zhou X, Lin H, Lan L, Hang B, Lv W, Geng Q, Xia Y. Prenatal exposure to maternal smoking during pregnancy and attention-deficit/hyperactivity disorder in offspring: a meta-analysis. *Reprod Toxicol*. (2018) 76:63–70. doi: 10.1016/j.reprotox.2017.12.010

31. Bann CM, Newman JE, Poindexter B, Okoniewski K, DeMauro S, Lorch SA. Outcomes of babies with opioid exposure (OBOE): protocol of a prospective longitudinal cohort study. *Pediatr Res*. (2022):1–8. doi: 10.1038/s41390-022-02279-2

32. Mactier H, Shipton D, Dryden C, Tappin DM. Reduced fetal growth in methadone-maintained pregnancies is not fully explained by smoking or socio-economic deprivation: fetal growth in methadone pregnancies. *Addiction*. (2014) 109:482–8. doi: 10.1111/add.12400

33. Mitchell J, Mactier H. Accommodation outcomes for children of drug-misusing women. *Arch Dis Child*. (2021) 106:80–2. doi: 10.1136/archdischild-2018-316440

frontiers | Frontiers in Pediatrics

TYPE Review
PUBLISHED 24 May 2023
DOI 10.3389/fped.2023.1045745

Check for updates

OPEN ACCESS

EDITED BY
Loretta Finnegan,
Finnegan Consulting, LLC, United States

REVIEWED BY
Alison Sally Poulton,
The University of Sydney, Australia
Jennifer McKinney,
Baylor College of Medicine, United States

*CORRESPONDENCE
Mishka Terplan
✉ mterplan@friendsresearch.org

RECEIVED 16 September 2022
ACCEPTED 17 April 2023
PUBLISHED 24 May 2023

CITATION
Barber CM and Terplan M (2023) Principles of care for pregnant and parenting people with substance use disorder: the obstetrician gynecologist perspective.
Front. Pediatr. 11:1045745.
doi: 10.3389/fped.2023.1045745

COPYRIGHT
© 2023 Terplan and Barber. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Principles of care for pregnant and parenting people with substance use disorder: the obstetrician gynecologist perspective

Cecily May Barber[1,2] and Mishka Terplan[3,4]*

[1]Grayken Center for Addiction, Boston Medical Center, Boston, MA, United States, [2]Department of Obstetrics and Gynecology, Boston University School of Medicine and Boston Medical Center, Boston, MA, United States, [3]Friends Research Institute, Baltimore, MD, United States, [4]Department of Family and Community Medicine, University of California, San Francisco, CA, United States

Substance use in pregnant and parenting persons is common, yet still underdiagnosed. Substance use disorder (SUD) is one of the most stigmatized and undertreated chronic medical conditions, and this is exacerbated in the perinatal period. Many providers are not sufficiently trained in screening or treatment for substance use, so gaps in care for this population persist. Punitive policies towards substance use in pregnancy have proliferated, lead to decreased prenatal care, do not improve birth outcomes, and disproportionately impact Black, Indigenous, and other families of color. We discuss the importance of understanding the unique barriers of pregnancy-capable persons and drug overdose as one of the leading causes of maternal death in the United States. We highlight the principles of care from the obstetrician-gynecologist perspective including care for the dyad, person-centered language, and current medical terminology. We then review treatment of the most common substances, discuss SUD during the birthing hospitalization, and highlight the high risk of mortality in the postpartum period.

KEYWORDS
addiction, pregnancy, parenting, disparities, stigma

Introduction

Substance use in pregnant and parenting persons is common, yet both underdiagnosed and undertreated in part due to misunderstanding and misinformation regarding substance use, misuse, and use disorder in pregnancy (1).

Most people in the US use drugs (opioids, alcohol, nicotine/tobacco, stimulants, and cannabis) to which some people develop an addiction, including people who are capable of pregnancy (2). Most people quit or cut back substance use when they become pregnant (3, 4). However, those who continue to use, likely have a substance use disorder (SUD) (5). Addiction, or SUD, is a chronic and treatable medical condition (6). Untreated SUD is associated with preterm delivery, low birth weight, and other negative birth outcomes. In contrast, people with treated addiction are more likely to deliver a normal weight infant at term (7). The old adage "healthy mother equals healthy baby" applies to addiction as it does to other chronic diseases in pregnancy.

Universal assessment of behavioral health is recommended in prenatal care (8–14); however, it is unevenly actualized and some providers and health systems deploy drug testing in place of proper screening (15, 16). Although the effectiveness of treatment in pregnancy is well established, most pregnant people receive no addiction treatment and

treatment (including medication) is inequitably distributed across populations (17, 18). In short, the field of addiction medicine as it concerns pregnancy and parenting suffers not from gaps in scientific knowledge, as much as it suffers from gaps in implementation. We know how to care for pregnant and parenting people with SUD. Many of the principles of care were first described almost 50 years ago (19, 20).

Pregnancy and postpartum are a period of significant change both biologically and socially and can lead to new or increased contact with healthcare providers. In this role, all providers have an obligation to present information, resources and support that strengthen this family unit. The complexity of the social and historical context in which people who use substances interact with the healthcare system is highlighted during the perinatal period (21)—most notably, this population faces unique threats of legal repercussions for reporting use and seeking treatment (22). This threat and stigma can lead to significant trauma for pregnant and postpartum persons and disproportionately affects non-White families (23).

This manuscript reviews the principles of care of pregnant and parenting people with SUD from the obstetrician gynecologist perspective. The authors are both obstetrician gynecologists and addiction medicine providers with combined almost three decades of clinical experience. The discussion is centered on the dyad—on the indivisible connection between a pregnant person and the fetus (the "maternal-fetal unit") and, following birth, the connection between a new mother and an infant—and grounded in both foundational texts as well as contemporary data.

Principles and context

Health care should be both evidence-based and person-centered. Pregnant people with SUD experience discrimination, are denied dignity and respect, and often lack access to evidence-based care (24). Pregnant people with SUD often have a significant history of trauma, including childhood physical or sexual abuse and current intimate partner violence (25–27). Many have interacted with the child welfare system in the past and the potential of child welfare involvement postpartum looms over the entire perinatal period (28, 29). Finally, the birth experience can be traumatizing which can reaffirm existing medical mistrust (30).

To address discrimination and structural inequities, to reflect evidence-based practice, and to actualize person-centered care, attention should focus first on language.

Language is important. The words we use can convey (intentionally or unintentionally) stigma and prejudice (31, 32). Creating a non-judgmental environment is important to provide appropriate care for persons with substance use disorder. Therefore, providers need to model language that is both evidence-based (i.e., clinically accurate) and person-centered (i.e., non-stigmatizing). Providers should avoid slang and use language that clearly communicates that substance use disorder is a chronic medical condition, that emphasizes treatment (especially medication and behavioral health), and that promotes recovery (see **Table 1**) (31, 33, 34). Finally, it is important to note that "stigma catches up" and therefore language that reflects the dignity and humanity of pregnant and parenting people who use drugs is constantly changing. As healthcare professionals, it will be necessary to adapt our terminology as needed.

Screening and assessment

Substance use and use disorder are common—nearly 1 in 5 pregnant women report any substance (including tobacco, alcohol, or illicit substances) within the past month, and rates of opioids, cannabis, and stimulants in pregnancy have increased in the past decade (2).

Universal verbal screening for substance use and misuse using a validated instrument is recommended as a routine part of prenatal care by professional societies and public health agencies (8–11, 35, 36). In addition, participation in screening is considered voluntary and rests upon the bioethical principle of autonomy and opposition to coercion (see **Table 2**) (36–38). Hence, it is recommended that providers ask permission prior to screening and recognize the patient's right of refusal if screening is declined. However, universal screening is vastly underutilized and "risk based" screening persists—a practice that operationalizes and perpetuates stigma and with no improvement of diagnostic accuracy (15, 39).

There are multiple validated tools to identify problematic substance use including maternal interview and screening questionnaires. Although many screening instruments have been used in pregnancy, only two studies have directly compared the screening instrument performance in pregnancy. Ondersma et al compared 5 instruments: the Substance Use Risk Profile—

TABLE 1 Addressing stigma by changing the language we use.

Stigmatizing language	Preferred language
Addict, junkie, abuser	Person in active addiction Person with a substance use disorder Person in recovery (1)
Addicted baby	Neonate with in-utero exposure to [substance] Neonatal abstinence syndrome (2)
Substance abuse	Substance use or misuse Substance use disorder
Clean or sober	Abstinent SUD in remission Testing "negative" for [substance]
Dirty	Using [substance] Testing "positive" for [substance] (3)
Replacement or substitution therapy, medication-assisted treatment	Medication for opioid use disorder (MOUD) Treatment
Getting or being high	Intoxicated Under the influence of [substance]
Shooting up	Intravenous or injection drug use
Relapse	Return to use SUD recurrence

TABLE 2 Tips for addressing mistrust and making clinical care welcoming.

Permission for Screening	Is it ok if I ask you some questions about smoking, drinking and other drugs?
Prenatal Care and SUD Treatment	What are you looking for in a provider? What is the most important thing to you about treatment or recovery?
Medication Decisions	What do you know about [methadone or buprenorphine]? Do you have any concerns from prior treatment experiences?
Postpartum Care	What do I need to know about your birthing experience to help you create an environment to best care for you and your child? What do you need to care for your infant?
In General	What do you need to feel safe?

Pregnancy (SURP-P), CRAFFT (acronym for five-item screener with items related to car, relax, alone, forget, friends and trouble), 5Ps (parents, peers, partner, pregnancy, past), Wayne Indirect Drug Use Screener (WIDUS), and the National Institute on Drug Abuse (NIDA) Quick Screen (40). Coleman-Cowger et al compared 3 instruments: 4P's Plus, NIDA Quick Screen-ASSIST, and the SURP-P (41). No instrument was superior in any of the analyses. Therefore, it is recommended that providers use whatever validated tool is most able to be integrated into the electronic health record.

Drug **screening** captures behaviors related to substance use. In contrast, drug **testing** is the evaluation of a biological matrix (such as urine, hair, or meconium) for the presence of drug metabolites or parent compounds. Drug testing is not recommended as an appropriate means to identify substance use or misuse, much less addiction (8, 36). The information obtained from a drug test is not uniform as the time of detection varies greatly across substances. In addition, both false positive and false negative results are common in drug tests (42, 43). Furthermore, the American Society of Addiction Medicine (ASAM) recommendations are clear that definitive testing (i.e., gas chromatography) is required "when the results will inform a decision with major clinical or non-clinical implications for the patient" which, given the realities of child welfare reporting, would be any drug test in pregnancy especially during the birthing hospitalization (44).

Screening is not diagnosis, and a positive screen must be followed up with the assessment of DSM criteria for the establishment of diagnosis. Screening helps to stratify patients into risk categories: those that meet criteria for a use disorder need treatment; those with "moderate risk" (history of use but without addiction) should receive a brief intervention grounded in motivational interviewing and (more) frequent follow up visits; and those with low risk (no past or current use) should receive brief advice and acknowledgement of their healthy behaviors (11).

Although screening is recommended, patients may be legitimately fearful of disclosure, including the threat of legal repercussions (45). It is important that all providers continue to create a safe and non-judgmental environment that encourages engagement in care. Providers should be honest and transparent regarding how information obtained from either screening or testing is shared with external agencies, including child welfare, and overreporting (use or positive drug testing without protective concerns) should be discouraged.

Treatment

SUD is a chronic medical condition and like other chronic conditions, outcomes are greatly improved by treatment (46). There is, however, a large gap in access to treatment (both medication and behavioral) by substance type, with the highest rate of treatment for opioids and the lowest for alcohol (17). The marked gap in treatment is further magnified by racial inequities. Compared to White individuals, Black and Hispanic populations are less likely to receive any SUD treatment, less likely to receive medication for OUD (MOUD), and if in treatment, receive lower doses of MOUD (18, 47).

Among people with SUD, polysubstance use is common and co-occurring substance use and use disorders can be treated simultaneously. Ideally, care should be delivered in a comprehensive and co-located capacity, that is, through the integration of addiction treatment and prenatal care. Integrated care models have been described since the 1970s, are considered the "standard of care", and are associated with improved birth outcomes (7, 20). However, some individuals need a higher level of care. ASAM categorizes addiction treatment along levels of care that range from outpatient to residential and inpatient (48). Level of care should be evaluated at treatment intake and throughout, especially if treatment is failing a patient at a particular moment. Medication should be available throughout levels of care as should childcare services, although both medication and childcare are often absent and are hence barriers to care for pregnant and parenting people (49, 50). In addition, treatment should address concomitant mental health disorders (51). Below we discuss treatment and outcomes by substance type.

Opioids

From 1999 to 2014, the rate of OUD complicating birth has increased by more than 4-fold and in some states the rate has increased nearly 10-fold, yet OUD treatment is still stigmatized and underutilized (8, 52). Despite public health and professional society recommendations supporting MOUD (14), pregnant and postpartum individuals with OUD continue to face barriers to treatment, including stigma (53), discrimination, lack of knowledgeable clinicians (54), and misinformation about NAS (55). Available data regarding negative fetal effects of opioids are inconsistent and some of the literature is cross-sectional, retrospective (hence subject to recall and other bias), or outcome assessments are not masked. However, there is no evidence that MOUD (either buprenorphine or methadone) increases risk of congenital anomalies (56).

MOUD, including methadone (a full mu-agonist and weak NMDA receptor antagonist), buprenorphine (partial mu-agonist with a high affinity for the mu-opioid receptor and partial mu-

antagonist) and naltrexone (nonselective opioid receptor antagonist), save lives and are the standard OUD treatment—among pregnant and postpartum individuals (8, 36). MOUD improve both substance use and pregnancy outcomes and decrease overdose risk compared with no treatment (57). Evidence for the safety and efficacy of methadone and buprenorphine is the strongest, however due to recent studies confirming safety and efficacy of the buprenorphine-naloxone combination product and persistent barriers to outpatient methadone access in the current flawed system, buprenorphine use is increasing (58), and a multisite injectable buprenorphine trial in pregnancy is ongoing (59). Detoxification, or medically supervised withdrawal, is not recommended in pregnancy. Naltrexone is the newest approved MOUD and the least studied in pregnancy; the urgency to close this research gap is currently being addressed in an ongoing multisite trial (59). Detoxification is not treatment, is associated with return to use and not associated with a decrease in NAS (60). However, it is important to respect patient autonomy and it may be attempted after shared decision making with counseling on the safety of detoxification and the risk of return to use (61).

Although MOUD with either methadone or buprenorphine are the safest and most effective treatment for OUD in pregnancy, most people with OUD receive no treatment in pregnancy (17), only 50% of people admitted to specialty addiction treatment programs receive medication (62), and there are marked racial inequities in medication receipt, type, and dose. Black pregnant people are less likely to receive medication compared to White pregnant people and overall, more likely to receive methadone than buprenorphine (18). Even among those who receive methadone, mean daily doses are highest for White (144.9 mg) compared to Black (97.5 mg) pregnant people (47).

MOUD dose (methadone or buprenorphine) is not correlated with neonatal abstinence syndrome (63, 64), however there is decreased incidence and severity of NAS associated with buprenorphine compared to methadone (65). Behavioral interventions, such as contingency management, cognitive behavioral therapy, and family therapy, are helpful (66, 67) but absence of or non-adherence with behavioral health should not be used as justification to withhold MOUD (68). Optimal duration of treatment with MOUD is not established and for some individuals may be lifelong, however MOUD discontinuation postpartum is common and is associated with increased rates of return to use, overdose, and death (57, 69). Providers should be aware of community resources including peer recovery support services and "12 step programs" because use of peer services is associated with increased attendance at OUD medical appointments (70). Recent qualitative studies suggest that peer services are valued among pregnant and postpartum individuals with OUD and are increasingly accessible through telehealth and online (71).

Naloxone (short-acting opioid antagonist) rapidly reverses opioid overdose and is not considered MOUD. Given the increase in intentional and unintentional fentanyl use, pregnant and postpartum individuals and their supports should be counseled on the increased risk of overdose, need for immediate naloxone administration in case of overdose, and to call emergency medical services because multiple doses of naloxone and/or oxygen support may be needed (72). Because fentanyl is increasing throughout the US and there are increasing reports of xylazine (alpha-2 adrenergic agonist) in the drug supply, further training in overdose prevention and management is needed. Xylazine is sympatholytic causing severe sedation, respiratory depression and slowed heart rate, further complicating overdose prevention and management, therefore provider training is needed on co-prescription of naloxone, education on naloxone-resistant overdoses, and increasing need for respiratory support in xylazine-opioid combination use and patient support training on overdose recognition (73).

Alcohol

Binge alcohol use—4 or more drinks on a single occasion for women—is common in pregnant individuals in the past month, yet rates of alcohol use and alcohol use disorder (AUD) are likely gravely miscalculated (2). Although alcohol is an established teratogen and there is no known safe lower limit of alcohol exposure. Fetal alcohol syndrome (FAS) is the leading modifiable cause of intellectual disability and developmental delay in the US, with a similar rate to Down syndrome, and 20 times more common in the US (1.95/1,000) than in Europe (0.08/1,000) (74). All individuals who report alcohol use should be evaluated for AUD and referred to treatment to avoid withdrawal which can be life-threatening. Untreated withdrawal is associated with a nearly 5% subsequent yearly mortality rate (75). The American Society of Addiction Medicine recommends initial inpatient management for individuals at risk of severe withdrawal, which includes pregnancy (76). Withdrawal management alone is not addiction treatment—the mainstay of treatment for AUD is medication with behavioral interventions because behavioral interventions alone are associated with high rates of return to use (77, 78). There are three approved medications for AUD: disulfiram (aldehyde dehydrogenase inhibitor), acamprosate (glutamate/GABA neuromodulator) and naltrexone (mu-opioid receptor antagonist). Due to the exclusion of pregnant individuals from medication trials, there is no evidence base regarding safety and effectiveness in pregnancy (79), and these medications are vastly underutilized. However, medications for AUD are almost certainly less harmful than untreated AUD and should be considered in the clinical care for pregnant and postpartum individuals (80, 81).

Nicotine/tobacco

There is significantly higher tobacco use in individuals who have other SUDs compared to those with no SUD and this does not change dramatically among pregnant and parenting individuals. Although 50% of individuals stop smoking during pregnancy, up to 90% resume within 1 year postpartum (82). Behavioral interventions, such as cognitive behavioral therapy

(CBT) or contingency management, remain the standard treatment for smoking cessation (83). Nicotine replacement therapy (NRT) has not been shown to be beneficial in smoking cessation in pregnancy, however, NRT can reduce maternal and fetal exposure to nicotine, mitigate maternal lung disease, and reduce second and third-hand smoke exposure postpartum. Although there are limited data on bupropion and varenicline use in pregnancy, a recent analysis suggests safety of bupropion both in pregnancy and breast/chestfeeding (84). Medications decisions, including NRT, should be individual clinical decisions, balancing risks and benefits, and center on patient autonomy.

Cocaine

Cocaine use in pregnancy has a shameful history of unscientific and racist rhetoric, filled with false claims of adverse child neurodevelopmental outcomes, teratogenicity, and lifelong mental and physical disability (53, 85–87). It is important to acknowledge that despite the research disproving these claims, significant stigma persists particularly for Black individuals. Because cocaine can cause hypertensive emergencies and increase myocardial oxygen demand, *in utero* exposure can be associated with preterm birth, placental abruption, preeclampsia-like symptoms, maternal coronary artery vasospasm, and myocardial ischemia, infarction or arrhythmia (88). A symptom of both the ongoing "war on drugs" and the subsequent unequal burden of "crack" or crystal cocaine use in Black and poor communities, research on cocaine use disorder (CUD) treatment is limited and there are no medications approved for (CUD) (89). There is modest evidence for bupropion, topiramate, and psychostimulants, but none of these have been studied in pregnancy (89). There is increasing evidence that contingency management increases abstinence, and behavioral modalities remain the mainstay of treatment in pregnancy (67, 90).

Methamphetamines

Methamphetamine is the second most used illicit substance globally and use has been increasing in pregnancy particularly in Western and rural regions of the US (present in 1% of births) and now also in Eastern and urban regions (particularly via injection and not inhalation) (91). Concurrent opioid and methamphetamine use and methamphetamine-related overdose rates are rapidly increasing globally and this trend is being described as "a new or fourth wave in the opioid crisis" (92). Methamphetamine has vasoconstrictive properties and is associated with preterm birth, low birth weight, and small for gestational age (93), but it not associated with placental abruption. The IDEAL (Infant Development and Lifestyle) is a prospective multisite cohort study designed to prevent repeating the racism and misleading science of early cocaine research (94) Results from IDEAL have demonstrated no differences in child development or motor skills at 3 years of age (95). There are no medications approved for treatment of methamphetamine use disorder (MUD) and none have been studied in pregnancy, however a systematic review of different medications and combinations, demonstrated possible positive effects on treatment outcomes most consistently with stimulant agonists, naltrexone and topiramate (96). There is also some evidence that mirtazapine results in a small reduction in methamphetamine use, less methamphetamine-positive urine tests, and decreased high risk sexual behaviors, yet it does not increase retention in treatment (97). Treatment rests primarily contingency management and motivational interviewing (67, 90).

Benzodiazepines

Benzodiazepines have benefit in the management of acute seizures and alcohol withdrawal, but they do not improve outcomes in the chronic management of depression or anxiety beyond the first month of treatment (98). Despite this, there are no national guidelines for prescribing and few interventions have been evaluated to reduce benzodiazepine-related problems (99). Yet benzodiazepines are ubiquitous and play a large role in the overdose crisis in the United States because concurrent use with opioids increases the risk of opioid-related accidental poisoning, particularly in the first 90 days of a new prescription (100). Benzodiazepines are prescribed more commonly to women as compared to men and may be over prescribed in pregnant and parenting individuals (101). Benzodiazepines are one of the most frequently prescribed medications in pregnancy: in privately insured individuals, 0.8% have a benzodiazepine prescription (102). Although concurrent use of benzodiazepines and opioids (including MOUD) is associated with overdose and death, MOUD should be continued despite patient report or detection of benzodiazepine use (103). Although *in utero* exposure does not suggest teratogenicity or negative effects on neurocognitive development in children, extended *in utero* exposure can cause neonatal withdrawal symptoms similar to opioids and is associated with longer NAS treatment especially in the context of methadone (104–106).

Similar to alcohol, abrupt cessation of benzodiazepines can be severe and life-threatening. Acute withdrawal is assessed and managed similarly to alcohol withdrawal; however benzodiazepine use disorder (BUD) requires more than withdrawal management and often includes gradual outpatient tapers, which have been shown to have higher efficacy as compared to short-term inpatient care (107). Effective treatment for BUD includes cognitive behavioral therapy and given the similarities with AUD should include consideration of medications for AUD (90).

Cannabis

Cannabis is the most common substance used in the United States that is illegal under federal law. Approximately 5% of pregnant individuals report past-month cannabis use (2). Many individuals use cannabis to self-treat medical and mental health

conditions prior to pregnancy and can continue this use into and during pregnancy especially for pregnancy specific symptoms such as nausea and vomiting (108, 109). Providers should also be aware of the increasing number of synthetic cannabinoids—also known as spice or K2—and of the limited data on maternal and perinatal outcomes (110). Synthetic cannabinoids have more potent effects than natural cannabinoids including respiratory distress, hypertension, acute renal failure, coagulopathy, psychosis, suicidal ideation, and death (111). The American College of Obstetricians and Gynecology, the American Academy of Pediatrics, and the US Surgeon General all advise against medical or recreational cannabis during preconception and pregnancy and lactation due to unknown and potential harmful maternal, fetal and child outcomes (112). Although there are no approved medications for cannabis use disorder, there is some evidence for consideration of *N*-acetylcysteine and gabapentin and there is good evidence for behavioral interventions including motivational enhancements, cognitive behavioral therapy, and contingency management (113).

The birthing hospitalization

Prior experiences of discrimination in healthcare settings, concern about pain management, and legitimate fear regarding child welfare intervention make the birthing hospitalization a stressful time for pregnant people with SUD.

For patients receiving MOUD, the medication should be continued throughout the birthing hospitalization (8, 36, 90). Dose verification through medical record review, prescription drug monitoring program, or contact with the opioid treatment program is helpful. MOUD does not provide analgesia, should be considered the patient's "baseline", and people with OUD may require more analgesia compared to people without OUD. Providers discuss options for pain control during prenatal care and upon admission to the birthing hospitalization using a trauma-informed approach founded upon shared decision-making. Some patients may have fears about how opioids analgesia could impact their recovery or may want to avoid opioids altogether, so ascertaining patient preference for pain management is paramount.

All MOUD (including methadone, buprenorphine, and naltrexone) should be continued including perioperatively for scheduled cesarean delivery to decrease the risk for both return to use and a difficult transition back to MOUD after acute pain has resolved (114). Existing research confirms better pain control with protocols that account for increased pain sensitivity and higher opioid tolerance in patients with OUD (115). This approach requires higher doses of short-acting opioids and a multimodal analgesic regimen.

Labor analgesia should be multi-modal and include topical, regional, and systemic approaches. Short-acting opioids can be safely prescribed and co-used with MOUD, including those on injectable naltrexone. Again, discussion of patient preference and a safety plan for opioids at home is crucial. Some patients may want opioids while in the hospital but may not want to have a prescription on discharge, while others may feel safer with a lock box, additional support, or family involvement. All people who may witness an overdose, including people with OUD and those receiving MOUD, should be co-prescribed naloxone upon hospital discharge (116, 117).

The American Academy of Pediatrics state that maternal substance use is "not a categorical contraindication to breastfeeding" (118). Breast or chest feeding is an important nonpharmacologic management of NAS and can be beneficial for all patients in recovery, although sociodemographic characteristics, race, and mental health status are all associated with decreased provider and nursing support of breastfeeding (119). Due to insufficient data on neurodevelopmental outcomes or risk of vertical infection transmission, breastfeeding in the context of continued illicit substance use is not encouraged. Clinical decisions regarding breastfeeding during the birthing hospitalization, however, must rest on the principles of bioethics including respect for bodily autonomy and adequate support to those who choose to breastfeed should be provided (118).

Assessment of behavioral health is an important component of admission and management during the birthing hospitalization. For people who present with untreated substance use disorder, the birthing hospitalization is a critical time to initiate treatment and bridge to continuing care. However, drug testing is grossly overused and misinterpreted despite professional society recommendations against routine drug testing of either the pregnant person or the newborn (120). A positive drug test result is not evidence of health or ill health, is not listed as a criterion for newborn discharge and is not essential to the diagnosis of NAS (121, 122). Yet presumptive positive drug test results are often reflexively reported to child welfare. This practice of "test and report" which reveals the drug test as not clinical but a primarily moral or parenting test, has been criticized by ACOG: "The laws, regulations, and policies that require health care practitioners and human service workers to respond to substance use and substance use disorder in a primarily punitive way, require health care providers to function as agents of law enforcement" (123). Although rare States mandate drug testing during the birthing hospitalization, Federal legislation is clear. CAPTA (the Child Abuse Prevention and Treatment Act) neither requires testing, nor the reporting of positive test results to child welfare and states unequivocally that substance use is not in-and-of-itself an indication of child abuse. Providers rarely understand the consequences of a report (124) and operate under the false assumption that an agency of surveillance can provide necessary services to families (125). Rates of child removal attributed to substance use have doubled in recent years, and the majority of infant reports come from health professionals (126).

As previously discussed, for all patients, it is crucial to prescribe naloxone upon discharge, particularly if co-prescribing opioids, but the need for naloxone should be assessed in all patients with OUD. Additionally, many geographic regions increasingly have a contaminated/poisoned illicit drug supply and therefore, there is an increase in unintentional fentanyl exposure. Safety around the potential for unintentional fentanyl use (i.e., in those with

non-opioid SUD) should be addressed and patients with any SUD should be encouraged to have a prescription for or access to naloxone.

Postpartum

Postpartum is a time of increased vulnerabilities for return to use, SUD recurrence, overdose, and overdose death. Care, which had been focused on the pregnant person, becomes less frequent and shifts from mother to infant and from medical to non-medical domains. Insurance churn, including loss of Medicaid coverage, contributes to care discontinuation especially for addiction treatment (57, 69, 127).

Maternal deaths have been increasing in the US and recent population-based data shows that the peak incidence of self-harm related death (specifically overdose and suicide) is 9–12 months postpartum (128–131). In contrast to a global trend in reduction of pregnant- and postpartum-related deaths, a large observational study reported a 26% increase in maternal deaths in 48 US states from 2000 to 2014 (131). Rates of discontinuation of MOUD have been shown to be greater than 50% at 6 months postpartum. Drug deaths are now the leading cause of maternal death in the US (69, 129). Naloxone prescribing and training is essential at delivery hospitalization discharge as is linkage to continuing care.

High rates of co-occurring mental health and substance use disorders put postpartum persons with SUD at especially high risk of psychiatric morbidity and mortality. Having any substance use disorder or use of illicit substances is associated with at least a threefold greater suicide risk (132). Additionally, many pregnant persons stop treatment, particularly medications, during pregnancy and do not resume immediately postpartum (133). Therefore, postpartum persons with SUD should be screened early and repeatedly for anxiety, depression and IPV in the postpartum period and should continue to follow closely with their addiction, obstetric and behavior health providers. Updated in 2018, ACOG recommends screening for depression, anxiety and IPV in all trimesters and the postpartum period and now recommends more and earlier postpartum follow up visits (134).

Appropriate continuing care should include postpartum services, Hepatitis C virus (HCV) treatment (if applicable), assessment of risk and discussion of initiation of pre-exposure prophylaxis (PrEP) for HIV, family planning counseling, behavioral health, peer recovery support and a "warm handoff" transition to primary care. Providers can partner with community-based organizations, peer support services, home visiting, and Early Head Start to support families and keep people engaged in care. The standard single postpartum visit from the prenatal care provider is likely insufficient for the needs of parenting people with SUD. ACOG recommends redesigning postpartum care to optimize health by focusing on care as an ongoing process with services and support tailored to individual and family needs (135). Postpartum care includes reproductive life planning and the provision of contraception within a shared decision-making context. Having an SUD is associated with higher rates of unintended pregnancy compared to the general population, especially in the immediate postpartum period (136)—86% of persons with SUD did not plan their pregnancy compared to 31%–47% in the general population (137). Contraceptive use, particularly the more effective LARC methods, among persons with SUD is lower (138, 139), however current data suggests that lower uptake of reproductive health services in this population is complex. A recent study found an association between increased postpartum contraceptive use and increased prenatal care visits, OBGYN buprenorphine prescribing and increased postpartum visits (140). Furthermore, HCV infection is rapidly increasing among reproductive-aged persons with injection drug use (141) leading to an ACOG recommendation for universal HCV screening in pregnancy (142). Enhanced engagement in care during pregnancy should not be a missed opportunity to provide persons with OUD access to treatment of other medical disorders such as HCV treatment.

Conclusion

Although drug use decreases significantly during pregnancy and continues to decrease from the first to the third trimester, overall substance use—including opioids, alcohol, cannabis, and cocaine—is increasing among pregnant people in the US. Substance use trends, treatment access, and child welfare policies differ widely by state and therefore it is important that all providers understand their specific geographic resources and climate. SUD outcomes are significantly improved by treatment, however a large gap in treatment access persists. Among those with need for SUD treatment, only 11% report receiving treatment. Although pregnant people are considered a priority population, structural and racial barriers that exist for all people with SUD persist through pregnancy and worsen postpartum in both access to and adequacy of treatment. Providers for the dyad can serve as another point in the healthcare system at which

TABLE 3 Resources for providers.

Resources for providers		Application
Movement for Family Power	https://www.movementforfamilypower.org/	Advocacy, Legal, Policy
Drug Policy Alliance	https://drugpolicy.org/	Advocacy, Legal, Policy
Academy of Perinatal Harm Reduction	https://www.perinatalharmreduction.org/	Advocacy, Clinical
Center on Parenting and Opioids	https://cpo.uoregon.edu/sites/cpo2.uoregon.edu/files/2022-05/substance-use-and-recovery-in-pregnancy-and-early-parenting-full_0.pdf	Clinical. Policy
SAMHSA	https://store.samhsa.gov/sites/default/files/d7/priv/sma18-5054.pdf	Clinical, Legal
NNPQC	https://www.cdc.gov/reproductivehealth/maternalinfanthealth/nnpqc.htm	Clinical
National Clinical Consultation Center: Substance Use Warmline	Substance Use Warmline (855) 300 3595, https://nccc.ucsf.edu/clinical-resources/substance-use-resources/	Clinical

patients can be appropriately screened and adequately referred to treatment, and therefore should be aware of all resources available to aid in breaking the cycle (see **Table 3**). Although it is established that punitive substance use policies increase adverse perinatal outcomes (143, 144), the unjust and inhuman separation of the dyad is not widely acknowledged (145, 146). In short, care should be both evidence-based and person-centered, reflect science and public health but also grounded in human rights, human dignity, and recognize the unique burdens we place on pregnant people, their bodies, and their minds.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Terplan M. Substance use and use disorder in pregnancy and postpartum. *Int Rev Psychiatry*. (2021) 33(6):501. doi: 10.1080/09540261.2021.1981098

2. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: results from the 2020 national survey on drug use and health, ed. N.S.H.-. HHS Publication No. PEP21-07-01-003. 2021, Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration.

3. Ebrahim SH, Gfroerer J. Pregnancy-related substance use in the United States during 1996–1998. *Obstet Gynecol*. (2003) 101(2):374–9. doi: 10.1016/s0029-7844(02)02588-7

4. Peltier MR, Roberts W, Verplaetse TL, Burke C, Zakiniaeiz Y, Moore K, et al. Licit and illicit drug use across trimesters in pregnant women endorsing past-year substance use: results from national survey on drug use and health (2009–2019). *Arch Womens Ment Health*. (2022) 25(4):819–27. doi: 10.1007/s00737-022-01244-6

5. Martin CE, Terplan M, Krans EE. Pain, opioids, and pregnancy: historical context and medical management. *Clin Perinatol*. (2019) 46(4):833–47. doi: 10.1016/j.clp.2019.08.013

6. Medicine, A.S.o.A. Definition of addiction. 2019. Available at: https://www.asam.org/quality-care/definition-of-addiction (Accessed September 15, 2022).

7. Kotelchuck M, Cheng ER, Belanoff C, Cabral HJ, Babakhanlou-Chase H, Derrington TM, et al. The prevalence and impact of substance use disorder and treatment on maternal obstetric experiences and birth outcomes among singleton deliveries in Massachusetts. *Matern Child Health J*. (2017) 21(4):893–902. doi: 10.1007/s10995-016-2190-y

8. Committee opinion No. 711: opioid use and opioid use disorder in pregnancy. *Obstet Gynecol*. (2017) 130(2):e81–94. doi: 10.1097/AOG.0000000000002235

9. Patrick SW, Schiff DM. A public health response to opioid use in pregnancy. *Pediatrics*. (2017) 139(3):e20164070. doi: 10.1542/peds.2016-4070

10. Ecker J, Abuhamad A, Hill W, Bailit J, Bateman BT, Berghella V, et al. Substance use disorders in pregnancy: clinical, ethical, and research imperatives of the opioid epidemic: a report of a joint workshop of the society for maternal-fetal medicine, American college of obstetricians and gynecologists, and American society of addiction medicine. *Am J Obstet Gynecol*. (2019) 221(1):B5–B28. doi: 10.1016/j.ajog.2019.03.022

11. Wright TE, Terplan M, Ondersma SJ, Yonkers K, Chang G, Creanga AA, et al. The role of screening, brief intervention, and referral to treatment in the perinatal period. *Am J Obstet Gynecol*. (2016) 215(5):539–47. doi: 10.1016/j.ajog.2016.06.038

12. Wong S, Ordean A, Kahan M. Substance use in pregnancy. *J Obstet Gynaecol Can*. (2011) 33(4):367–84. doi: 10.1016/S1701-2163(16)34855-1

13. Klaman SL, Isaacs K, Leopold A, Perpich J, Hayashi S, Vender J. Treating women who are pregnant and parenting for opioid use disorder and the concurrent care of their infants and children: literature review to support national guidance. *J Addict Med*. (2017) 11(3):178–90. doi: 10.1097/ADM.0000000000000308

14. Reddy UM, Davis JM, Ren Z, Greene MF; Opioid Use in Pregnancy, Neonatal Abstinence Syndrome, and Childhood Outcomes Workshop Invited Speakers. Opioid use in pregnancy, neonatal abstinence syndrome, and childhood outcomes: executive summary of a joint workshop by the eunice kennedy shriver national institute of child health and human development, American college of obstetricians and gynecologists, American academy of pediatrics, society for maternal-fetal medicine, centers for disease control and prevention, and the march of dimes foundation. *Obstet Gynecol*. (2017) 130(1):10–28. doi: 10.1097/AOG.0000000000002054

15. Ko JY, Tong VT, Haight SC, Terplan M, Stark L, Snead C, et al. Obstetrician–gynecologists' practices and attitudes on substance use screening during pregnancy. *J Perinatol*. (2020) 40(3):422–32. doi: 10.1038/s41372-019-0542-3

16. Koy JY, Nielsen T, Hoeppner BB, Terplan W, Hansen H, Bernson D, et al. Obstetrician–gynecologists' practice patterns related to opioid use during pregnancy and postpartum—United States, 2017. *J Perinatol*. (2020) 40(3):412–21. doi: 10.1038/s41372-019-0535-2

17. Martin CE, Scialli A, Terplan M. Unmet substance use disorder treatment need among reproductive age women. *Drug Alcohol Depend*. (2020) 206:107679. doi: 10.1016/j.drugalcdep.2019.107679

18. Schiff DM, Nielsen T, Hoeppner BB, Terplan W, Hansen H, Bernson D, et al. Assessment of racial and ethnic disparities in the use of medication to treat opioid use disorder among pregnant women in Massachusetts. *JAMA Network Open*. (2020) 3(5):e205734. doi: 10.1001/jamanetworkopen.2020.5734

19. Connaughton JF Jr, Finnegan LP, Schut J, Emich JP. Current concepts in the management of the pregnant opiate addict. *Addict Dis*. (1975) 2(1-2):21–35. PMID: 1163364

20. Finnegan LP. Management of pregnant drug-dependent women. *Ann N Y Acad Sci*. (1978) 311:135–46. doi: 10.1111/j.1749-6632.1978.tb16770.x

21. Terplan M. Women and the opioid crisis: historical context and public health solutions. *Fertil Steril*. (2017) 108(2):195–9. doi: 10.1016/j.fertnstert.2017.06.007

22. Wakeman SE, Bryant A, Harrison N. Redefining child protection: addressing the Harms of structural racism and punitive approaches for birthing people, dyads, and families affected by substance use. *Obstet Gynecol*. (2022) 140(2):167–73. doi: 10.1097/AOG.0000000000004786

23. Nguemeni Tiako MJ, Sweeney L. The government's involvement in prenatal drug testing may be toxic. *Matern Child Health J*. (2022) 26(4):761–3. doi: 10.1007/s10995-020-03110-2

24. Goodwin M. *Policing the womb: Invisible women and the criminalization of motherhood*. Cambridge University Press (2020).

25. Kors S, Kurdziel-Adams G, Towers C, Fortner K, Macfie J. Sexual abuse as a risk factor for opioid misuse in pregnancy. *J Child Sex Abus*. (2022) 31(5):538–49. doi: 10.1080/10538712.2022.2056104

26. Torchalla I, Linden IA, Strehlau V, Neilson EK, Krausz M. "Like a lots happened with my whole childhood": violence, trauma, and addiction in pregnant and postpartum women from Vancouver's downtown eastside. *Harm Reduct J*. (2015) 11:34. doi: 10.1186/1477-7517-11-34

27. Sanjuan PM, Pearson MR, Fokas K, Leeman LM. A mother's bond: an ecological momentary assessment study of posttraumatic stress disorder symptoms and substance craving during pregnancy. *Psychol Addict Behav*. (2020) 34(2):269–80. doi: 10.1037/adb0000543

28. Leiner C, Cody T, Mullins N, Ramage M, Ostrach BMM. "The elephant in the room;" a qualitative study of perinatal fears in opioid use disorder treatment in

southern appalachia. *BMC Pregnancy Childbirth*. (2021) 21(1):143. doi: 10.1186/s12884-021-03596-w

29. Paris R, Herriott AL, Maru M, Hackign SE, Sommer AR. Secrecy versus disclosure: women with substance use disorders share experiences in help seeking during pregnancy. *Matern Child Health J*. (2020) 24(11):1396–403. doi: 10.1007/s10995-020-03006-1

30. Berman H, Mason R, Hall J, Rodger S, Classen CC, Evans MK, Ross LE, et al. Laboring to mother in the context of past trauma: the transition to motherhood. *Qual Health Res*. (2014) 24(9):1253–64. doi: 10.1177/1049732314521902

31. Schiff DM, Halvorson AE, Dupont W, Davis MM, Patrick SW. Impact of stigmatizing language describing opioid-exposed mother infant dyads: a randomized case vignette study. *Subst Abus*. (2022) 43(1):551–5. doi: 10.1080/08897077.2021.1975866

32. Schiff DM, Stoltman JJK, Nielsen T, Myers S, Nolan M, Terplan M, et al. Assessing stigma towards substance use in pregnancy: a randomized study testing the impact of stigmatizing language and type of opioid use on attitudes toward mothers with opioid use disorder. *J Addict Med*. (2022) 16(1):77–83. doi: 10.1097/ADM.0000000000000832

33. Atayde AMP, Hauc SC, Bessette LG, Danckers H, Saitz R. Changing the narrative: A call to end stigmatizing terminology related to substance use disorders. *Addict Res Theory*. 29(5):1–4. doi: 10.1080/16066359.2021.1875215

34. Saitz R. International statement recommending against the use of terminology that can stigmatize people. *J Addict Med*. (2016) 10(1):1–2. doi: 10.1097/ADM.0000000000000178

35. Medicine, A.S.o.A. Substance use and substance use disorder among pregnant and postpartum people (2022). Available at: https://www.asam.org/advocacy/public-policy-statements/details/public-policy-statements/2022/10/12/substance-use-and-substance-use-disorder-among-pregnant-and-postpartum-people (Accessed January 11, 2023).

36. Administration, S.A.a.M.H.S. *Clinical guidance for treating pregnant and parenting women with opioid use disorder and their infants, ed. H.P.N.S. 18-5054*. Rockville, MD: Substance Abuse and Mental Health Services Administration (2018).

37. Committee opinion 664: refusal of medically recommended treatment during pregnancy. *Obstet Gynecol*, 2016. 127:e175–82. doi: 10.1097/AOG.0000000000001485

38. Association, A.M. Legal interventions during pregnancy. Policy statement H-420.969 (2018). Available at: https://policysearch.ama-assn.org/policyfinder/detail/women?uri=%2FAMADoc%2FHOD.xml-0-3712.xml (Accessed September 15, 2022).

39. Kerker BD, Horwitz SM, Leventhal JM. Patients' characteristics and providers' attitudes: predictors of screening pregnant women for illicit substance use. *Child Abuse Negl*. (2004) 28(2):209–23. doi: 10.1016/j.chiabu.2003.07.004

40. Ondersma SJ, Chang G, Blake-Lamb T, Gilstad-Hayden K, Orav J, Beatty JR, et al. Accuracy of five self-report screening instruments for substance use in pregnancy. *Addiction*. (2019) 114(9):1683–93. doi: 10.1111/add.14651

41. Coleman-Cowger V, Oga EA, Peters EN, Trocin KE, Koszowski B, Mark K. Accuracy of three screening tools for prenatal substance use. *Obstet Gynecol*. (2019) 133(5):952–61. doi: 10.1097/AOG.0000000000003230

42. Wanar A, Isley BC, Saia K, Field TA. False-positive fentanyl urine detection after initiation of labetalol treatment for hypertension in pregnancy: a case report. *J Addict Med*. (2012) 16(6):e417–9. doi: 10.1097/ADM.0000000000001010

43. Yee LM, Wu D. False-positive amphetamine toxicology screen results in three pregnant women using labetalol. *Obstet Gynecol*. (2011) 117(Part 2):503–6. doi: 10.1097/AOG.0b013e318206c07c

44. Jarvis M, Williams J, Hurford M, Lindsay D, Lincoln P, Giles L, et al. Appropriate use of drug testing in clinical addiction medicine. *J Addict Med*. (2017) 11(3):163–73. doi: 10.1097/ADM.0000000000000323

45. Stone R. Pregnant women and substance use: fear, stigma, and barriers to care. *Health Justice*. (2015) 3(1):1–15. doi: 10.1186/s40352-015-0015-5

46. McLellan AT, Lewis DC, O'Brien CP, Kleber HD. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *J Am Med Assoc*. (2000) 284(13):1689–95. doi: 10.1001/jama.284.13.1689

47. Rosenthal EW, Short VL, Cruz Y, Barber C, Baxter JK, Abatemarco DJ, et al. Racial inequity in methadone dose at delivery in pregnant women with opioid use disorder. *J Subst Abuse Treat*. (2021) 131:108454. doi: 10.1016/j.jsat.2021.108454

48. Gastfriend DR, Mee-Lee D. Thirty years of TheASAMCriteria: a report card. *Psychiatr Clin North Am*. (2022) 45(3):593–609. doi: 10.1016/j.psc.2022.05.008

49. Madras BK, Ahmad NJ, Wen J, Sharfstein JS. Improving access to evidence-based medical treatment for opioid use disorder: strategies to address key barriers within the treatment system. *NAM Perspect*. (2020) 2020. doi: 10.31478/202004b

50. Terplan M, Longinaker N, Appel L. Women-centered drug treatment services and need in the United States, 2002-2009. *Am J Public Health*. (2015) 105(11):e50–4. doi: 10.2105/AJPH.2015.302821

51. Clark HW. Residential substance abuse treatment for pregnant and postpartum women and their children: treatment and policy implications. *Child Welfare*. (2001) 80(2):179–98. PMID: 11291900

52. Haight SC, Ko JY, Tong VT, Bohm MK, Callaghan WM. Opioid use disorder documented at delivery hospitalization - United States, 1999-2014. *Morb Mortal Wkly Rep*. (2018) 67(31):845–9. doi: 10.15585/mmwr.mm6731a1

53. Terplan M, Kennedy-Hendricks A, Chisolm MS. Prenatal substance use: exploring assumptions of maternal unfitness. *Subst Abuse*. (2015) 9(Suppl 2):1–4. doi: 10.4137/SART.S23328

54. Clearly EM, Smid MC, Charles JE, Costantine MM, Saade G, Rood KM, et al. Buprenorphine X-waiver exemption - beyond the basics for the obstetrical provider. *Am J Obstet Gynecol MFM*. (2021) 3(6):100451. doi: 10.1016/j.ajogmf.2021.100451

55. Loyal J, Nguyen VN, Picagli D, Petrucelli A, O'Mara E, Grossman MR, et al. Postpartum nurses' experience caring for infants with neonatal abstinence syndrome. *Hosp Pediatr*. (2019) 9(8):601–7. doi: 10.1542/hpeds.2019-0087

56. Zedler BK, Mann AL, Kim MM, Amick HR, Joyce AR, Murrelle L, et al. Buprenorphine compared with methadone to treat pregnant women with opioid use disorder: a systematic review and meta-analysis of safety in the mother, fetus and child. *Addiction*. (2016) 111(12):2115–28. doi: 10.1111/add.13462

57. Schiff DM, Nielsen T, Terplan M, Hood M, Bernson D, Diop H, et al. Fatal and nonfatal overdose among pregnant and postpartum women in Massachusetts. *Obstet Gynecol*. (2018) 132(2):466–74. doi: 10.1097/AOG.0000000000002734

58. Morgan JR, Schackman BR, Weinstein ZM, Walley AY, Linas BP. Overdose following initiation of naltrexone and buprenorphine medication treatment for opioid use disorder in a United States commercially insured cohort. *Drug Alcohol Depend*. (2019) 200:34–9. doi: 10.1016/j.drugalcdep.2019.02.031

59. Winhusen T, Lofwall M, Jones HE, Wilder C, Lindblad R, Schiff DM, et al. Medication treatment for opioid use disorder in expectant mothers (MOMs): design considerations for a pragmatic randomized trial comparing extended-release and daily buprenorphine formulations. *Contemp Clin Trials*. (2020) 93:106014. doi: 10.1016/j.cct.2020.106014

60. Terplan M, Laird H, Hand D, Wright TE, Premkumar A, Martin CE, et al. Opioid detoxification during pregnancy: a systematic review. *Obstet Gynecol*. (2018) 131(5):803–14. doi: 10.1097/AOG.0000000000002562

61. Jones HE, Terplan M, Meyer M. Medically assisted withdrawal (detoxification): considering the mother-infant dyad. *J Addict Med*. (2017) 11(2):90–2. doi: 10.1097/ADM.0000000000000289

62. Short VL, Hand DJ, MacAfee L, Abatemarco DJ, Terplan M. Trends and disparities in receipt of pharmacotherapy among pregnant women in publically funded treatment programs for opioid use disorder in the United States. *J Subst Abuse Treat*. (2018) 89:67–74. doi: 10.1016/j.jsat.2018.04.003

63. McCarthy JJ. Methadone and buprenorphine for opioid dependence during pregnancy: a retrospective cohort study: Re Meyer, et al. *J Addict Med*. (2016) 10(2):133–4. doi: 10.1097/ADM.0000000000000183

64. Wong K, Saver B, Scanlan JM, Gianutsos LP, Bhakta Y, Walsh J, et al. Does maternal buprenorphine dose affect severity or incidence of neonatal abstinence syndrome? *J Addict Med*. (2018) 12(6):435–41. doi: 10.1097/ADM.0000000000000427

65. Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med*. (2010) 363(24):2320–31. doi: 10.1056/NEJMoa1005359

66. Dugosh K, Abraham A, Seymour B, McLoyd K, Keli JD, Chalk M, et al. A systematic review on the use of psychosocial interventions in conjunction with medications for the treatment of opioid addiction. *J Addict Med*. (2016) 10(2):93–103. doi: 10.1097/ADM.0000000000000193

67. Terplan M, Ramanadhan S, Locke A, Longinaker N, Lui S. Psychosocial interventions for pregnant women in outpatient illicit drug treatment programs compared to other interventions. *Cochrane Database Syst Rev*. (2015) 4:Cd006037. doi: 10.1002/14651858.CD006037.pub3

68. National Academies of Sciences, Engineering, and Medicine. *Medications for opioid use disorder save lives*. National Academies Press (2019).

69. Wilder C, Lewis D, Winhusen T. Medication assisted treatment discontinuation in pregnant and postpartum women with opioid use disorder. *Drug Alcohol Depend*. (2015) 149:225–31. doi: 10.1016/j.drugalcdep.2015.02.012

70. Kleinman MB, Felton JW, Johnson A, Magidson JF. "I have to be around people that are doing what i'm doing": the importance of expanding the peer recovery coach role in treatment of opioid use disorder in the face of COVID-19 health disparities. *J Subst Abuse Treat*. (2021) 122:108182. doi: 10.1016/j.jsat.2020.108182

71. Fallin-Bennett A, Elswick A, Ashford K. Peer support specialists and perinatal opioid use disorder: someone that's been there, lived it, seen it. *Addict Behav*. (2020) 102:106204. doi: 10.1016/j.addbeh.2019.106204

72. Blandthorn J, Bowman E, Leung L, Bonomo Y, Dietze P. Managing opioid overdose in pregnancy with take-home naloxone. *Aust N Z J Obstet Gynaecol*. (2018) 58(4):460–2. doi: 10.1111/ajo.12761

73. Haffajee RL, Cherney S, Smart R. Legal requirements and recommendations to prescribe naloxone. *Drug Alcohol Depend*. (2020) 209:107896. doi: 10.1016/j.drugalcdep.2020.107896

74. May PA, Baete A, Russo J, Elliott AJ, Blankenship J, Kalberg WO, et al. Prevalence and characteristics of fetal alcohol spectrum disorders. *Pediatrics*. (2014) 134(5):855–66. doi: 10.1542/peds.2013-3319

75. Campos J, Roca L, Gude F, Gonzalez-Quintela A. Long-term mortality of patients admitted to the hospital with alcohol withdrawal syndrome. *Alcohol Clin Exp Res*. (2011) 35(6):1180–6. doi: 10.1111/j.1530-0277.2011.01451.x

76. Crotty K, Freedman KI, Kampman KM. Executive summary of the focused update of the ASAM national practice guideline for the treatment of opioid use disorder. *J Addict Med*. (2020) 14(2):99–112. doi: 10.1097/ADM.0000000000000635

77. Pettinati HM. A structured approach to medical management: a psychosocial intervention to support pharmacotherapy in the treatment of alcohol dependence. *J Stud Alcohol Suppl*. (2005) 15:170–8; discussion 168–9. doi: 10.15288/jsas.2005.s15.170

78. Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. *J Am Med Assoc*. (2006) 295 (17):2003–17. doi: 10.1001/jama.295.17.2003

79. Smith EJ, Lui S, Terplan M. Pharmacologic interventions for pregnant women enrolled in alcohol treatment. *Cochrane Database Syst Rev*. (2009) 2009(3): Cd007361. doi: 10.1002/14651858.CD007361.pub2

80. Kelty E, Terplan M, Greenland M, Preen D. Pharmacotherapies for the treatment of alcohol use disorders during pregnancy: time to reconsider? *Drugs*. (2021) 81(7):739–48. doi: 10.1007/s40265-021-01509-x

81. DeVido J, Bogunovic O, Weiss RD. Alcohol use disorders in pregnancy. *Harv Rev Psychiatry*. (2015) 23(2):112–21. doi: 10.1097/HRP.0000000000000070

82. Tong VT, Dietz PM, Morrow B, D'Angelo DV, Farr SL, Rockhill KM. Trends in smoking before, during, and after pregnancy–pregnancy risk assessment monitoring system, United States, 40 sites, 2000-2010. *MMWR Surveill Summ*. (2013) 62 (6):1–19. PMID: 24196750

83. Claire R, Chamberlain C, Davey MA, Cooper SE, Berlin I, Leonardi-Bee J, Coleman T. Pharmacological interventions for promoting smoking cessation during pregnancy. *Cochrane Database Syst Rev*. (2020) 3(3):Cd010078. doi: 10.1002/14651858.CD010078.pub3

84. McKee SE, Smith PH, Kaufman M, Mazure CM, Weinberger AH. Sex differences in varenicline efficacy for smoking cessation: a meta-analysis. *Nicotine Tob Res*. (2016) 18(5):1002–11. doi: 10.1093/ntr/ntv207

85. Coles CD. Saying "goodbye" to the "crack baby". *Neurotoxicol Teratol*. (1993) 15 (5):290–2; discussion 311–2. doi: 10.1016/0892-0362(93)90024-I

86. Metzl JM, Roberts DE. Structural competency meets structural racism: race, politics, and the structure of medical knowledge. *AMA J Ethics*. (2014) 16 (9):674–90. doi: 10.1001/virtualmentor.2014.16.9.spec1-1409

87. Frank DA, Augustyn M, Knight WG, Pell T, Zuckerman B. Growth, development, and behavior in early childhood following prenatal cocaine exposure: a systematic review. *J Am Med Assoc*. (2001) 285(12):1613–25. doi: 10.1001/jama.285.12.1613

88. Moore TR, Sorg J, Miller L, Key TC, Resnik R. Hemodynamic effects of intravenous cocaine on the pregnant ewe and fetus. *Am J Obstet Gynecol*. (1986) 155(4):883–8. doi: 10.1016/S0002-9378(86)80044-8

89. Chan B, Kondo K, Freeman M, Ayers C, Montgomery J, Kansagara D. Pharmacotherapy for cocaine use disorder-a systematic review and meta-analysis. *J Gen Intern Med*. (2019) 34(12):2858–73. doi: 10.1007/s11606-019-05074-8

90. Smid MC, Terplan M. What obstetrician-gynecologists should know about substance use disorders in the perinatal period. *Obstet Gynecol*. (2022) 139 (2):317–37. doi: 10.1097/AOG.0000000000004657

91. Lewis D, Kenneally M, Van DenHeuvel C, Byard RW. Methamphetamine deaths: changing trends and diagnostic issues. *Med Sci Law*. (2021) 61(2):130–7. doi: 10.1177/0025802420986707

92. Jenkins RA, Whitney BM, Nance RM, Allen TM, Cooper HLF, Feinberg J, et al. The rural opioid initiative consortium description: providing evidence to understand the fourth wave of the opioid crisis. *Addict Sci Clin Pract*. (2022) 17(1):38. doi: 10.1186/s13722-022-00322-5

93. Smith LM, LaGasse LL, Derauf C, Grant P, Shah R, Arria A, et al. The infant development, environment, and lifestyle study: effects of prenatal methamphetamine exposure, polydrug exposure, and poverty on intrauterine growth. *Pediatrics*. (2006) 118(3):1149–56. doi: 10.1542/peds.2005-2564

94. Kiblawi ZN, Smith LM, Diaz SD, LaGasse LL, Derauf C, Newman E, et al. Prenatal methamphetamine exposure and neonatal and infant neurobehavioral outcome: results from the IDEAL study. *Subst Abus*. (2014) 35(1):68–73. doi: 10.1080/08897077.2013.814614

95. Smith LM, LaGasse LL, Derauf C, Grant P, Shah R, Arria A, et al. Prenatal methamphetamine use and neonatal neurobehavioral outcome. *Neurotoxicol Teratol*. (2008) 30(1):20–8. doi: 10.1016/j.ntt.2007.09.005

96. Siefried KJ, Acheson LS, Lintzeris N, Ezard N. Pharmacological treatment of methamphetamine/amphetamine dependence: a systematic review. *CNS Drugs*. (2020) 34(4):337–65. doi: 10.1007/s40263-020-00711-x

97. Naji L, Dennis B, Rosic T, Wiercioch W, Paul J, Worster A, et al. Mirtazapine for the treatment of amphetamine and methamphetamine use disorder: a systematic review and meta-analysis. *Drug Alcohol Depend*. (2022) 232:109295. doi: 10.1016/j.drugalcdep.2022.109295

98. Ogawa Y, Takeshima N, Hayasaka Y, Tajika A, Watanabe N, Streiner D, Furukawa TA. Antidepressants plus benzodiazepines for adults with major depression. *Cochrane Database Syst Rev*. (2019) 6(6):Cd001026. doi: 10.1002/14651858.CD001026.pub2

99. Murphy Y, Wilson E, Goldner EM, Fischer B. Benzodiazepine use, misuse, and harm at the population level in Canada: a comprehensive narrative review of data and developments since 1995. *Clin Drug Investig*. (2016) 36(7):519–30. doi: 10.1007/s40261-016-0397-8

100. Hernandez I, He M, Brooks MM, Zhang Y. Exposure-response association between concurrent opioid and benzodiazepine use and risk of opioid-related overdose in medicare part D beneficiaries. *JAMA Netw Open*. (2018) 1(2):e180919. doi: 10.1001/jamanetworkopen.2018.0919

101. Venkatesh KK, Pate V, Boggess KA, Jones HE, Jonsson Funk M, Smid MC. Trends in opioid and psychotropic prescription in pregnancy in the United States from 2001 to 2015 in a privately insured population: a cross-sectional study. *Ann Intern Med*. (2020) 173(11 Suppl):S19–s28. doi: 10.7326/M19-3249

102. Bais B, Molenaar NM, Bijma HH, Hoogendijk WJG, Mulder CL, Luik AI, et al. Prevalence of benzodiazepines and benzodiazepine-related drugs exposure before, during and after pregnancy: a systematic review and meta-analysis. *J Affect Disord*. (2020) 269:18–27. doi: 10.1016/j.jad.2020.03.014

103. Park TW, Larochelle MR, Saitz R, Wang N, Bernson D, Walley AY. Associations between prescribed benzodiazepines, overdose death and buprenorphine discontinuation among people receiving buprenorphine. *Addiction*. (2020) 115(5):924–32. doi: 10.1111/add.14886

104. Grigoriadis S, Graves L, Peer M, Mamisashvili L, Dennis C-L, Vigod SN, et al. Benzodiazepine use during pregnancy alone or in combination with an antidepressant and congenital malformations: systematic review and meta-analysis. *J Clin Psychiatry*. (2019) 80(4):18r12412. doi: 10.4088/JCP.18r12412

105. Rementería JL, Bhatt K. Withdrawal symptoms in neonates from intrauterine exposure to diazepam. *J Pediatr*. (1977) 90(1):123–6. doi: 10.1016/S0022-3476(77)80785-3

106. Seligman NS, Salva N, Hayes EJ, Dysart KC, Pequignot EC, Baxter JK. Predicting length of treatment for neonatal abstinence syndrome in methadone-exposed neonates. *Am J Obstet Gynecol*. (2008) 199(4):396. doi: 10.1016/j.ajog.2008.06.088

107. Voshaar RCO, Couvee JE, Van Balkom AJLM, Mulder PGH, Zitman FG. Strategies for discontinuing long-term benzodiazepine use: meta-analysis. *Br J Psychiatry*. (2006) 189:213–20. doi: 10.1192/bjp.189.3.213

108. Chang JC, Tarr JA, Holland CL, De Genna NM, Richardson GE, Rodrigues KL, et al. Beliefs and attitudes regarding prenatal marijuana use: perspectives of pregnant women who report use. *Drug Alcohol Depend*. (2019) 196:14–20. doi: 10.1016/j.drugalcdep.2018.11.028

109. Young-Wolff KC, Sarovar V, Tucker LY, Avalos LA, Alexeeff S, Conway A, et al. Trends in marijuana use among pregnant women with and without nausea and vomiting in pregnancy, 2009-2016. *Drug Alcohol Depend*. (2019) 196:66–70. doi: 10.1016/j.drugalcdep.2018.12.009

110. Carlier J, Huestis MA, Zaami S, Pichini S, Busardo FP. Monitoring perinatal exposure to cannabis and synthetic cannabinoids. *Ther Drug Monit*. (2020) 42 (2):194–204. doi: 10.1097/FTD.0000000000000667

111. Cohen K, Weinstein A. The effects of cannabinoids on executive functions: evidence from Cannabis and synthetic cannabinoids-A systematic review. *Brain Sci*. (2018) 8(3):133. doi: 10.3390/brainsci8030040

112. Ryan SA, Ammerman SD, O'Connor ME, AAP Committee on Substance Use and Prevention, AAP Section on Breastfeeding. Marijuana use during pregnancy and breastfeeding: implications for neonatal and childhood outcomes. *Pediatrics*. (2018) 142(3):e20181889. doi: 10.1542/peds.2018-1889

113. Kondo KK, et al. Pharmacotherapy for the treatment of Cannabis use disorder: a systematic review. *Ann Intern Med*. (2020) 172(6):398–412. doi: 10.7326/M19-1105

114. Kondo KK, Morasco BJ, Nugent SM, Ayers CK, O'Neil ME, Freeman M, et al. Treating perioperative and acute pain in patients on buprenorphine: narrative literature review and practice recommendations. *J Gen Intern Med*. (2020) 35 (12):3635–43. doi: 10.1007/s11606-020-06115-3

115. Buresh M, Ratner J, Zgierska A, Gordin V, Alvanzo A. Managing acute pain in patients taking medication for opioid use disorder: a rapid review. *J Gen Intern Med*. (2020) 35(Suppl 3):945–53. doi: 10.1007/s11606-020-06256-5

116. Veazie S, Mackey K, Peterson K, Bourne D. National partnership for maternal safety: consensus bundle on obstetric care for women with opioid use disorder. *Obstet Gynecol*. (2019) 134(2):365–75. doi: 10.1097/AOG.0000000000003381

117. Krans EE, Campopiano M, Cleveland L, Goodman D, Kilday D, Kendig SJD, et al. Care for pregnant and postpartum people with substance use disorder (2021). Available at: https://saferbirth.org/psbs/care-for-pregnant-and-postpartum-people-with-substance-use-disorder/ (Accessed September 15, 2022).

118. Association of women's health, obstetric and neonatal nurses. Breastfeeding and the use of human milk. *Pediatrics*. (2012) 129(3):e827–41. doi: 10.1542/peds.2011-3552

119. Grywacheski V, et al. Opioid and Cannabis use during pregnancy and breastfeeding in relation to sociodemographics and mental health status: a descriptive study. *J Obstet Gynaecol Can*. (2021) 43(3):329–36. doi: 10.1016/j.jogc.2020.09.017

120. Grywacheski V, Ali J, Baker MM, Gheorghe M, Wong SL, Orpana HM. Test or talk: empiric bias and epistemic injustice. *Obstet Gynecol*. (2022) 140(2):150–2. doi: 10.1097/AOG.0000000000004884

121. Benitz WE, et al. Hospital stay for healthy term newborn infants. *Pediatrics*. (2015) 135(5):948–53. doi: 10.1542/peds.2015-0699

122. Benitz WE, Aucott S, Benitz WE, Cummings JJ, Eichenwald EC, Goldsmith J, et al. Standardizing the clinical definition of opioid withdrawal in the neonate. *J Pediatr*. (2022) 243:33–9. doi: 10.1016/j.jpeds.2021.12.021

123. Jilani SM, Jones HE, Grossman M, Jansson LM, Terplan M, Faherty LJ, et al. Opposition to criminalization of individuals during pregnancy and the postpartum period (2020).

124. Suomi A, Bolton A, Pasalich D. The prevalence of post-traumatic stress disorder in birth parents in child protection services: systematic review and meta-analysis. *Trauma Violence Abuse*. (2021) 24(2):1032–46. doi: 10.1177/15248380211048444

125. Sangoi L. Whatever they do, I'm her comfort, I'm her protector. How the foster system has become ground zero for the US drug war. Movement for family power (2020).

126. Meinhofer A, Angleró-Díaz Y. Trends in foster care entry among children removed from their homes because of parental drug use, 2000 to 2017. *JAMA Pediatr*. (2019) 173(9):881–3. doi: 10.1001/jamapediatrics.2019.1738

127. Admon LK, Zivin K, Kozhimannil KB. Perinatal insurance coverage and behavioural health-related maternal mortality. *Int Rev Psychiatry*. (2021) 33 (6):553–6. doi: 10.1080/09540261.2021.1903843

128. MacDorman MF, et al. Causes contributing to the excess maternal mortality risk for women 35 and over, United States, 2016-2017. *PLoS One*. (2021) 16(6): e0253920. doi: 10.1371/journal.pone.0253920

129. MacDorman MF, Thorma M, Declercq E, Howell EA. Early lessons from maternal mortality review committees on drug-related deaths-time for obstetrical providers to take the lead in addressing addiction. *Am J Obstet Gynecol MFM*. (2020) 2(4):100177. doi: 10.1016/j.ajogmf.2020.100177

130. Smid MC, Schauberger CW, Terplan M, Wright TE. Recent increases in the U.S. maternal mortality rate: disentangling trends from measurement issues. *Obstet Gynecol*. (2016) 128(3):447–55. doi: 10.1097/AOG.0000000000001556

131. Grigoriadis S, et al. Perinatal suicide in Ontario, Canada: a 15-year population-based study. *Can Med Assoc J*. (2017) 189(34):E1085–e1092. doi: 10.1503/cmaj.170088

132. Grigoriadis S, Wilton AE, Kurdyak PA, Rhodes AE, VonderPorten EH, Levitt A, et al. Associations between substance use disorders and suicide or suicide attempts in people with mental illness: a danish nation-wide, prospective, register-based study of patients diagnosed with schizophrenia, bipolar disorder, unipolar depression or personality disorder. *Addiction*. (2017) 112(7):1250–9. doi: 10.1111/add.13788

133. Forray A, Yonkers KA. The collision of mental health, substance use disorder, and suicide. *Obstet Gynecol*. (2021) 137(6):1083–90. doi: 10.1097/AOG.0000000000004391

134. American College of Obstetricians and Gynecologists. Committee opinion no. 757: screening for perinatal depression. *Obstet Gynecol*. (2018) 132(5):e208–12. doi: 10.1097/AOG.0000000000002927

135. ACOG Committee opinion No. 736 summary: optimizing postpartum care. *Obstet Gynecol*. (2018) 131(5):949–51. doi: 10.1097/AOG.0000000000002628

136. Martino SC, et al. Exploring the link between substance use and abortion: the roles of unconventionality and unplanned pregnancy. *Perspect Sex Reprod Health*. (2006) 38(2):66–75. doi: 10.1363/3806606

137. Martino SC, Collins RL, Ellickson PL, Klein DJ. The prevalence of unplanned pregnancy and associated factors in britain: findings from the third national survey of sexual attitudes and lifestyles (natsal-3). *Lancet*. (2013) 382(9907):1807–16. doi: 10.1016/S0140-6736(13)62071-1

138. Wellings K, Jones KG, Mercer CH, Tanton C, Clifton S, Datta J, et al. Unintended pregnancy in opioid-abusing women. *J Subst Abuse Treat*. (2011) 40 (2):199–202. doi: 10.1016/j.jsat.2010.08.011

139. Heil SH, Jones HE, Arria A, Kaltenbacj K, Coyle M, Fischer G, et al. Contraceptive use and method choice among women with opioid and other substance use disorders: a systematic review. *Prev Med*. (2015) 80:23–31. doi: 10.1016/j.ypmed.2015.04.008

140. Terplan M, Hand DJ, Hutchinson M, Salisbury-Afshar E, Heil SH. Factors associated with contraceptive use among postpartum women with substance use disorder. *Sex Reprod Healthc*. (2022) 33:100764. doi: 10.1016/j.srhc.2022.100764

141. Shelton D, Ramage M, Hughes P, Tak C. Hepatitis C virus infection among reproductive-aged women and children in the United States, 2006 to 2014. *Ann Intern Med*. (2017) 166(11):775–82. doi: 10.7326/M16-2350

142. Ly KN, Jiles RB, Teshale EH, Foster MA, Pesano RL, Holmberg SD. Routine hepatitis C virus screening in pregnant individuals.

143. Faherty LJ, et al. Association between punitive policies and neonatal abstinence syndrome among medicaid-insured infants in complex policy environments. *Addiction*. (2022) 117(1):162–71. doi: 10.1111/add.15602

144. Faherty LJ, Heins S, Kranz AM, Patrick SW. Forty years of state alcohol and pregnancy policies in the USA: best practices for public health or efforts to restrict women's reproductive rights? *Alcohol Alcohol*. (2017) 52(6):715–21. doi: 10.1093/alcalc/agx047

145. Roberts SCM, Thomas S, Treffers R, Drabble L. Association between state-level criminal justice-focused prenatal substance use policies in the US and substance use-related foster care admissions and family reunification. *JAMA Pediatr*. (2020) 174 (8):782–8. doi: 10.1001/jamapediatrics.2020.1027

146. Sanmartin MX, Ali MM, Lynch S, Aktas A. The racial geography of child welfare. *Child Welfare*. (2008) 87(2):125–50. PMID: 18972935

frontiers | Frontiers in Pediatrics

TYPE Mini Review
PUBLISHED 14 July 2023
DOI 10.3389/fped.2023.1239107

Check for updates

OPEN ACCESS

EDITED BY
Loretta Finnegan,
Finnegan Consulting, LLC, United States

REVIEWED BY
Elizabeth Yen,
Tufts University, United States

*CORRESPONDENCE
Enrique Gomez Pomar
✉ enrique.gomez@uky.edu

RECEIVED 12 June 2023
ACCEPTED 28 June 2023
PUBLISHED 14 July 2023

CITATION
Gomez Pomar E (2023) A mini review of what matters in the management of NAS, is ESC the best care?
Front. Pediatr. 11:1239107.
doi: 10.3389/fped.2023.1239107

COPYRIGHT
© 2023 Gomez Pomar. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

A mini review of what matters in the management of NAS, is ESC the best care?

Enrique Gomez Pomar[1,2]*

[1]Division of Neonatology, Department of Pediatrics, University of Kentucky, Lexington, KY, United States, [2]Department of Pediatrics, St. Bernards Regional Medical Center, Jonesboro, AR, United States

As the use of opioids and polysubstance by pregnant women has increased over the years, there has also been a sharp increase in cases of neonatal abstinence syndrome (NAS). Classically, infants affected by NAS have been cared for in neonatal intensive care units resulting in an increase of healthcare expenditure and resource utilization as well as separation from the families. Consequently, the Eat, Sleep, and Console (ESC) tool was developed and promoted as a novel method that focuses on maternal/infant dyad during hospital stay while decreasing the use of pharmacological interventions and therefore decreasing the length of stay and healthcare expenditure. Thus, it has been implemented in several hospitals in the United States. Although the training of staff has been proposed and the interventions of sleep, eat, and console are defined, there still exists a lack of standardization of this practice specifically in regard to the type of associated non-pharmacological practices as well as the reports of its short- and long-term outcomes.

KEYWORDS

NAS, ESC, opioid withdrawal, neonatal withdrawal, rooming-in

Introduction

Neonatal abstinence syndrome (NAS) refers to a constellation of signs experienced by some newborns born from mothers that have used opioids during pregnancy. Because of the opioid epidemic and the increase in the number of infants born following *in-utero* opioid exposure, NAS has recently been referred to as neonatal opioid withdrawal syndrome (NOWS). For the purpose of this perspective on Eat, Sleep, and Console (ESC), the term NAS would be more appropriate since most of those with opioid use disorders also use other drugs, and withdrawal symptomatology may not all be attributable to opioid withdrawal. NAS occurs when there is an abrupt termination of the trans-placental transfer of addictive substances. Maternal opioid use and its effects on newborns were first described in 1875, and its incidence has dramatically increased over the years (1). From 2010 to 2017, maternal opioid use increased from 3.5 to 8.2 per 1,000 delivery hospitalizations resulting in an increase in NAS cases from 4 to 7.3 per 1,000 birth hospitalizations (2).

Assessment and management of infants with NAS

The evaluation and management of NAS also remains non-standardized. Studies showed and experts recommend that each institution develop a protocol establishing the prenatal screening for drug use, the postnatal follow-up of infants at risk, and, for those affected, the use of non-pharmacological measures while promoting rooming-in as much as

possible (3, 4). Tools to objectively evaluate infants at risk for NAS have been developed over the years, and the Finnegan NAS (FNAS) tool remains the most used (3). Once affected infants are identified to need pharmacological treatment; despite the use of non-pharmacological measures, it is recommended that these infants are monitored for cardiorespiratory events (1, 5, 6).

Infants with NAS are often admitted to the NICU for pharmacological treatment; however, this model resulted in increased costs and length of stay (LOS) (7). Therefore, a novel model called the eat, sleep, and console (ESC) was proposed wherein infants stayed with their parents during the entire hospitalization, and pharmacological intervention was given only if the infant was inconsolable, not eating or sleeping adequately (8). This initiative only focuses on three outcomes: decrease pharmacological intervention, decrease LOS, and decrease hospital cost, while lacking in standardized approaches regarding pharmacological and non-pharmacological interventions or as basic as to what constitutes adequate feeding in infants with NAS (1, 8–10). Since then, multiple institutions have adopted the ESC model without considering any clinical outcomes or short- and long-term consequences on these infants (11–15).

The ESC tool focuses, as its name suggests, on the ability of the neonate to eat, sleep, and be consoled. If the infant was able to breastfeed effectively or take ≥ 1 oz from a bottle per feed, to sleep undisturbed for ≥ 1 h, and, if crying, to be consoled within 10 min, then the infant was deemed to be well. Otherwise, non-pharmacological interventions were maximized and, if unsuccessful, then morphine was initiated or increased (8). Subsequent evaluation of the implementation of the ESC tool shows that most reports are from quality improvement (QI) projects focusing on LOS, rate of medication use, non-pharmacological care, and limited use of the FNAS (15).

There are important variations in the way that the ESC tool is implemented, even within the QI reports (16). Variations are found on the "assessment method" [the original study used ≥ 1 oz of feeding volume as successful (8), which is different from others (14, 17, 18)] and in areas as important as proposed medications and dosages. To consider, the ranges of the initial dose of morphine went from 0.03 to 0.1 mg/kg/dose (6, 14, 19), and the original ESC report used 0.05 mg/kg/dose (8) (**Table 1**).

Recently, a cluster randomized clinical trial was published comparing ESC vs. the traditional management of infants with NAS (18). Initially, the trial involved 26 US sites and enrolled 1,305 infants. Only 837 infants met *a priori* definition of primary outcome of birth to discharge duration, and other outcomes included LOS, pharmacological interventions, and monitoring of adverse outcomes up to 3 months of life from various sources. The study showed a shorter readiness for discharge [8.2 vs. 14.9 days; adjusted mean difference, 6.7 days; 95% confidence interval (CI), 4.7–8.8] when the ESC model was implemented. The proportion of infants who received opioid treatment was 52.0% in the usual-care group and 19.5% in the ESC group (absolute difference, 32.5 percentage points; relative risk, 0.38; 95% CI, 0.30–0.47). Of notice, the trial showed that ~60% of the participants were exposed to polysubstance; however, most of the participants were in a medications for opioid disorder (MOUD)" program (~70%). In addition, 83% and 91% of the participants, respectively, were in the metropolitan area in the pre- and post-intervention groups (18).

Even though this trial is the first to prospectively and objectively analyze the management of NAS under the ESC model and showed consistent results regarding LOS and use of pharmacological agents, it does mention heterogeneity of treatment effect due to multiple factors: location of care and feeding regimen. The trial defined "Eat" as the ability to coordinate feed (breast or bottle) within 10 min, breastfeeding ≥ 10 min and taking ≥ 10 ml. The non-pharmacological interventions were also dependent on the available resources of each site. Moreover, there were variations among individual sites as to the choice of pharmacotherapy (type, dose, and use of adjunct medications) (18).

Short- and long-term effects of NAS

Infants born of mothers who used opioids were reported to be at increased risk for prematurity, small for gestational age, NICU admission lower 5-min APGAR scores (20), and smaller head circumference and body length. Infants with *in-utero* opioid exposure have higher mortality (21, 22) compared with non-exposed infants. A retrospective analysis of 864 infants with NAS showed that infants had growth retardation between birth and discharge in all parameters with no improvement despite increased caloric content (23). Affected infants also have decreased feeding efficiency, more apneic swallows, and less respiratory rhythmic stability (24). Dysregulations in the growth curve have been tracked into adulthood (25).

Studies looking at the neurodevelopmental outcomes in newborns during the first days of life show conflicting data (26). Early signs of NAS include motor and autonomic dysregulations, manifested as lower quality of movements, lower self-regulation, and higher levels of arousal; however, the reports are inconsistent as whether this dysregulation results in neurodevelopmental impairments after the first week of life (26). On the other hand, a study published in 2020 showed that infants being treated pharmacologically for NAS had more adverse cardiorespiratory events compared with those who were not treated (5), which correlated with the reported changes in heart rate variability and autonomic stability (27). Also, it has been established that infants affected by NAS are at an increased risk of hospital readmissions (most commonly due to respiratory issues) and to require intensive care treatment (28) with increased risk of mortality (29).

Long-term negative effects in the outcome of infants with NAS were initially described as early as 1973, noticing behavioral disturbances and growth impairment (30). A systematic review that examined 79 studies including infants with polysubstance exposure showed that infants and toddlers performed worse on tests of cognitive and motor skills and on behavioral assessments (31). This finding has been reported in other studies as well; however, neurodevelopmental outcomes are also influenced by many other factors that must be taken into consideration (26, 32, 33).

TABLE 1 Comparison of studies on the "Eat, Sleep, and Console" approach in the management and assessment of infants with NAS.

	Grossman et al. (8)	Blount et al. (19)	Dodds et al. (14)	Miller and Willier (11)	Ryan et al. (6)	Amin et al. (17)	Young et al. (18)
Number of patients	287	76	82	135	158	71	837
Setting	Urban	Not specified	Urban	Urban	Rural/urban	Rural	Urban
MOUD	100%	~85%	Not specified	~94%	Not specified	Not specified	~73%
Eat	1 oz	>1 oz	Breastfed well or took the prescribed amount of formula	0.5–1 oz	Breastfeed well or took >1 oz	0.5–1 oz	Ability to coordinate feeding (breast or bottle) within 10 min, breastfeeding ≥ 10 min and taking ≥ 10 ml
Sleep	>1 h	>1 h	>1 h	>1 h	>1 h	>1 h	>1 h
Console	Within 10 min	Within 10 min	Within 10 min	Within 10 min	Within 10 min	Within 10 min	Within 10 min
Pharmacological intervention	Morphine 0.05 mg/kg/dose	Morphine 0.03 mg/kg/dose	Morphine 0.1 mg/kg/dose	Methadone	Morphine 0.04 mg/kg/dose	Methadone	Per institution
Short-term outcomes	30-day readmissions	Percent weight change 30-day readmission	Readmission rate	30-day readmission	30-day readmission	30-day readmission	3-months composite safety measure

As the child grows, there have been reports of differences in IQ and in the neurological and language performance; however, most of these differences disappear when other confounders are controlled (26, 31). Even though the cognitive outcomes have inconsistent findings in the studies reporting long-term effects of NAS, there are also similar inconsistencies in related behavioral outcomes, and therefore follow-up of exposed children is crucial (26).

Short- or long- term consequences of the ESC tool specifically have not been studied. Some reports indicate that weight loss increased with its implementation (11, 19), and another report stated that no differences in weight loss after implementation; however, discharge weight was obtained only at day 5 of life (11). Some of the reports include re-hospitalization rate at 30 days post-discharge; however, this rate was only reported for NAS-related admissions (8, 12, 14, 19). Young et al. reported outcomes after hospital discharge that were assessed at 3 months of age by means of a review of electronic medical records and media review through a search of public records. An evaluation of the neurodevelopmental outcomes at 2 years of age is included in the protocol (18).

A retrospective review comparing FNAS and ESC tool focused on the correlation between both methods during the implementation of the ESC model in three hospital settings (6). A receiver operating characteristic analysis showed that an FNAS cutoff of 7.5 corresponded to at least one negative component on the ESC tool (sensitivity = 0.84, specificity = 0.70, area under the curve = 0.842), which indicates the need for pharmacological intervention. This correlation has been reported by others (17). The study also found an increase in the care of infant/mother dyads in the community hospital rather than at the referral center as well as more maternal referrals for substance abuse treatment after the implementation of the method, consistent with a more family-oriented intervention (6). However, lack of proper communication can be an issue as shown in a study by McRae et al. looking at parental perspectives of the ESC model in which inadequate communication and support of the parents created feelings of guilt, fear, and stress as well as uncertainty in what happens after delivery (34).

Since the ESC model has gained much momentum despite its lack of well-controlled studies, standardized assessment, and management, careful consideration must be made as to other factors that may have an impact on the LOS and initiation of pharmacological treatment. Advocates of the ESC model refer to parental involvement in NAS care as something novel (8, 35); however, long before the ESC tool was proposed, the study by Holmes et al. focusing on rooming-in and parental involvement reported similar outcomes (36), i.e., shorter length of stay and decrease the need for pharmacological treatment. This QI project was conducted at a rural academic tertiary center focusing on standardization of the assessment and management of these infants by training of the staff (nurses and providers) on how NAS symptoms affected individual infants as well as implementing rooming-in, family support, and education. The authors reported a decrease in the cumulative dose of morphine (from 13.7 to 6.6 mg) as well as LOS (from 16.9 to 12.3 days) and therefore, an associated decrease in hospitalization costs. The authors did not report increased readmission rate during the 30 days after discharge and further, follow-up of newborns with high scores, and no treatment did not show complications at 1–4 months after discharge (36).

On the other hand, none of the ESC QI reports have evaluated what non-pharmacological interventions are most effective and how to standardize them. Even as early as 1974, non-pharmacological interventions have been described and recommended as an approach to the management of withdrawal manifestations noted from a comprehensive assessment of infants with NAS (37). A 2018 systematic review focusing on rooming-in found consistent evidence that rooming-in reduces both the use of pharmacological intervention as well as LOS (38). However, a retrospective review from the Appalachian region after the implementation of the ESC model showed no significant changes in the number of infants needing pharmacotherapy or the length of stay (17). This study found that in 41% of NAS cases, there was not a parent present, and their presence decreased further in infants that required pharmacotherapy, which could explain their results (17). Others have reported that a lack of parental

involvement was significantly correlated to the need for pharmacological intervention (11). Considering these results, we can infer that the key to a successful model that manages infants affected by NAS must consider the environmental settings where the mother/infant dyad resides. A large proportion of mothers with opioid use disorder from rural areas of the country encounter inherent barriers regarding the availability and access to healthcare (1). Considering that rooming-in seems to be the common determinant to a successful management of these babies (6, 8, 10, 14, 15, 36, 38) with NAS, the question arises as to what happens in the areas in where access to healthcare and rooming-in is more difficult.

Infants affected by NAS are at risk of multiple factors, including the effects of maternal co-morbidities, types of drugs used, and socio-cultural determinants, as well as a myriad of changes in the autonomic stability and the neurodevelopmental outcomes of the infant (16, 17, 39). Public health efforts aiming to increase access to antenatal counseling and treatment are needed as well as standardization of the care for the neonate affected by maternal drug use (1, 16). To date, there is no consisted approach to the ESC tool, and success to its implementation should not only be measured as to the reduction in the LOS and hospital cost. However, rooming-in paired with intensive non-pharmacological interventions seems to have consistent positive results in the management of infants affected by NAS (38). There are a myriad of signs in NAS, besides disorganized sleep, poor disorganized or dysfunctional feeding, and irritability. Additional or other ways of non-pharmacological approach would be needed to minimize the other signs not addressed by the ESC.

Conclusion

The interventions that appear to ameliorate the effects of maternal drug use include the following: access to prenatal care as well as to treatment programs and mitigation of polysubstance use (40, 41) paired with identification and intervention of adverse Social Determinants of Health (1, 17, 32); for hospitals that manage infants with NAS, an established protocol (1, 4) to define, promptly initiate and reinforce non-pharmacological interventions, and, if needed, continuous cardiorespiratory monitoring of infants that require pharmacotherapy (1, 19) while facilitating rooming-in (38) and breastfeeding when appropriate (42); and prompt follow-up needs to be established to ensure that any nutritional, growth, and/or neurodevelopmental challenges are rapidly identified and intervened (32, 42). Further research needs to standardize the outcome data to provide more homogenous results to compare different interventions for the management of maternal drug use and infants affected by NAS (43). Currently, standardization of ESC method is needed. Furthermore, there have been no research studies that have adequately evaluated the short- and long- term outcomes of the ESC tool (1, 16).

Author contributions

EGP drafted, reviewed, and approved the final manuscript as submitted.

Acknowledgments

A special thanks to Dr Henrietta Bada for her continuing support and guidance during the development of this article.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Patrick SW, Barfield WD, Poindexter BB, Committee on Fetus and Newborn, Committee on Substance Use and Prevention. Neonatal opioid withdrawal syndrome. *Pediatrics*. (2020) 146(5). doi: 10.1542/peds.2020-029074

2. Hirai AH, Ko JY, Owens PL, Stocks C, Patrick SW. Neonatal abstinence syndrome and maternal opioid-related diagnoses in the US, 2010–2017. *JAMA*. (2021) 325 (2):146–55. doi: 10.1001/jama.2020.24991

3. Lacaze-Masmonteil T, O'Flaherty P. Managing infants born to mothers who have used opioids during pregnancy. *Paediatr Child Health*. (2018) 23(3):220–6. doi: 10.1093/pch/pxx199

4. Hall ES, Wexelblatt SL, Crowley M, Grow JL, Jasin LR, Klebanoff MA, et al. A multicenter cohort study of treatments and hospital outcomes in neonatal abstinence syndrome. *Pediatrics*. (2014) 134(2):e527–34. doi: 10.1542/peds.2013-4036

5. Davala S, Hansbury A, Miller M, Boateng J, Shrestha H, Wachman EM. Pilot study comparing adverse cardiorespiratory events among pharmacologically and nonpharmacologically treated infants undergoing monitoring for neonatal abstinence syndrome. *J Pediatr X*. (2020) 3:100027. doi: 10.1016/j.ympdx.2020.100027

6. Ryan K, Moyer A, Glait M, Yan K, Dasgupta M, Saudek K, et al. Correlating scores but contrasting outcomes for eat sleep console versus modified Finnegan. *Hosp Pediatr*. (2021) 11(4):350–7. doi: 10.1542/hpeds.2020-003665

7. Winkelman TNA, Villapiano N, Kozhimannil KB, Davis MM, Patrick SW. Incidence and costs of neonatal abstinence syndrome among infants with Medicaid: 2004–2014. *Pediatrics*. (2018) 141(4):99–106. doi: 10.1542/peds.2017-3520

8. Grossman MR, Berkwitt AK, Osborn RR, Xu Y, Esserman DA, Shapiro ED, et al. An initiative to improve the quality of care of infants with neonatal abstinence syndrome. *Pediatrics*. (2017) 139(6):1560–9. doi: 10.1542/peds.2016-3360

9. Grossman MR, Osborn RR, Berkwitt AK. Neonatal abstinence syndrome: time for a reappraisal. *Hosp Pediatr*. (2017) 7(2):115–6. doi: 10.1542/hpeds.2016-0119

10. Grossman MR, Lipshaw MJ, Osborn RR, Berkwitt AK. A novel approach to assessing infants with neonatal abstinence syndrome. *Hosp Pediatr*. (2018) 8(1):1–6. doi: 10.1542/hpeds.2017-0128

11. Miller PA, Willier T. Baby STRENGTH: eat, sleep, console for infants with neonatal abstinence syndrome. *Adv Neonatal Care*. (2021) 21(2):99–106. doi: 10.1097/ANC.0000000000000840

12. Wachman EM, Houghton M, Melvin P, Isley BC, Murzycki J, Singh R, et al. A quality improvement initiative to implement the eat, sleep, console neonatal opioid withdrawal syndrome care tool in Massachusetts' PNQIN collaborative. *J Perinatol*. (2020) 40(10):1560–9. doi: 10.1038/s41372-020-0733-y

13. Rhoads SC, Waskosky A. Eat, sleep, console method and the management of neonatal opioid withdrawal syndrome: a literature review. *J Neonatal Nurs*. (2022) 28(4):236–9. doi: 10.1016/j.jnn.2021.10.006

14. Dodds D, Koch K, Buitrago-Mogollon T, Horstmann S. Successful implementation of the eat sleep console model of care for infants with NAS in a community hospital. *Hosp Pediatr*. (2019) 9(8):632–8. doi: 10.1542/hpeds.2019-0086

15. Nicholson S, Waskosky A. The eat, sleep, console method: a literature review. *Neonatal Netw*. (2022) 41(6):333–40. doi: 10.1891/NN-2021-0003

16. Jansson LM, Velez ML. Optimal care for NAS: are we moving in the wrong direction? *Hosp Pediatr*. (2019) 9(8):655–8. doi: 10.1542/hpeds.2019-0119

17. Amin A, Frazie M, Thompson S, Patel A. Assessing the eat, sleep, console model for neonatal abstinence syndrome management at a regional referral center. *J Perinatol*. (2023) 43(7):916–22. doi: 10.1038/s41372-023-01666-9

18. Young LW, Ounpraseuth ST, Merhar SL, Hu Z, Simon AE, Bremer AA, et al. Eat, sleep, console approach or usual care for neonatal opioid withdrawal. *N Engl J Med*. (2023) 388(25):2326–37. doi: 10.1056/NEJMoa2214470

19. Blount T, Painter A, Freeman E, Grossman M, Sutton AG. Reduction in length of stay and morphine use for NAS with the "eat, sleep, console" method. *Hosp Pediatr*. (2019) 9(8):615–23. doi: 10.1542/hpeds.2018-0238

20. Corsi DJ, Hsu H, Fell DB, Wen SW, Walker M. Association of maternal opioid use in pregnancy with adverse perinatal outcomes in Ontario, Canada, from 2012 to 2018. *JAMA Netw Open*. (2020) 3(7):e208256. doi: 10.1001/jamanetworkopen.2020.8256

21. Graeve R, Balalian AA, Richter M, Kielstein H, Fink A, Martins SS, et al. Infants' prenatal exposure to opioids and the association with birth outcomes: a systematic review and meta-analysis. *Paediatr Perinat Epidemiol*. (2022) 36(1):125–43. doi: 10.1111/ppe.12805

22. Towers CV, Hyatt BW, Visconti KC, Chernicky L, Chattin K, Fortner KB. Neonatal head circumference in newborns with neonatal abstinence syndrome. *Pediatrics*. (2019) 143(1). doi: 10.1542/peds.2018-0541

23. Favara MT, Smith J, Friedman D, Lafferty M, Carola D, Adeniyi-Jones S, et al. Growth failure in infants with neonatal abstinence syndrome in the neonatal intensive care unit. *J Perinatol*. (2022) 42(3):313–8. doi: 10.1038/s41372-021-01183-7

24. Gewolb IH, Fishman D, Qureshi MA, Vice FL. Coordination of suck-swallow-respiration in infants born to mothers with drug-abuse problems. *Dev Med Child Neurol*. (2004) 46(10):700–5. doi: 10.1111/j.1469-8749.2004.tb00984.x

25. Yen E, Maron JL. Aberrant feeding and growth in neonates with prenatal opioid exposure: evidence of neuromodulation and behavioral changes. *Front Pediatr*. (2021) 9:805763. doi: 10.3389/fped.2021.805763

26. Conradt E, Flannery T, Aschner JL, Annett RD, Croen LA, Duarte CS, et al. Prenatal opioid exposure: neurodevelopmental consequences and future research priorities. *Pediatrics*. (2019) 144(3). doi: 10.1542/peds.2019-0128

27. Hambleton MT, Reynolds EW, Sithisarn T, Traxel SJ, Patwardhan AR, Crawford TN, et al. Autonomic nervous system function following prenatal opiate exposure. *Front Pediatr*. (2013) 1:27. doi: 10.3389/fped.2013.00027

28. Milliren CE, Melvin P, Ozonoff A. Pediatric hospital readmissions for infants with neonatal opioid withdrawal syndrome, 2016–2019. *Hosp Pediatr*. (2021) 11(9):979–88. doi: 10.1542/hpeds.2021-005904

29. Leyenaar JK, Schaefer AP, Wasserman JR, Moen EL, O'Malley AJ, Goodman DC. Infant mortality associated with prenatal opioid exposure. *JAMA Pediatr*. (2021) 175(7):706–14. doi: 10.1001/jamapediatrics.2020.6364

30. Wilson GS, Desmond MM, Verniaud WM. Early development of infants of heroin-addicted mothers. *Am J Dis Child*. (1973) 126(4):457–62.

31. Balalian AA, Graeve R, Richter M, Fink A, Kielstein H, Martins SS, et al. Prenatal exposure to opioids and neurodevelopment in infancy and childhood: a systematic review. *Front Pediatr*. (2023) 11:1071889. doi: 10.3389/fped.2023.1071889

32. Larson JJ, Graham DL, Singer LT, Beckwith AM, Terplan M, Davis JM, et al. Cognitive and behavioral impact on children exposed to opioids during pregnancy. *Pediatrics*. (2019) 144(2). doi: 10.1542/peds.2019-0514

33. Lee SJ, Bora S, Austin NC, Westerman A, Henderson JMT. Neurodevelopmental outcomes of children born to opioid-dependent mothers: a systematic review and meta-analysis. *Acad Pediatr*. (2020) 20(3):308–18. doi: 10.1016/j.acap.2019.11.005

34. McRae K, Sebastian T, Grossman M, Loyal J. Parent perspectives on the eat, sleep, console approach for the care of opioid-exposed infants. *Hosp Pediatr*. (2021) 11(4):358–65. doi: 10.1542/hpeds.2020-002139

35. Worth T. Caring for people and their babies in the opioid crisis. *Nature*. (2022) 612(7941):S56–8. doi: 10.1038/d41586-022-04347-3

36. Holmes AV, Atwood EC, Whalen B, Beliveau J, Jarvis JD, Matulis JC, et al. Rooming-in to treat neonatal abstinence syndrome: improved family-centered care at lower cost. *Pediatrics*. (2016) 137(6). doi: 10.1542/peds.2015-2929

37. Finnegan LP, MacNew BA. Care of the addicted infant. *Am J Nurs*. (1974) 74(4):685–93.

38. MacMillan KDL, Rendon CP, Verma K, Riblet N, Washer DB, Volpe Holmes A. Association of rooming-in with outcomes for neonatal abstinence syndrome: a systematic review and meta-analysis. *JAMA Pediatr*. (2018) 172(4):345–51. doi: 10.1001/jamapediatrics.2017.5195

39. Ecker J, Abuhamad A, Hill W, Bailit J, Bateman BT, Berghella V, et al. Substance use disorders in pregnancy: clinical, ethical, and research imperatives of the opioid epidemic: a report of a joint workshop of the Society for Maternal-Fetal Medicine, American College of Obstetricians and Gynecologists, and American Society of Addiction medicine. *Am J Obstet Gynecol*. (2019) 221(1):B5–28. doi: 10.1016/j.ajog.2019.03.022

40. Devlin LA, Hu Z, Ounpraseuth S, Simon AE, Annett RD, Das A, et al. The influence of mediators on the relationship between antenatal opioid agonist exposure and the severity of neonatal opioid withdrawal syndrome. *Matern Child Health J*. (2023) 27(6):1030–42. doi: 10.1007/s10995-022-03521-3

41. Garrison-Desany HM, Nawa N, Kim Y, Ji Y, Susan Chang HY, Hong X, et al. Polydrug use during pregnancy and preterm birth in a low-income, multiethnic birth cohort, Boston, 1998–2018. *Public Health Rep*. (2020) 135(3):383–92. doi: 10.1177/0033354920915437

42. Yen E, Davis JM. The immediate and long-term effects of prenatal opioid exposure. *Front Pediatr*. (2022) 10:1039055. doi: 10.3389/fped.2022.1039055

43. Kelly LE, Shan F, MacVicar S, Czaplinksi E, Moulsdale W, Simpson S, et al. A core outcome set for neonatal opioid withdrawal syndrome. *Pediatrics*. (2020) 146(1). doi: 10.1542/peds.2020-0018

frontiers | Frontiers in Pediatrics

TYPE Review
PUBLISHED 18 December 2023
DOI 10.3389/fped.2023.1305508

Check for updates

OPEN ACCESS

EDITED BY
Henrietta S. Bada,
University of Kentucky, United States

REVIEWED BY
Bryanne Colvin,
Washington University in St. Louis, United States
Enrique Gomez-Pomar,
University of Kentucky, United States

*CORRESPONDENCE
Trecia A. Wouldes
t.wouldes@auckland.ac.nz

RECEIVED 01 October 2023
ACCEPTED 20 November 2023
PUBLISHED 18 December 2023

CITATION
Wouldes TA and Lester BM (2023) Opioid, methamphetamine, and polysubstance use: perinatal outcomes for the mother and infant. Front. Pediatr. 11:1305508. doi: 10.3389/fped.2023.1305508

COPYRIGHT
© 2023 Wouldes and Lester. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Opioid, methamphetamine, and polysubstance use: perinatal outcomes for the mother and infant

Trecia A. Wouldes[1]* and Barry M. Lester[2]

[1]Department of Psychological Medicine, The University of Auckland, Auckland, New Zealand, [2]Center for the Study of Children at Risk, Warren Alpert Medical School, Brown University, Providence, RI, United States

The escalation in opioid pain relief (OPR) medications, heroin and fentanyl, has led to an increased use during pregnancy and a public health crisis. Methamphetamine use in women of childbearing age has now eclipsed the use of cocaine and other stimulants globally. Recent reports have shown increases in methamphetamine are selective to opioid use, particularly in rural regions in the US. This report compares the extent of our knowledge of the perinatal outcomes of OPRs, heroin, fentanyl, two long-acting substances used in the treatment of opioid use disorders (buprenorphine and methadone), and methamphetamine. The methodological limitations of the current research are examined, and two important initiatives that will address these limitations are reviewed. Current knowledge of the perinatal effects of short-acting opioids, OPRs, heroin, and fentanyl, is scarce. Most of what we know about the perinatal effects of opioids comes from research on the long-acting opioid agonist drugs used in the treatment of OUDs, methadone and buprenorphine. Both have better perinatal outcomes for the mother and newborn than heroin, but the uptake of these opioid substitution programs is poor (<50%). Current research on perinatal outcomes of methamphetamine is limited to retrospective epidemiological studies, chart reviews, one study from a treatment center in Hawaii, and the US and NZ cross-cultural infant Development, Environment And Lifestyle IDEAL studies. Characteristics of pregnant individuals in both opioid and MA studies were associated with poor maternal health, higher rates of mental illness, trauma, and poverty. Infant outcomes that differed between opioid and MA exposure included variations in neurobehavior at birth which could complicate the diagnosis and treatment of neonatal opioid withdrawal (NOWs). Given the complexity of OUDs in pregnant individuals and the increasing co-use of these opioids with MA, large studies are needed. These studies need to address the many confounders to perinatal outcomes and employ neurodevelopmental markers at birth that can help predict long-term neurodevelopmental outcomes. Two US initiatives that can provide critical research and treatment answers to this public health crisis are the US Environmental influences on Child Health Outcomes (ECHO) program and the Medication for Opioid Use Disorder During Pregnancy Network (MAT-LINK).

KEYWORDS

maternal substance use disorders, opioids, methamphetamine, perinatal outcomes, polysubstance use

1. Introduction

The use and misuse of prescription and illicit opioids and amphetamine-type stimulants (ATS) among women of childbearing age has escalated worldwide (1–4). The stimulant that is responsible for the steep escalation in the use of ATS worldwide is crystalline methamphetamine (MA), also known as "ice," "crystal meth," "P" in New Zealand (NZ), and "tick" in South Africa (1, 3, 5). Although the global illicit use of these substances during pregnancy is difficult to estimate, three indicators suggest this is a significant public health challenge. The first is the increase in the number of women of childbearing age seeking treatment for substance use disorders or requiring hospitalization due to the abuse of these drugs (5–7). Second is the dramatic increase in rates of neonatal abstinence syndrome (NAS), more recently termed neonatal opioid withdrawal syndrome (NOWS), and adverse perinatal outcomes for the prenatally exposed newborn (1, 3, 8, 9). For example, in the US, from 1999 to 2014, the prenatal use and abuse of opioids, and more recently heroin, resulted in a 333% increase in fetal exposure and a significant increase in NICU admission rates (4, 8, 10). In addition, current estimates of the prevalence of neonatal withdrawal from opioids suggest that in the US, one newborn is diagnosed with NOWs every 18 min (11). Third is the increase in overdose deaths involving methamphetamine and where the use of illicit opioids was reported (12).

The surge in maternal use of opioids was first attributed to the sale of opioid pain relievers (OPRs), with 9.5% to 41.6% filling a prescription in 2007 across 46 states in the United States (US) and 6% in Norway between 2004 and 2007 (13, 14). US national estimates for the total number of opioid prescriptions dispensed also showed a 35% increase between 2000 and 2010. While prevalence data is not available for OPRs during pregnancy in other countries, data from the general population suggest increasing use of prescription opioids in Australia (4), New Zealand (15), Canada (16–18), Germany, Israel, and the United Kingdom (14).

Attempts to curb the opioid epidemic through legislation, education, and the development of abuse-deterrent formulations designed to make inhalation and injection of prescription opioids more difficult meant that abuse of OPRs declined in favor of heroin and synthetic opioids, mainly non-pharmaceutical fentanyl (NPF) (19–21). Misusing these drugs has significantly increased overdose mortality among pregnant and postpartum women and women of childbearing age (21). Using data from the National Vital Statistics mortality files of 7,642 pregnancy-associated deaths between 2017 and 2020, researchers found 1,249 were overdose-related, increasing from 6.56 to 11.85 per 100,000 or a relative increase of 81%. Overdose deaths among women of childbearing age increased from 14.37 to 19.76 per 100,000, a relative increase of 38%. Increased opioid-associated overdose deaths have continued to affect the United States (US) and many developed countries, including Canada, Australia, and countries in the European Union (7). MA overdose deaths during pregnancy have also increased and have been reported to include opioids (7, 12, 20, 22, 23).

In US treatment admissions data reported in the 2008–2017 Treatment Episode Data Set (TEDS), the percentage of primary heroin treatment admissions showed MA use increasing each year from 2.1% in 2008 to 12.4% in 2017, a relative percentage increase of 490% and an annual percent change (APC) of 23.4%. And women of childbearing age had higher percentages of heroin treatment admissions involving MA (2.8% in 2008 to 15.1% in 2017) than males (1.7% in 2008 to 10.8% in 2017). The Survey of Key Informant Patients Program database, which comprises individuals who have entered treatment for an opioid use disorder (OUD) at one of their treatment centers in 49 states and Washington, DC, also reported increased co-use of MA. Of all the non-opioid drugs tracked in this population between 2011 and 2018, MA was the only drug with a significant prevalence increase (85%).

While many people who use licit and illicit psychoactive drugs may prefer a specific drug or drug class, polysubstance use is nearly ubiquitous in people with substance use disorders (SUDs) (23–32). In addition, polysubstance use during pregnancy is only one of several related risk factors. Maternal mental illness, poverty, poor nutrition, involvement with child protective services, and domestic violence are common in women with SUDs (24, 28–30). Understanding the co-use of opioids and MA, and other psychoactive drugs and the context of their use is necessary to prevent maternal morbidity and mortality, inform clinical interventions, and reduce or mitigate adverse perinatal outcomes such as NOWs.

Given the escalation of MA use associated with opioid and opioid use disorders (OUD), the purpose of this narrative review is twofold: first, to briefly review the perinatal effects on mothers and their offspring exposed prenatally to opioids and MA during pregnancy, and second, to explore what we know about the perinatal impact of the co-use of opioids, MA and other commonly used psychoactive drugs, and the social and environmental risk factors associated with maternal SUDs.

2. Maternal and perinatal outcomes from prenatal exposure to opioids

Opioids include a wide range of natural and synthetic alkaloid derivates that act as agonists of at least one of the three types of opioid receptors: mu (μ), lambda (δ), and kappa (κ). Drugs from the poppy plant, such as heroin, codeine, and morphine, were initially referred to as "opiates." Now, the term opiates is often used interchangeably with the term opioid, a more general term that includes natural agonists such as heroin and codeine and synthetic agonists such as fentanyl and oxycodone that, when injected, insufflated, or smoked, enter the brain rapidly and create feelings of pleasure or euphoria, relief from pain, or a state of relaxation or drowsiness.

If more than a medically necessary amount of prescription OPRs such as Oxycontin® and Vicodin® are used, they will have similar pharmacological effects to heroin. Repeated use often results in tolerance to their psychoactive effects and, in turn, dependence to prevent withdrawal symptoms. Opioids like

heroin, oxycodone, morphine, and fentanyl are categorized as short-acting opioids or immediate-response opioids. In contrast, oxymorphone hydrochloride extended-release, methadone, and buprenorphine are long-acting or sustained response opioids. Long-acting opioids are mainly prescribed for opioid substitution treatment (OST) but may also be used for pain relief or illicitly for their psychoactive effects.

2.1. Maternal outcomes

OUDs during pregnancy are associated with various health and mental health problems. These often depend on the type of opioid (short- or long-acting) and whether the individual is receiving OST. Comorbidities include SUDs of other drugs, chronic pain, HIV, hepatitis C virus, obstetric complications including miscarriage, more terminations, and significant mental health disorders (18, 25, 26, 33). A study ($N = 174$) investigating the relationship of psychiatric symptoms to the severity of drug use and drug-related problems in individuals receiving OST found co-occurring psychiatric symptoms are common and impact the severity of opioid dependence (33). A large percentage (64.6%) of the sample presented with symptoms of a co-occurring psychiatric disorder, 33% with depression, 16% with PTSD, and 39% endorsed hypomania. A large Canadian study comparing methadone maintenance treatment (MMT) with maintenance treatment with buprenorphine (BUP) found 92% of their sample reported mental health disorders (18). A recent study of 21,905 pregnant people in the Environmental Influences on Child Health Outcomes (ECHO) Program reporting opioid use ($N = 591$) found maternal depression was associated with an increased odds of opioid use during pregnancy by more than two-fold (aOR: 2.42, 95% CI: 1.95–3.01) (31).

2.2. Perinatal outcomes from prenatal exposure to OPRs

OPRs are prescribed for back and pelvic pain in late pregnancy, which occurs in approximately 68 to 72% of women, and for joint pain, migraine, and myalgia (34). OPRs are associated with an increased prevalence of OUDs; however, studies investigating the perinatal outcomes of the prenatally-exposed infant are sparse (35). One report that reviewed the use of short-acting OPRs, including codeine, tramadol, acetaminophen, oxycodone, and hydrocodone, as well as opioids used for OST (methadone and buprenorphine) during pregnancy, found mixed results in birth outcomes (36). Of the studies examining fetal growth, three studies in this review found no association between low birth weight (<2,500 gms) and oxycodone, codeine, and short-acting opioids overall (37–39). In comparison, one study reported an association between infants born small for gestational age (SGA, <10th percentile) and acetaminophen with oxycodone, codeine, or hydrocodone (11.5% exposed vs. 7.8% unexposed neonates) (40). In contrast, a further study found no association with OPRs but reported an increased rate of large for gestational age (LGA) infants among mothers who used propoxyphene (39).

Preterm birth (<37 weeks) results also varied between studies, with a report from the First Nations population in northwestern Ontario, Canada, reporting a higher percentage of preterm birth in oxycodone-exposed pregnancies (11.5%) compared to nonexposed (7.8%) (38). A Swedish Medical Birth Register study also found a relationship between maternal tramadol use and preterm birth. Still, no association was found in the same study for very preterm births (<32 weeks) (39). Two further investigations found no association with preterm birth, one examining the relationship between codeine use in pregnancy (37) and one where most opioid use was acetaminophen with oxycodone, codeine, or hydrocodone (40).

Case-control and cohort studies have identified a relationship between prenatal exposure to OPRs and congenital heart defects (CHDs), neural tube defects (NTDs), cleft palate, and clubfoot (36, 39, 41). Many of these studies grouped opioids (e.g., different combinations of codeine, hydrocodone, oxycodone, tramadol, and meperidine) and reported on associated congenital disabilities. Of those studies investigating the association between individual opioids and congenital disabilities, more studies found higher odds for a relationship between codeine and CHDs (4 studies) and NTDs (2 studies). Propoxyphene and tramadol had higher odds for clubfoot (36). However, these reviews were published before the dramatic increase in OPRs. Therefore, they did not capture the effects of repeated misuse of these or other prescribed or illicit opioids, psychostimulants, or psychological or lifestyle factors associated with substance use disorders (SUDs) (36, 39, 41).

2.3. Perinatal outcomes from prenatal exposure to fentanyl

Fentanyl is a synthetic opioid that is 50 times more potent than heroin and 100 times more potent than morphine. There are two types of fentanyl: pharmaceutical and illicitly-manufactured or non-pharmaceutical fentanyl (NPF) (street names, Apache, Dance Fever, Friend, Goodfellas, Jackpot, and Murder 8). NPF is sold as a powder, dropped onto blotter paper, and put in eye droppers and nasal spray. Some drug dealers are mixing it with cocaine, heroin, MA, and MDMA as a cheap way to boost the psychoactive effects (42). Clinically, fentanyl is used widely in patients undergoing general anesthesia, including women having a variety of surgical procedures throughout pregnancy and for epidurals during labor (43). Human research on the perinatal effects of pharmaceutical fentanyl or NPF is limited. However, a human study and animal models have documented placental transfer to the fetus (44, 45). In a study of 38 women undergoing a termination of pregnancy between 8 and 14 weeks, a rapid transfer of fentanyl to the placenta and the fetal brain was found after an intravenous bolus dose was administered under anesthesia (44). Fentanyl was detected in all 38 placental and all seven of the available brain samples but not in any amniotic fluid. Subsequently, there was a rapid decrease in fentanyl concentrations in maternal serum. However, there was no decline in placental or fetal brain concentrations over the

study period (10–30 min), indicating a likely accumulation in the fetus. In animal models, prenatal exposure to fentanyl has been linked to a higher prevalence of newborn mortality, signs of withdrawal, and lasting deficits in sensory processing that extend to adolescence. Impaired sensory processing in children is associated with attention deficit disorder, autistic-like characteristics, schizophrenia, and synesthesia (45).

2.4. Perinatal outcomes from prenatal exposure to heroin

Before the 1950s, only a few cases of adverse perinatal outcomes due to prenatal exposure to heroin were reported. In 1956, a review of the literature found ten instances where infants born to mothers dependent on heroin exhibited the characteristic signs of neonatal abstinence syndrome (NAS), including restlessness, yawning, high-pitched cry, tremors, watery stools, hypertonia, seizures, and vomiting (46). An increase in the number of heroin-dependent women presenting to antenatal clinics precipitated further research examining the obstetric and perinatal consequences associated with heroin (47–53). Small numbers, retrospective designs, and selection bias limited the findings in early studies investigating the obstetric and perinatal complications of maternal heroin use. Still, researchers identified some consistent perinatal risks for the mother and her child. Maternal complications were those typically associated with intravenous drug use, such as malnutrition, blood-borne infections (Hepatitis B and C), and skin abscesses. Complications specific to pregnancy included pre-eclampsia, premature rupture of membranes, toxemia, amnionitis, and a high incidence of breech position on delivery.

Perinatal complications for the infant included a high rate of preterm births (28% to 57%), intrauterine growth retardation (IUGR), fetal and neonatal death (3% to 17%), and signs of NAS (8% to 79%). Four studies reported sudden unexplained death in infancy (SUDI) (47, 49, 52, 53), but only two found congenital anomalies greater than the current hospital population (48, 51). Autopsies of 82 infants born to heroin-dependent women between 1954 and 1972 compared to 1,044 consecutive well-preserved stillborn and newborn infants explained the high rate of infant mortality, IUGR, and preterm deliveries (54). Growth retardation was associated with significant reductions in the number of cells in various organs. Almost 60% of heroin-exposed specimens had meconium in the amnion. In several, it was present in the chorion, suggesting fetal distress or withdrawal, resulting in preterm birth or mortality. The mean gestational age of heroin-exposed infants or infants with chorioamnionitis or fevers was 35 ± 3 weeks compared to 39 ± 2 weeks for no observed infection, and heroin-exposed infants who were stillborn or died as newborns also had a high incidence of infection (57%). Notable in the few studies examining the perinatal effects of heroin use in pregnancy was the lack of information about prenatal care, multiple drug use, mental illness, and other lifestyle factors associated with OUDs (55).

More recently, findings from a small randomized controlled trial (RCT) comparing prenatal exposure to heroin, MMT, and BUP found the lowest birthweight, the highest number of newborns with IUGR, and the most numerous placental changes were in heroin-exposed infants. Still, no deaths or congenital abnormalities were reported. However, the severity and course of NOWS were the poorest for infants born to mothers receiving MMT (56).

2.5. Maternal and perinatal outcomes from OST with methadone and buprenorphine

With the introduction of MMT in the 1970s as an opioid substitution treatment, many of the adverse outcomes associated with the maternal use of "street heroin," such as malnutrition, anemia, blood-borne illnesses from shared needles (Hepatitis C and HIV), and obstetric complications were mitigated (57–59). Advantages of MMT included stabilization of opioid levels, reduced illicit drug use, criminal activity, maternal mortality, and improved engagement with healthcare (60–62). Improved clinical outcomes at birth for infants whose mothers were receiving MMT compared to heroin were also reported (60, 63–67). MMT-exposed infants weighed significantly more than heroin-exposed infants and infant mortality was reduced. However, several studies have shown methadone crosses the placenta, affecting fetal motor activity, breathing movements, heart rate, and parasympathetic tone due to altered fetal neurodevelopment (68–71). Infants are at increased risk of being born early and, when born at term, to be symmetrically smaller (weigh less, be shorter, with smaller head circumferences) than infants born to mothers using multiple non-opioid drugs (25, 26, 72–74). The risk of SUDI strabismus, nystagmus, and hyaline membrane disease is also greater for MMT-exposed infants compared to non-opioid exposed infants (25, 75–79). More recently, research has shown that BUP may provide better clinical outcomes for neonates (18, 80–84).

Methadone is a synthetic full opioid agonist that primarily activates the μ-opioid receptor and the κ- and δ-opioid receptors. These are widely distributed across the CNS and peripheral and gastrointestinal systems (85). Its psychoactive effect is mild euphoria but also results in respiratory depression. In comparison, buprenorphine is a partial μ-opioid agonist and κ-opioid antagonist that produces similar morphine-like psychoactive effects at a relatively lower dose. However, these effects are weaker than full opioid agonists. At higher doses, buprenorphine has a "ceiling effect" where higher doses are associated with much smaller increases in the psychoactive effects and less respiratory depression, reducing the risk of abuse and accidental overdose (86).

The effects of BUP and MMT on the developing nervous system are evident in fetal behavior and infant clinical and neurobehavioral outcomes (26, 68, 70, 87–89). Two reports of participants enrolled in the Maternal Opioid Treatment: Human Experimental Research (MOTHER) study compared indices of fetal neurobehaviour in BUP-exposed fetuses to MMT-exposed

before and after dosing with buprenorphine or methadone (90, 91). The first, a pilot study ($N = 3$ BUP vs. 3 MMT) at two-time points in gestation (24–28 and 32–36 weeks), found BUP was associated with higher levels of FHR variability, more accelerations and greater fetal movement-FHR coupling as well as a trend towards longer movement duration at the earlier gestation period (91). No differences in cardiac measures were found later in gestation, but overall motor activity was significantly depressed in the MMT-exposed fetuses (91). The second study compared BUP- and MMT-exposed fetuses at 31–32 weeks gestation ($N = 33$ BUP vs. $N = 48$ MMT). No group differences were found in FHR or FHR accelerations, but there was a significant decrease in FHR accelerations from pre- to post-dose in the MMT group. A non-reactive stress test occurred more frequently in the MMT group overall. However, depressed fetal movement was observed in both groups post-dose (90). More recently, depressed FHR, fewer heart rate accelerations, and depressed fetal movements were observed 2.5 h post-dose in BUP-exposed pregnancies at 24, 28, 32, and 36 weeks gestation. The magnitude of these effects increased across gestation (87).

2.6. Clinical outcomes at birth from prenatal exposure to MMT and BUP

Of the studies that have compared BUP- to MMT-exposed infants, some have found no differences in the risks of fetal death, preterm birth, low birth weight, and SGA/growth restriction (56, 92, 93), while others have reported a lower risk of preterm birth and higher birth weights for BUP-exposed compared to MMT-exposed infants (94, 95).

A particular focus of outcomes at birth has been the incidence of NAS or NOWs and, more recently, the neurobehavior in children born to mothers receiving MMT or BUP (80, 86, 96–102). The percentage of children exposed to MMT with any signs of NAS varies between 24% and 100%, with 54%–85% requiring pharmacological treatment to alleviate the severity of withdrawal symptoms (96, 101, 102). Several international studies comparing MMT with BUP show NAS is equally common among children born to mothers receiving BUP, occurring in approximately 40%–90% of exposed neonates, with a similar proportion requiring pharmacotherapy (50%) (83, 92, 93, 95, 103–105). In comparison, several studies have found MMT-exposed infants required higher doses of opioid agonist medication to treat NAS than BUP (83, 105, 106) and were more likely to spend more time in the hospital postnatally (83, 104–106). The variability in NOWS may be associated with differences in the clinical assessment and management of these infants postnatally, opioid type, and daily dose. For instance, larger maternal methadone doses in pregnancy have been associated with an increased risk of withdrawal (79, 107–112), but other studies found no relationship (101, 113–117). Other factors associated with the risk of NOWS are exposure to other substances, including stimulants, barbiturates, nicotine, and SSRIs (9, 18, 96) and preterm birth. Preterm infants exhibited fewer signs of withdrawal and a less severe or prolonged course of symptoms (109, 112, 118). Finally, a recent study found the duration of stay in hospital and the need for pharmacological treatment were related to variants in the *OPRM1* and *COMT* genes (119).

2.7. Neurobehavior at birth from prenatal exposure to MMT and BUP

Infant adaptation to the postnatal environment is essential for promoting organized patterns of feeding and sleep and in the early development of the parent-infant relationship (120). Neurobehavioral studies using the Brazelton Neonatal Assessment Scale (NBAS) and the Neonatal Intensive Care Unit Network Neurobehaviour Scale (NNNS) have found neurobehavioral differences between OST-exposed and nonexposed infants (26, 88, 89, 120, 121). The NNNS is a well-validated neurobehavioral scale explicitly designed for detecting neurological and behavioral function and stress abstinence in the drug-exposed infant at birth (123). Two US studies compared MMT-exposed infants requiring pharmacotherapy for NAS with those who did not (88, 89). One compared MMT-exposed to a published normative sample of healthy, unexposed infants (88, 124). A NZ study compared MMT-exposed infants at birth with a nonexposed group in the prospective, longitudinal Methadone in Pregnancy Study (MIPS) (26). All studies found MMT-exposed infants had a more dysregulated pattern of neurobehaviour at birth than unexposed infants. Significant differences were found in habituation scores, attention, handling, non-optimal reflexes, hypertonicity, hypotonicity, and stress abstinence. A small study compared MMT-exposed ($N = 21$) neurobehaviour with BUP-exposed ($N = 16$) infants on days 3, 5, 7, 10, 14–15, and 28–30 days postpartum. The neurobehavior of both MMT and BUP-exposed infants improved over time. Still, infants exposed to BUP *in utero* exhibited fewer stress-abstinence signs, less hypertonia, better self-regulation, and required less handling (122).

Several studies have suggested the improved outcomes for BUP over MMT may be due to the differences in social or lifestyle factors and psychological or substance use problems between those prescribed BUP compared to those prescribed MMT during pregnancy. For instance, significantly more mothers randomized to buprenorphine treatment in RCTs have dropped out of studies, reportedly because of dissatisfaction with the study medication (83, 92, 125). Additionally, in cohort studies, buprenorphine was more likely to be prescribed to women with less serious social and substance dependence problems and more stable lifestyles (103, 126–128). In the MOTHER RCT, women randomized to buprenorphine were likelier to have less prior opioid use (125). Still, a recent cohort study involving pregnant persons enrolled in a public insurance program in the US ($N =$ 2,548,372) from 2000 to 2018 found no association between the above differences and perinatal outcomes (84). Analyses adjusted for several factors associated with OUDs found NAS occurred in 52% of infants exposed to BUP compared with 69.2% exposed to MMT. Preterm birth occurred in 14.4% of infants exposed to

BUP and 24.9% to MMT. SGA (12.1% vs. 15.3%) and LBW (8.3% vs. 14.9%) were less prevalent in BUP-exposed infants, respectively. Still, the risk of adverse maternal outcomes was similar between BUP- and MMT-exposed persons.

Although several studies report more favorable neonatal outcomes for BUP than MMT (84), both can be safely used in pregnancy and are recommended over untreated OUDs. Illicit use of short-acting opioids such as heroin and fentanyl exposes the mother and fetus to dangerous fluctuations in blood morphine levels, unknown drugs and contaminants, and infections such as hepatitis B and C and HIV with the potential for severe morbidity and mortality for the mother and her infant (94, 104, 106, 129, 130). Still, reports show that, on average, less than 50% of pregnant individuals with OUDs are receiving OST (18, 131), and discontinuation of MMT was reported to be higher for individuals who reported weekly use of MA (132).

3. Maternal and perinatal outcomes from prenatal exposure to methamphetamine

3.1. Maternal outcomes

MA is classed as a psychostimulant, chemically similar to amphetamine but with significantly more potential for harm due to its higher potency and longer half-life (10–12 h). MA is a vasoconstrictor, decreasing blood flow leading to hypoxia (133, 134). Its effects are mediated through the release of dopamine, serotonin, and norepinephrine and blockage of intracellular vesicular monoamine transporter 2 activity. Its psychoactive effects are euphoria, increased alertness, libido, a feeling of extreme well-being, and decreased appetite (1). Withdrawal symptoms are fatigue, drowsiness, and depression (135). Craving may start within a few hours and last for two weeks. Tolerance to MA is rapid, leading to "telescoping" of use where more MA and shortened duration of use is required to maintain the desired psychoactive effects. The pattern of use is episodes of bingeing that can last for two weeks (136). The longer half-life and broader target sites of MA in the CNS mean there may be more severe outcomes for the exposed mother, the fetus, and the developing child than from other stimulants (137).

Consistent with the current evidence on the impact of OPRs and short-acting opioids in pregnancy, most existing studies on prenatal MA use tend to focus on the prevalence of prenatal exposure rather than the perinatal outcomes for the mother (7). In one US study, a high percentage of women who used MA were found to have early pregnancy loss (41%) before 26 weeks gestation, which is twice the National average (137). Yet, no indication of whether this loss was due to miscarriage or termination was reported. A further study showed that 33% of pregnancies in women who use MA end in termination of pregnancy, compared to 18% in the general population in the US (137). A large retrospective study in the US found amphetamine-affected births had the highest rates of pre-eclampsia (9.3% vs. 4.4% opioid, 4.8% other), cesarean delivery (37.4% vs. 34.5% opioid, 32.6% other), placental abruption (4.3% vs. 3.1% opioid, 1.0% other), preterm delivery, <37 weeks (16.7%, vs. 12.6% opioid, 5.8% other), and severe maternal morbidity or mortality (2.9% vs. 2.4% opioid, 1.6% other) (138).

MA use during pregnancy is also associated with a higher risk of cardiovascular disease (CVD) (139). A report investigating CVD in women with delivery hospitalizations between 2004 and 2018 in a Nationwide Inpatient Sample showed substance use (SU) was associated with several risk factors related to CVD (139). The prevalence of CV risk factors increased across the study period and included obesity, chronic hypertension, pregestational diabetes, tobacco use, and hyperlipidemia. A total of 60,014,368 delivery hospitalizations occurred, with SU complicating 955,531 deliveries (1.6%). Substances of interest were cocaine, alcohol, cannabis, amphetamine/methamphetamine, polysubstance use, and opioids. Adjusting for demographics, risk factors, and pre-existing conditions, SU use was independently associated with CV events (aOR: 1.61; 95% CI: 1.53–1.70), major adverse cardiac events (aOR: 1.53; 95% CI: 1.46–1.61), and maternal mortality (aOR: 2.65; 95% CI: 2.15–3.12). All substances were associated with an increased risk of acute CV events. However, the risk was most significant in those deliveries with documented amphetamine/methamphetamine use, including a 9-fold increased risk of acute cardiomyopathy or heart failure (aOR: 9.06; 95% CI: 7.52–10.93), acute myocardial infarction (aOR: 7.57; 95% CI: 4.12–13.92), cardiac arrest (aOR: 7.29; 95% CI: 4.19–12.68), and maternal mortality (aOR: 3.20; 95% CI: 1.59–6.41). Opioid use had the strongest association with endocarditis, alcohol use had the strongest association with arrhythmias, and cocaine had the strongest association with stroke. All substances were strongly associated with maternal mortality and major adverse cardiac events, except cocaine and cannabis, which were related to increased maternal mortality.

Consistent with reports on OUDs, prenatal MA use was associated with maternal mental illness, increased reports of domestic violence, poverty, and maternal histories of physical or sexual abuse in the cross-cultural multisite US and NZ Infant Development, Environment And Lifestyle (IDEAL) studies (24, 140). MA use in both the US and NZ studies was associated with being single, waiting longer to attend the first prenatal visit, being more likely to have child protection (CPS) referrals, and using several other drugs than a matched comparison group. MA use in the US study was associated with less prenatal care than the US comparison group and less adequate prenatal care than MA use in the NZ study. Additionally, inadequate prenatal care in the US was associated with increased child protection referrals related to MA use. In contrast, referral to CPS in NZ required more serious social issues related to child safety other than MA use (140). A comparison of maternal mental illness in the US and NZ IDEAL study found MA use was associated with more symptoms associated with paranoid ideation, depression, and interpersonal sensitivity. US ($N = 127$) and NZ ($N = 97$) mothers who used MA were 10 times more likely than their respective matched comparison group (US $N = 193$. NZ $N = 110$) to have an SUD and twice as likely to meet the criteria for a psychiatric disorder. In NZ, but not the US, women who used MA in

pregnancy had a significantly heightened risk (five-fold) for comorbid SUD and a positive diagnosis for a psychiatric disorder. This disparity may be due to higher quantities of alcohol use in the NZ sample than in the US. In addition, up to 31% of individuals using MA enrolled in the US and NZ IDEAL studies self-reported continued psychiatric comorbidities one month after birth (141, 142).

3.2. Clinical outcomes at birth from prenatal exposure to MA

Early studies of prenatal exposure to MA found associations with an increased incidence of cardiac defects, cleft lip, biliary atresia, stillbirth, cerebral hemorrhage, Mongolian spots, systolic murmur, and undescended testes (143). Adverse somatic growth effects were also reported (144, 145). Yet, these reports were reliant on chart review, were retrospective, had small samples, and lacked adjustment for the confounding factors associated with maternal SUD, such as mental health, other drug use, and poverty. A Swedish longitudinal study found female infants exposed to MA were lighter and shorter, but there was no difference between exposed and nonexposed males (146). They also reported that exposed infants were more likely to be drowsy in the first postnatal months (147). Their study, however, lacked a matched comparison group, had a small sample ($N = 65$), and included other drugs along with amphetamine. Also, as this study began in 1980, it is unlikely that MA-exposure was the primary amphetamine used in these studies.

No differences between MA and comparison groups in the incidence of facial dysmorphism, skeletal or cardiac defects, or respiratory problems were observed in the IDEAL Study at birth (142). Admission to the NICU was higher for the MA-exposed infant, and after adjusting for covariates, MA exposure remained significantly associated with poor suck and less likely to be breastfed. No difference between MA and nonexposed comparisons was observed for central nervous system signs of drug withdrawal, and none of the infants required pharmacological interventions.

Studies examining the growth of MA-exposed infants have found, after adjusting for covariates, lower birth weights, smaller head circumferences, and shorter length at birth (148–150). In one study, infants with positive toxicology (meconium) for MA at birth were smaller than infants with first-trimester exposure only (2,932 g v. 3,300 g, $P = 0.01$) and compared to nonexposed infants were born significantly earlier (37.3 weeks vs. 39.1, $P = 0.0002$). Those women in this report who stopped using MA during pregnancy had normal births (148).

The impact of prenatal exposure to MA on growth in the US vs. the NZ IDEAL cohorts found a stronger negative effect on infant and child length/height in the US (151). NZ has a harm reduction policy around maternal drug use and provides free prenatal and postpartum care for all. These findings suggest that improved antenatal care for mothers with a SUD can potentially prevent decreased growth observed in the US (152).

Examination of neurobehavior at birth using the NNNS found MA-exposed infants in the US and NZ samples exhibited poorer quality of movement and increased physiological stress, total stress/abstinence, and CNS stress (153). Additionally, infants with heavy MA exposure exhibited lower arousal and less excitability when compared with nonexposed infants. These findings from the US and NZ increase the generalizability of MA exposure across cultures.

4. Polysubstance use and other risk factors associated with OUDs

4.1. Diagnosing NOWS in the context of polysubstance use during pregnancy

Models of cumulative risk would suggest that there is a continuum of impairment in perinatal outcomes where there is prenatal exposure to multiple drugs compared to a single drug (154). For instance, there were significant differences in fetal neurobehaviour, NAS, and preterm birth in a study comparing maternal exposure to MMT alone (MMT/A), MMT plus polysubstance use (MMT/P), and no MMT or drug exposure (NMP) (155). Substance exposure in the MMT/P group, in addition to methadone, included cocaine, benzodiazepines, barbituates, cannabis, and non-methadone opioids. MMT/P exposure was associated with acute suppression of fetal breathing and body movements (155), with evidence of a continuum of impairment in fetal heart rate (FHR) and FHR variability. At peak levels of methadone exposure, FHR and FHR variability were significantly decreased in the MMT/P group compared to the MMT/A and NMP groups. Neonatal differences were found between the MM/P and MMT/A group, with the former group being born on average one week earlier and twice as many requiring pharmacotherapy to treat NAS (83.3% vs. 42.1%).

More recently, a large population study of mothers with OUD who were receiving opioid agonist treatment (OST) with either MMT ($N = 26{,}740$), BUP ($N = 211$), or slow-release opioid morphine injectable agonist treatment (SROM) ($N = 19$), found a high prevalence during pregnancy of other non-opioid and non-alcohol substance use disorders (SUD) (92%) (18). Co-prescription of SSRIs, benzodiazepines, antipsychotics, or the use of stimulants increased the odds of preterm birth [1.6 (95% CI: 1.2–2.1)] and disorders related to SGA or low birth weight [1.4 (95% CI: 1.1–1.8)] after adjusting for treatment duration (18). Over 90% of the women in the study population were diagnosed with a mental health disorder before delivery, with 37% receiving prescribed psychotropic medications during pregnancy.

Polysubstance use may provide a synergistic effect when two drugs are used together, or individual drugs may counteract or modify the perinatal effects of another drug. For instance, while several drugs can cause NAS on their own, co-exposure with opioids can cause differing signs of withdrawal and short- and long-term outcomes and alter withdrawal severity, duration, and timing (156–159). Co-use of benzodiazepines and other psychotropics, such as SSRIs and gabapentin, have been reported

in studies of opioid use during pregnancy, predominantly with MMT or BUP. Evidence of their co-use during pregnancy is known to increase the severity, duration, and onset of withdrawal (156, 158, 159). A study of 822 confirmed cases of NAS found infants exposed antenatally to benzodiazepines had greater than 50% increased odds of developing pharmacologically treated NAS ($N = 598$, 72.7%) than a group not requiring pharmacological treatment ($N = 224$). Both treated and non-treated groups had similar exposures to tobacco, tetrahydrocannabinol (THC), cocaine, MA, phencyclidine (PCP), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and gabapentin (158).

Increased use of gabapentin with methadone has also been reported during pregnancy with atypical signs of withdrawal, including tongue thrusting, nystagmus, excessive arching of the back, and exaggerated myoclonic jerks (160). Gabapentin is usually prescribed to treat partial seizures, neuropathic pain, and restless leg syndrome. Of a survey of 129 respondents who were using non-prescribed gabapentin, 22% reported using gabapentin in conjunction with methadone, with 38% of those citing gabapentin's ability to potentiate the "high" of methadone as their reason for the concurrent use (161).

Finally, a report investigating the effects of polysubstance use on length of treatment and length of stay for prenatal opioid exposure found similar outcomes between infants exposed to opioids alone ($N = 33$, 19%) or with polysubstance use ($N = 142$. (81%), suggesting opioids were the main driver of hospital outcomes (162). However, a higher percentage of infants with both short- and long-acting opioid exposure required pharmacologic treatment compared to either opioid alone. Results comparing short-acting and long-acting opioids found short-acting opioids decreased the length of treatment. In contrast, long-acting opioids increased the length of treatment, length of stay, and the need for adjunctive therapy. Notably, coexposure of opioids with stimulants decreased the length of treatment and reduced the need for adjunctive treatment. As short-acting opioids were shown to reduce the length of treatment, this observation may reflect the properties of short-acting opioids rather than exposure to stimulants.

4.2. The context and risk factors of perinatal outcomes in OUDs during pregnancy

Understanding the characteristics of individuals and the risk factors associated with OUDs during pregnancy has policy, treatment, and clinical implications. Data from the US Environmental Influences on Child Health Outcomes (ECHO) Program obtained characteristics of 21,905 pregnancies that occurred between 1,990 and 2021 (31). Participants who used opioids during pregnancy were more likely to be non-Hispanic White (67%), have a lower socioeconomic status, and 69% reported some college education. Opioid use was present in 2.8% ($N = 591$) of pregnancies. Opioid use, compared to non-use, was associated with high rates of alcohol use (32% vs. 19%), tobacco use (39% vs. 11%), marijuana use (16% vs. 5%), and illegal drugs (10% vs. 1%). Stimulant (MA and cocaine) use was also significantly higher in those pregnancies where opioid use was reported. Only 5% reported heroin use, and 86% of opioid use originated from a prescription. After adjustment for socioeconomic factors, comorbidities, and prenatal use of other substances, only prenatal use of tobacco and any illegal drugs were associated with higher odds of prenatal opioid use. In addition, maternal depression was associated with a two-fold increase in opioid-exposed pregnancies (aOR = 2.42, 95% CI: 1.95–3.01).

A retrospective review of a nationally representative sample of hospital discharges in the US using data from 2014 to 2015 compared birth outcomes and polysubstance use between ATS-affected ($N = 18{,}050$), opioid-affected, and ($N = 50$, 011) other hospital births ($N = 7{,}545{,}380$) (138). A higher percentage of participants in both ATS and opioid use groups had Medicaid as the primary payer, resided in rural counties (ATS 21.5%, opioid 21.7% vs. other 13.3%), and lived in areas where there is the poorest national income quartile compared with other deliveries. Perinatal outcomes were adjusted for age, payer, income, rural vs. urban, and hospital region. Comorbid tobacco use was reported in approximately half of the deliveries of ATS- and opioid-affected pregnancies (46% and 55%, respectively) compared to other hospital deliveries (5.1%). Polysubstance use was more prevalent in ATS- and opioid-exposed pregnancies overall. However, cannabis (26.4% vs. 10.4%) and alcohol (5.1% vs. 1.9%) use were significantly higher in ATS-exposed pregnancies than in opioid-exposed pregnancies. And in 12.6% of ATS-exposed deliveries, co-use of opioids was identified.

A large US representative sample of pregnant women with an OUD living in urban ($N = 81{,}515$) and rural ($N = 25{,}545$) regions found the rate of polysubstance use varied by region and drug used (163). The rate of polysubstance use diagnosis among women with OUD at delivery increased more among those women residing in rural (13.8% increase) compared with urban counties (3.5% increase). Diagnosed use of ATS and OUD nearly doubled among those living in rural (255.4% increase) compared to urban counties (150.7% increase). Equally, tobacco use and OUD increased in rural (30.4% increase) more than in urban (23.2% increase) regions. Whereas diagnosed use of cocaine and OUD declined significantly in rural (70.5% decline) and urban (61.9% decline) counties.

The characteristics of the population who are pregnant with an OUD or using MA are from lower socio-economic areas. Currently, increased use of OUD and MA are reported in rural counties in the US compared to urban areas, which has implications for whether specialized prenatal and maternity services exist in these areas. In addition to poverty, maternal health, trauma, domestic violence, mental illness, and CPS involvement (140).

5. Discussion

This report highlights the significant increase in the use of opioids and stimulants in pregnancy, along with a constellation of other drugs (31, 138, 163). The opioids that are currently

associated with prenatal use are immediate reward or short-acting OPRs, heroin or non-prescribed fentanyl (NPF), or illicitly manufactured fentanyl. The perinatal effects of these are largely unknown. Long-acting or sustained-release drugs, methadone and buprenorphine, which are predominantly used in the treatment of OUDs, have received the most attention in the extant literature. Maintenance programs using these drugs show improved maternal health and perinatal outcomes for opioid exposure. Despite the availability of MMT and BUP programs to treat OUDs during pregnancy, less than 50% of pregnant individuals and individuals of childbearing age with an OUD are enrolled in these. The lack of uptake of these programs is likely due to the many barriers to reporting SU and engaging with the health care system that need to be addressed, particularly for women and other already marginalized populations (164–168). These populations may under-report their SU due to the stigma of drug use, lower socioeconomic status, racism, involvement with the criminal justice system, and the threat of child custody proceedings. Women are less likely to seek treatment when there is no accommodation to accept their children or specialist services are lacking, particularly in rural regions (169).

Notable is the finding that opioid use has shown a parallel increase in SUDs associated with MA. And MA use has now eclipsed the use of cocaine and other stimulants globally in women of childbearing age (1, 131). Our review of the perinatal outcomes for individuals with OUDs compared to individuals reporting SUDs associated with MA shows higher rates of severe morbidity and mortality with MA use. MA is associated with significantly higher rates of pre-eclampsia, cesarean delivery, placental abruption, and preterm birth than opioids and other drugs (138). CV events during hospitalizations for delivery are also significantly higher in MA-exposed pregnancies than opioid-, cocaine-, alcohol- or cannabis-exposed pregnancies, including a 9-fold risk for cardiomyopathy or heart failure (139). Still, little is known about the ongoing physical health of those mothers who may be using a combination of opioids, MA, and other drugs. Mental illness, poverty, domestic violence, homelessness, and food insecurity occur frequently in pregnant individuals with substance use disorders. Yet, the complexity of these circumstances has made it difficult to determine the impact of these on the ability to parent an already vulnerable child exposed prenatally to opioids and MA.

This review has shown differences in the neurobehavioral outcomes between opioid-exposed and MA-exposed infants. What is unclear is the effect that using both of these drugs will have on perinatal outcomes and the management of these infants in the context of polysubstance use. For instance, Polysubstance use is ubiquitous and, depending on the type or class of drug, may impair fetal neurodevelopment, increase the need, duration, and adjunctive treatment for NOWs, or suppress or change the signs typically associated with NOWs (156–158, 160, 161). Lacking in many studies is the ability to determine the frequency of use or dose of a particular drug or drugs. Biological measures are often limited to detecting prenatal drug exposure after 20 weeks gestation but not during preconception, embryogenesis, or the first trimesters. In addition, they can not tell us the frequency or pattern of prenatal exposure (164). This is of particular importance in determining the extent of short-acting drugs or MA or the range of new psychoactive substances that continue to emerge in the illicit drug market (131). The pattern of MA use is often bingeing that lasts for weeks, where significant amounts of tobacco, cannabis, and alcohol are consumed. Although self-report measures are limited by recall, combined with biological measures, they may provide a better estimate of the extent of prenatal drug exposure to the mother and newborn (164).

Knowing which drugs have been used prenatally, their frequency, and timing also affect clinical decision-making during the perinatal period. In mothers who are receiving OST, breastfeeding is encouraged as small amounts of opioids in breast milk may moderate signs or severity of NOWs. However, the evidence for breastfeeding infants exposed to MA is less clear. Recommendations for small amounts of MA early in pregnancy suggest the benefits of breastfeeding outweigh the risks of MA exposure. However, breastfeeding is not recommended if there is long-term use or use in the third trimester (170, 171). Therefore, mothers may need to be counseled on alternative ways of feeding or providing breast milk to their infants if there is co-use of substantial amounts of MA use with opioids.

Additionally, infants exposed to MA prenatally have not displayed the typical signs of NOWS (153). Neurobehavioral assessments using the NNNS have found differences between opioid-exposed and MA-exposed infants, with MA-exposed infants exhibiting lower arousal and less excitability (26, 153). Again, the co-use of opioids and MA may depress or exacerbate the effects of opioids and impact the assessment and diagnosis of NOWs (162).

5.1. Diagnosing and treating NOWs

A further limitation of current research is the need for more consensus around the best method of assessing and diagnosing NOWs when physiological signs are atypical due to exposure to a combination of different substances (156). In these cases, the decision to use pharmacological or non-pharmacological interventions is left to the clinician. The gold standard for assessing NOWs is the Finnegan Neonatal Abstinence Score Sheet (172), but some researchers and clinicians have conveyed concerns about its subjectivity, length, reliability, and validity (173). Typically, the signs of opioid withdrawal include evidence of some or all of the following: central nervous system (CNS) irritability, high-pitched continuous crying, decreased sleep, increased muscle tone, hyperactive Moro reflex and potential seizures, gastrointestinal dysfunction, feeding difficulties, and vomiting, and autonomic nervous system activation that includes fever, sweating increased respiratory rate and nasal stuffiness and flaring (174).

Recently, a newer function-based—Eat, Sleep, Console (ESC) care—approach was proposed (175). The ESC waives the identification of these typical signs and symptoms unique to each infant and their impact on dyadic functioning and neurodevelopment. Instead, the focus of ESC is evaluating infants

in 3 functional capacities: the ability to eat (infant able to eat >1 oz per feed or breastfeed well), sleep (sleeps undisturbed for ≥1 h), and be consoled from crying within 10 min. The reported goal of this method of identifying and treating NOWs was shorter length of stay, reduced medication, and lower costs, all of which are important goals (175). However, concerns have been raised about the widespread use of this tool before it was subjected to randomized controlled trials compared to traditional care (176). Early concerns were the minimized appreciation of the complex neurobehavior that occurs at birth that is disrupted by NOWs when the focus of treatment is only 3 areas of function in the newborn. And the unstated lack of concern for the importance of typical and atypical neurobehavior to later neurodevelopment.

Subsequent research has provided evidence that ESC meets its intended goals in a multisite study of 26 US hospitals. When it was compared to usual care no predetermined adverse outcomes were observed (177). These included seizures or accidental trauma, respiratory insufficiency related to opioid therapy, or a composite safety measure through 3 months of age that included acute or urgent or emergency department visits or hospital readmission. Still, ESC discounts the usefulness of identifying typical and atypical neurobehavior exhibited in multiple systems of infants prenatally exposed to opioids and other substances limits our ability to understand the linkages between NOWs and later neurodevelopment (178).

Finally, few studies examine how the timing of opioid exposure and other substances can impact neurodevelopmental outcomes, nor have the research accounted for the potential confounding of the genetic makeup of the parents or epigenetic factors associated with addiction.

5.2. Addressing the limitations and gaps in our knowledge

To address the many limitations of the extant literature and the long-term effects of prenatal exposure to opioids, MA, and other licit and illicit substances, we first need to design large studies that can address the many confounders associated with OUDs and other SUDs. Second, we need to develop evidence-based assessments that will improve the diagnosis and management of prenatal exposure to opioids, MA, and other drugs. This means we need to assess every infant with atypical signs or symptoms associated with maternal drug use. To do this, studies should include a short-term marker of neurodevelopment as a marker for risk for later neurodevelopmental impairment in infancy and childhood (178). For example, this review has shown the differences at birth in neurobehavior between mothers receiving MMT and BUP during pregnancy. We have also demonstrated the differences in neurobehavioral signs in MA-exposed compared to opioid-exposed infants using a standardized measure, the NNNS. Studies employing the NNNS have shown this measure can be used to measure neurodevelopment at birth and is predictive of cognitive and motor development at 24 months (26) and low IQ, adaptive behavior, and problem behavior in 4.5-year-old children (179).

One research program that will be able to address the many limitations of the current studies on SUD during pregnancy is the US Environmental Influences on Child Health Outcomes (ECHO) program, which was initiated in 2016 to examine how environmental exposures in early life can impact health across the life-course (180). This study is designed to identify the mechanisms and intervention targets to address 5 pediatric health outcomes: prenatal, perinatal, and early postnatal outcomes; childhood obesity; airways; neurodevelopment; and positive health outcomes. The Person Reported Outcomes (PRO) Core is a key component of the ECHO program. This unifying measurement framework takes a lifespan development approach to assess how physical, mental, and social health interact within families across the life course to promote or hinder child health outcomes (181). Recent evidence from the ECHO program reported in this review provided the characteristics of 21,905 pregnant individuals who used opioids during pregnancy (31). For a comprehensive review of how the ECHO program can address the methodologic limitations associated with the current literature on maternal OUD and other SUDs, see Condradt et al. (178).

A further important initiative that will inform the treatment of maternal OUDs is the Maternal and Infant Network to Understand Outcomes Associated with Use of Medication for Opioid Use Disorders During Pregnancy or MAT-LINK (182, 183). This project is a surveillance system that examines the demographic characteristics and clinical information of pregnant persons receiving medication for OUDs (MOUD) compared to those who are not receiving treatment. This initiative aims to understand better the effect of treatment outcomes and, in turn, inform public health and clinical care for this population. Data collected in this longitudinal project includes outcomes at delivery and short- and long-term outcomes for children, including physical growth and development, diagnoses of chronic conditions, health care use, vaccinations, and neurodevelopmental outcomes. Given the lack of uptake of BUP and MMT programs (<50%), this initiative will likely provide evidence to improve enrolments in OST programs.

6. Conclusions

The conclusions that can be derived from the current literature regarding the perinatal outcomes of the combined increase in prenatal opioid and MA exposure are limited due to the lack of current research and the methodological limitations of available research. Illicit drug use during pregnancy has spiraled out of control since the 1970s, and research on its effects has struggled to keep up. Most studies have focused on the drug "crisis" of the moment. Therefore, many studies are retrospective or epidemiological and can tell us we have a problem but not how to address it. Many of the limitations of the current research have been addressed by the ECHO and MAT-LINK studies, but more studies that address

the limitations of past research are needed. To engage participation in research and increase enrolment in treatment programs, we need to reduce the barriers and the stigma around SUDs.We need surveillance of all SU throughout pregnancy and postnatally so that clinicians can make informed decisions about the clinical care of the mother and the developing child. A standardized measure of typical and atypical neurobehaviour should be used early in the postnatal period to identify those infants especially at risk for poor neurodevelopment. Treatment programs for SUDs during pregnancy should provide tailored, comprehensive care that considers polysubstance use and includes treatment for the co-morbidity of psychiatric problems and trauma. Finally, reducing the risks to parenting from the constellation of risk factors that are repeatedly reported in studies of prenatal drug use is paramount.

Author contributions

TW: Conceptualization, Writing – original draft. BL: Conceptualization, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Wouldes TA, Lester BM. Stimulants: how big is the problem and what are the effects of prenatal exposure? *Semin Fetal Neonatal Med*. (2019) 24(2):155–60. doi: 10.1016/j.siny.2019.01.011

2. United Nations Office on Drugs and Crime. World Drug Report 2018 (United Nations Publication, Sales No. E.18.XI.9). United Nations. (2018).

3. Smid MC, Metz TD, Gordon AJ. Stimulant use in pregnancy: an under-recognized epidemic among pregnant women. *Clin Obstet Gynecol*. (2019) 62 (1):168–84. doi: 10.1097/GRF.0000000000000418

4. Blandthorn J, Leung L, Loke Y, Lloyd-Jones DM, Thurman R, Bowman E, et al. Prescription opioid use in pregnancy. *Aust N Z J Obstetr Gynaecol*. (2018) 58:494–8. doi: 10.1111/ajo.12823

5. Terplan M, Smith EJ, Kozloski MJ, Pollack HA. Methamphetamine use among pregnant women. *Obstet Gynecol*. (2009) 113(6):1285–91. doi: 10.1097/AOG.0b013e3181a5ec6f

6. ACOG Committee Opinion. Opioid use and opioid use disorder in pregnancy. Committee opinion No. 711. *Am Coll Obstetr Gynecol*. (2017) 711:e81–94. doi: 10.1097/AOG.0000000000002235

7. Jones CM, Underwood N, Compton WM. Increases in methamphetamine use among heroin treatment admissions in the United States, 2008–17. *Addiction*. (2020) 115(2):347–53. doi: 10.1111/add.14812

8. Haight SC, Ko JY, Tong VT, Bohm MK, Callaghan. Opioid use disorder documented at delivery hospitalization—united States, 1999–2014. *MMWR Morb Mortal Wkly Rep*. (2018) 67:845–9. doi: 10.15585/mmwr.mm6731a1

9. Patrick SW, Davis MM, Lehman CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: united States 2009 to 2012. *J Perinatol*. (2015) 35(8):667. doi: 10.1038/jp.2015.63

10. Tolia VN, Patrick SW, Bennett MM, Murthy K, Sousa J, Smith PB, et al. Increasing incidence of the neonatal abstinence syndrome in U. S. Neonatal ICUs. *N Engl J Med*. (2015) 372(22):2118–26. doi: 10.1056/NEJMsa1500439

11. Agency for Healthcare Research and Quality. HCUP Fast Stats. Available at: https:.hcup-us.ahrq.gov/faststats/landing.jspMay (2022).

12. Scholl L, Seth P, Kariisa M, Wilson N, Baldwin G. Drug and opioid-involved overdose deaths—united States 2013–2017. *Morb Mortal Wkly Rep*. (2019) 67:1419–27. doi: 10.15585/mmwr.mm675152e1

13. Desai RJ, Hernandez-Diaz S, Bateman BT, Huybrechts KF. Increase in prescription opioid use during pregnancy among medicaid-enrolled women. *Obstet Gynecol*. (2014) 123(5):997–1002. doi: 10.1097/AOG.0000000000000208

14. Desai RJ, Huybrechts KF, Hernadez-Diaz S, Mogun H, Patorno E, Klatenbach K, et al. Exposure to prescription opioid analgesics in utero and risks of neonatal abstinence syndrome: population based cohort study. *Br Med J*. (2015) 350:h2101. doi: 10.11136/bmj.h2102

15. Atlas of Healthcare Variation: Opioids. (2017).

16. Meth RF. The forgotten killer, is Back. And it's everywhere. The New York Times. (2018).

17. Savage J, Johnston K, Reed C. Documentary Fighting the Demon: Inside New Zealand's Meth Crisis. Available at: https://www.nzherald.co.nz/indepth/national/new-zealands-meth-crisis-documentary/2019

18. Piske M, Homayra F, Min JE, Zhou H, Marchand C, Mead A, et al. Opioid use disorder and perinatal outcomes. *Pediatrics*. (2021) 148(4):e2021050279. doi: 10.1542/peds.2021-050279

19. Substance Abuse and Mental Health Services Administration. Associations of nonmedical pain reliever use and initiation of heroin use in the United States. (2013). Available at: https://www.samhsa.gov/data/

20. Cicero TJ, Ellis MS, Harney J. Shifting patterns of prescription opioid and heroin abuse in the United States. *N Engl J Med*. (2015) 373(18):1789–90. doi: 10.1056/NEJMc1505541

21. Bruzelius E, Martins SS. US trends in drug overdose mortality among pregnant and postpartum persons, 2017-2020. *JAMA*. (2022) 328(21):2159. doi: 10.1001/jama.2022.17045

22. Strickland JC, Stoops WW, Dunn KE, Smith KE, Havens JR. The continued rise of methamphetamine use among people who use heroin in the United States. *Drug Alcohol Depend*. (2021) 225:108750. doi: 10.1016/j.drugalcdep.2021.108750

23. Cicero TJ, Ellis MS, Kasper ZA. Polysubstance use: a broader understanding of substance use during the opioid crisis. *Am J Public Health*. (2020) 110(2):244–50. doi: 10.2105/AJPH.2019.305412

24. Wouldes TA, LaGasse LL, Derauf C, Newman E, Shah R, Smith LM, et al. Co-morbidity of substance use disorder and psychopathology in women who use methamphetamine during pregnancy in the US and New Zealand. *Drug Alcohol Depend*. (2013) 127(1–3):101–7. doi: 10.1016/j.drugalcdep.2012.06.016

25. Wouldes TA, Woodward LJ. Maternal methadone dose during pregnancy and infant clinical outcome. *Neurotoxicol Teratol*. (2010) 32(3):406–13. doi: 10.1016/j.ntt.2010.01.007

26. Wouldes TA, Woodward LJ. Neurobehavior of newborn infants exposed prenatally to methadone and identification of a neurobehavioral profile linked to

poorer neurodevelopmental outcomes at age 24 months. *PLOS ONE*. (2020) 15(10): E0240905. doi: 10.1371/journal.pone.0240905

27. Cleary BJ, Donnelly JM, Strawbridge JD, Gallagher PJ, Fahey T, White MJ, et al. Methadone and perinatal outcomes: a retrospective cohort study. *Am J Obstet Gynecol*. (2011) 204(2):139.e1–e9. doi: 10.1016/j.ajog.2010.10.004

28. Cleary BJ, Eogan M, O'Connell MP, Fahey T, Gallagher PJ, Clarke T, et al. Methadone and perinatal outcomes: a prospective cohort study. *Addiction*. (2012) 107(8):1482–92. doi: 10.1111/j.1360-0443.2012.03844.x

29. Davie-Gray A, Moor S, Spencer C, Woodward LJ. Psychosocial characteristics and poly-drug use of pregnant women enrolled in methadone maintenance treatment. *Neurotoxicol Teratol*. (2013) 38:46–52. doi: 10.1016/j.ntt.2013.04.006

30. Derauf C, LaGasse LL, Smith LM, Grant P, Shah R, Arria A, et al. Demographic and psychosocial characteristics of mothers using methamphetamine during pregnancy: preliminary results of the infant development, environment, and lifestyle study (IDEAL). *Am J Drug Alcohol Abuse*. (2007) 33:281–9. doi: 10.1080/00952990601175029

31. Nguyen RHN, Knapp EA, Li X, Camargo CA, Conradt E, Cowell W, et al. Characteristics of individuals in the United States who used opioids during pregnancy. *J Women's Health*. (2023) 32(2):161–70. doi: 10.1089/jwh.2022.0118

32. Han B, Compton WM, Blanco C, Crane E, Lee JY, Jones CM. Prescription opioid use, misuse, and use disorders in US adults: 2015 national survey on drug use and health. *Ann Intern Med*. (2017) 167(5):293–301. doi: 10.7326/M17-0865

33. Benningfield MM, Arria AM, Kaltenbach K, Heil SH, Stine SM, Coyle MG, et al. Co-occurring psychiatric symptoms are associated with increased psychological, social and medical impairment in opioid dependent pregnant women. *Am J Addict*. (2010) 19:416–21. doi: 10.1111/j.1521-0391.2010.00064.x

34. Wang SM, Dezinno P, Maranets I, Berman MR, Caldwell-Andrews AA, Kain ZN. Low back pain during pregnancy: prevalence, risk factors, and outomes. *Obstet Gynecol*. (2004) 104(1):65–70. doi: 10.1097/01.AOG.0000129403.54061.0e

35. Patrick SW, Dudley J, Martin PR, Harrell FE, Warren MD, Hartmann KE, et al. Prescription opioid epidemic and infant outcomes. *Pediatrics*. (2015) 135(5):842–50. doi: 10.1542/peds.2014-3299

36. Yazdy MM, Desai RJ, Brogly SB. Prescription opioids in pregnancy and birth outcomes: a review of the literature. *J Pediatr Genet*. (2015) 4:56–70. doi: 10.1055/s-0035-1556740

37. Nezvalová-Henriksen K, Spigset O, Nordeng H. Effects of codeine on pregnancy outcome: results from a large population-based cohort study. *Eur J Clin Pharmacol*. (2011) 67(12):1253–61. doi: 10.1007/s00228-011-1069-5

38. Kelly L, Dooley J, Cromarty H, Minty B, Morgan A, Madden S, et al. Narcotic-exposed neonates in a first nations population in northwestern Ontario: incidence and implications. *Can Fam Physician*. (2011) 57(11):e441–e7.

39. Källén B, Borg N, Reis M. The use of central nervous system active drugs during pregnancy. *Pharmaceuticals*. (2013) 6(10):1221–86. doi: 10.3390/ph6101221

40. Smith MV, Costello D, Yonkers KA. Clinical correlates of prescription opioid analgesic use in pregnancy. *Matern Child Health J*. (2015) 19(3):548–56. doi: 10.1007/s10995-014-1536-6

41. Lind JN, Interrante JD, Ailes EC, Gilboa SM, Khan S, Frey MT, et al. Maternal use of opioids during pregnancy and congenital malformations: a systematic review. *Pediatrics*. (2017) 139(6):e20164131. doi: 10.1542/peds.2016-4131

42. CDC Centers for Disease Control. Fentanyl Test Strips: A harm reduction strategy Atlanta, Georgia: Centers for Disease Control and Prevention. (2022). Available at: Https://www.cdc.gov/stopoverdose/fentanyl/fentanyl-test-strips.html

43. Births: Final Data 2016. (2018). Available from: Available at: https://www.cdc.gov/nchs/data/nvsr/nvsr67/nvsr_01-tables.pdf

44. Cooper J, Jauniaux E, Gulbis B, Quick D, Bromley L. Placental transfer of fentanyl in early human pregnancy and its detection in fetal brain. *Br J Anaesth*. (1999) 82:929–31. doi: 10.1093/bja/82.6.929

45. Alipio JB, Haga C, Fox ME, Arakawa K, Balaji R, Cramer N, et al. Perinatal fentanyl exposure leads to long-lasting impairments in somatosensory circuit function and behavior. *J Neurosci*. (2021) 41(15):3400–17. doi: 10.1523/JNEUROSCI.2470-20.2020

46. Goodfriend MJ, Shey IA, Klein MD. The effects of maternal narcotic addiction on the newborn. *Am J Obstet Gynecol*. (1956) 71:29. doi: 10.1016/0002-9378(56)90674-3

47. Sussman S. Narcotic and methamphetamine use during pregnancy. *Am J Dis Child*. (1963) 106:125–30. doi: 10.1001/archpedi.1963.02080050327013

48. Alroomi LG, Davidson J, Evans TJ, Galea P, Howat R. Maternal narcotic abuse and the newborn. *Arch Dis Child*. (1987) 63:81–3. doi: 10.1136/adc.63.1.81

49. Blinick G, Wallach RC, Jerez E. Pregnancy in narcotics addicts treated by medical withdrawal. *Am J Obstet Gynecol*. (1969) 105(7):997–1003. doi: 10.1016/0002-9378(69)90117-3

50. Little BB, Snell LM, Klein VR, Gilstrap LC, Knoll KA, Breckenridge JD. Maternal and fetal effects of heroin addiction during pregnancy. *J Reprod Med*. (1990) 35:159–62. PMID: 2304039.

51. Perlmutter JF. Heroin addiction and pregnancy. *Obstet Gynecol Surv*. (1974) 29:439–46. doi: 10.1097/00006254-197407000-00001

52. Rementeria JL, Nunag NN. Narcotic withdrawal in pregnancy: stillbirth incidence with a case report. *Am J Obstet Gynecol*. (1973) 116(8):1152–6. doi: 10.1016/0002-9378(73)90953-8

53. Stone ML, Salerno LJ, Green M, Zelson C. Narcotic addiction in pregnancy. *Am J Obstet Gynecol*. (1971) 109(5):716–20. doi: 10.1016/0002-9378(71)90757-5

54. Naeye RL, Blanc W, Leblanc W, Khatamee MA. Fetal complications of maternal heroin addiction: abnormal growth, infections, and episodes of stress. *J Pediatr*. (1973) 83(6):1055–61. doi: 10.1016/S0022-3476(73)80550-5

55. Alroomi LG, Davidson J, Evans TJ, Galea P, Howat R. Maternal narcotic abuse and the newborn. *Arch Dis Child*. (1988) 63(1):81–3. doi: 10.1136/adc.63.1.81

56. Binder T, Vavrinkova B. Prospective randomised comparative study of the effect of buprenorphine, methadone and heroin on the course of pregnancy, birthweight of newborns, early postpartume adaptation and course of the neonatal abstinence syndrome (NAS) in women followed up in the outpatient department. *Neuro Endocrinol Lett*. (2008) 29(1):80–6. PMID: 18283247.

57. Kaltenbach K, Berghella V, Finnegan L. Opioid dependence during pregnancy. *Obstet Gynecol Clin North Am*. (1998) 25(1):139–51. doi: 10.1016/S0889-8545(05)70362-4

58. Archie C. Methadone in the management of narcotic addiction in pregnancy. *Curr Opin Obstet Gynecol*. (1998) 10(6):435–40. doi: 10.1097/00001703-199812000-00001

59. Center for Substance Abuse Treatment. Medication-assisted treatment for opioid addiction treatment programs.: Substance Abuse and Mental Health Service Administration (US) (2005). Available at: www.ncbi.nlm.nih.gov/books/NBK64164/

60. Kandall SR, Albin S, Lowinson J, Berle B, Eidelman AI, Gartner LM. Differential effects of maternal heroin and methadone use on birthweight. *Pediatrics*. (1976) 58(5):681–5. doi: 10.1542/peds.58.5.681

61. Ward J, Mattick RP, Hall W. The effectiveness of methadone maintenance treatment: an overview. *Drug Alcohol Rev*. (1994) 13:327–36. doi: 10.1080/09595239400185431

62. Gaalema DE, Scott TL, Heil SH, Coyle MG, Kaltenbach K, Badger GJ, et al. Differences in the profile of neonatal abstinence syndrome signs in methadone-versus buprenorphine-exposed neonates. *Addiction*. (2012) 107(S1):53–62. doi: 10.1111/j.1360-0443.2012.04039.x

63. Zelson C, Sook JL, Casalino M. Neonatal narcotic addiction. Comparative effects of maternal intake of heroin and methadone. *N Engl J Med*. (1973) 289(23):1216–20. doi: 10.1056/NEJM197312062892303

64. Connaughton JF, Finnegan LP, Schut J, Emich JP. Current concepts in the management of the pregnant opiate addict. *Addict Dis*. (1975) 2(1):21–35. PMID: 1163358.

65. Finnegan LP. Management of pregnant drug-dependent women. *Ann N Y Acad Sci*. (1978) 311:136–46. doi: 10.1111/j.1749-6632.1978.tb16770.x

66. Olofsson M, Buckley W, Andersen GE, Friis-Hansen B. Investigation of 89 children born by drug-dependent mothers. I neonatal course. *Acta Paediatrica Scandanavia*. (1983) 72:403–6. doi: 10.1111/j.1651-2227.1983.tb09736.x

67. Olofsson M, Buckley W, Andersen GE, Friis-Hansen B. Investigation of 89 children born by drug-dependent mothers. II follow-up 1-10 years after birth. *Acta Paediatrica Scandinavia*. (1983) 72:407–10. doi: 10.1111/j.1651-2227.1983.tb09737.x

68. Jansson LM, DiPietro J, Elko A. Fetal response to maternal methadone administration. *Am J Obstet Gynecol*. (2005) 193(3):611–7. doi: 10.1016/j.ajog.2005.02.075

69. Jansson LM, Dipietro JA, Velez CH, Elko A, Knauer H, Kivlighan KT. Maternal methadone dosing schedule and fetal neurobehavior. *J Matern-Fetal Neonatal Med*. (2009) 22(1):29–35. doi: 10.1080/14767050802452291

70. Wouldes TA, Roberts AB, Pryor JE, Bagnall C, Gunn TR. The effect of methadone treatment on the quantity and quality of human fetal movement. *Neurotoxicol Teratol*. (2004) 26(4):23–34. doi: 10.1016/j.ntt.2003.09.003

71. Walhovd KB, Watts R, Amlien I, Woodward LJ. Neural tract development of infants born to methadone-maintained mothers. *Pediatr Neurol*. (2012) 47(1):1–6. doi: 10.1016/j.pediatrneurol.2012.04.008

72. Hagopian GS, Wolfe HM, Sokol RJ, Ager JW, Wardell JN, Cepeda EE. Neonatal outcome following methadone exposure in utero. *J Matern Fetal Med*. (1996) 5:348–54. doi: 10.1002/(SICI)1520-6661(199611/12)5:6<348::AID-MFM11>3.0.CO;2-D

73. Chasnoff IJ, Hatcher R, Burns WJ. Early growth patterns of methadone-addicted infants. *Am J Dis Child*. (1980) 134:1049–51. doi: 10.1001/archpedi.1980.02130230029009

74. Chasnoff IJ, Burns KA, Burns WJ, Schnoll SH. Prenatal drug exposure: effects on neonatal and infant growth and development. *Neurobehav Toxicol Teratol*. (1986) 8:357–62. PMID: 3762846.

75. Blinick G, Jerez E, Wallach RC. Methadone maintenance, pregnancy, and progeny. *J Am Med Assoc*. (1973) 225(5):477–9. doi: 10.1001/jama.1973.03220320013004

76. Connaughton JF, Reeser D, Schut J, Finnegan LP. Perinatal addiction: outcome and management. *Am J Obstet Gynecol*. (1977) 129:679–86. doi: 10.1016/0002-9378(77)90652-4

77. Ellwood DA, Sutherland P, Kent C, O'Connor M. Maternal narcotic addiction: pregnancy outcome in patients managed by a specialized drug-dependency antenatal clinic. *Aust N Z J Obstet Gynaecol*. (1987) 27:92–8. doi: 10.1111/j.1479-828X.1987.tb00952.x

78. Giles W, Patterson T, Sanders F, Batey R, Thomas D, Collins J. Outpatient methadone programme for pregnant heroin using women. *Aust N Z J Obstetr Gynaecol*. (1989) 29:225–9. doi: 10.1111/j.1479-828X.1989.tb01724.x

79. Ostrea EM, Chavez CJ, Strauss ME. A study of factors that influence the severity of neonatal narcotic withdrawal. *J Pediatr*. (1976) 88(4 part 1):642–5. doi: 10.1016/S0022-3476(76)80027-3

80. Wouldes TA. Neurobehaviour of neonates born to mothers receiving opioid maintenance treatment: methadone and buprenorphine. In: Preedy VR, editors. *Neuropathology of drug addictions and substance misuse. Volume 3: General processes and mechanisms, prescription medications, caffeine and areca, polydrug misuse, emerging addictions and non-drug addictions*. London: Academic Press (2016). p. 577–88.

81. Kinsella M, Capel Y, Nelson SM, Kearns RJ. Opioid substitution in pregnancy a narrative review: contemporary evidence for use of methadone and buprenorphine in pregnancy. *J Subst Use*. (2022) 28(6):919–24. doi: 10.1080/14659891.2022.2106600

82. Jones HE, Finnegan LP, Kaltenbach K. Methadone and buprenorphine for the management of opioid dependence in pregnancy. *Drugs*. (2012) 72(6):747–57. doi: 10.2165/11632820-000000000-00000

83. Jones HE, Johnson RE, Jasinski DR, O'Grady KE, Chisholm CA, Choo RE, et al. Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome. *Drug Alcohol Dependence*. (2005) 79(1):1–10. doi: 10.1016/j.drugalcdep.2004.11.013

84. Suarez EA, Huybrechts KF, Straub L, Hernández-Díaz S, Jones HE, Connery HS, et al. Buprenorphine versus methadone for opioid use disorder in pregnancy. *N Engl J Med*. (2022) 387(22):2033–44. doi: 10.1056/NEJMoa2203318

85. Feng Y, He X, Yang Y, Chao D, Lazarus LH, Xia Y. Current research on opioid receptor function. *Curr Drug Targets*. (2012) 13(2):230–46. doi: 10.2174/138945012799201612

86. Farid WO, Dunlop SA, Tait RJ, Hulse GK. The effects of maternally administered methadone, buprenorphine and naltrexone on offspring: review of human and animal data. *Curr Neuropharmacol*. (2008) 6:125–50. doi: 10.2174/157015908784533842

87. Jansson LM, Velez M, McConnell K, Spencer N, Tuten M, Jones HE, et al. Maternal buprenorphine treatment and fetal neurobehavioral development. *Am J Obstet Gynecol*. (2017) 216(5):529.e1–e8. doi: 10.1016/j.ajog.2017.01.040

88. Velez ML, Jansson LM, Schroeder JR, Williams E. Prenatal methadone exposure and neonatal neurobehavioral functioning. *Pediatr Res*. (2009) 66(6):704–9. doi: 10.1203/PDR.0b013e3181bc035d

89. Heller NA, Logan BA, Morrison DG, Paul JA, Brown MS, Hayes MJ. Neonatal abstinence syndrome: neurobehavior at 6 weeks of age in infants with or without phrmacological treatment for withdrawal. *Dev Psychobiol*. (2017) 59:574–82. doi: 10.1002/dev.21532

90. Salisbury AL, Coyle MG, O'Grady KE, Heil SH, Martin PR, Stine SM, et al. Fetal assessment before and after dosing with buprenorphine or methadone. *Addiction*. (2012) 107(Suppl 1):36–44. doi: 10.1111/j.1360-0443.2012.04037.x

91. Jansson LM, Di Pietro JA, Velez M, Elko A, Williams E, Milio L, et al. Fetal neurobehavioral effects of exposure to methadone or buprenorphine. *Neurotoxicol Teratol*. (2011) 33(2):240–3. doi: 10.1016/j.ntt.2010.09.003

92. Fischer G, Ortner R, Rohrmeister K, Jagsch R, Baewert A, Langer M, et al. Methadone versus buprenorphine in pregnant addicts: a double-blind, double-dummy comparison study. *Addiction*. (2006) 101(2):275–81. doi: 10.1111/j.1360-0443.2006.01321.x

93. Lejeune C, Simmat-Durand L, Gourarier L, Aubisson S, Groupe d'Etudes Grossesse et Addictions (GEGA). Prospective multicenter observational study of 260 infants born to 259 opiate-dependent mothers on methadone or high-dose buprenorphine substitution. *Drug Alcohol Depend*. (2006) 82:250–7. doi: 10.1016/j.drugalcdep.2005.10.001

94. Zedler BK, Mann AL, Kim MM, Amick HR, Joyce AR, Murrelle EL, et al. Buprenorphine compared with methadone to treat pregnant women with opioid use disorder: a systematic review and meta-analysis of safety in the mother, fetus and child. *Addiction*. (2016) 111(12):2115–28. doi: 10.1111/add.13462

95. Welle-Strand GK, Skurtveit S, Jones HE, Waal H, Bakstad B, Bjarkø L, et al. Neonatal outcomes following in utero exposure to methadone or buprenorphine: a national cohort study of opioid-agonist treatment of pregnant women in Norway from 1996 to 2009. *Drug Alcohol Depend*. (2013) 127(1–3):200–6. doi: 10.1016/j.drugalcdep.2012.07.001

96. Hudak ML, Tan RC. The committee on drugs and the committee on Fetus and newborn. Neonatal drug withdrawal. *Pediatrics*. (2012) 129:e540–e60. doi: 10.1542/peds.2011-3212

97. Brogly SB, Saia KA, Walley AY, Du HM, Sebastiani P. Prenatal buprenorphine versus methadone exposure and neonatal outcomes: systematic review and meta-analysis. *Am J Epidemiol*. (2014) 180(7):673–86. doi: 10.1093/aje/kwu190

98. Jones HE, Heil SH, Baewert A, Arria AM, Kaltenbach K, Martin PR, et al. Buprenorphine treatment of opioid-dependent pregnant women: a comprehensive review. *Addiction*. (2012) 107(Suppl 1):5–27. doi: 10.1111/j.1360-0443.2012.04035.x

99. Soyka M. Buprenorphine use in pregnant opioid users: a critical review. *CNS Drugs*. (2013) 27(8):653–62. doi: 10.1007/s40263-013-0072-z

100. Minozzi S, Amato L, Bellisario C, Ferri M, Davoli M. Maintenance agonist treatments for opiate-dependent pregnant women. *Cochrane Database Syst Rev*. (2013) 23(12):CD006318. doi: 10.1002/14651858.CDC006318.pub3. Update in *Cochrane Database Syst Rev*. (2020) 11:CD006318. PMID: 24366859.

101. Cleary IJ, Donnelly J, Strawbridge J, Gallagher PJ, Fahey T, Clarke M, et al. Methadone dose and neonatal abstinence syndrome-systematic review and meta-analysis. *Addiction*. (2010) 105(12):2071–84. doi: 10.1111/j.1360-0443.2010.03120.x

102. Wouldes TA. Methadone maintenance during pregnancy: The consequences of low-dose vs high-dose for the fetus, the neonate and the infant. (Doctoral). Auckland, New Zealand: University of Auckland. (2001).

103. Bakstad B, Sarfi M, Welle-Strand GK, Ravndal E. Opioid maintenance treatment during pregnancy: occurrence and severity of neonatal abstinence syndrome. A national prospective study. *Eur Addict Res*. (2009) 15(3):128–34. doi: 10.1159/000210042

104. Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med*. (2010) 363(24):2320–31. doi: 10.1056/NEJMoa1005359

105. Metz V, Jagsch R, Ebner N, Würzl J, Pribasnig A, Aschauer C, et al. Impact of treatment approach on maternal and neonatal outcome in pregnant opioid-maintained women. *Hum Psychopharmacol*. (2011) 26(6):412–21. doi: 10.1002/hup.1224

106. Kakko J, Heilig M, Sarman I. Buprenorphine and methadone treatment of opiate dependence during pregnancy: comparison of fetal growth and neonatal outcomes in two consecutive case series. *Drug Alcohol Depend*. (2008) 96:69–78. doi: 10.1016/j.drugalcdep.2008.01.025

107. Madden JD, Chappel JN, Zuspan F, Gumpel J, Mejia A, Davis R. Observation and treatment of neonatal narcotic withdrawal. *Am J Obstet Gynecol*. (1977) 127:199–201. doi: 10.1016/S0002-9378(16)33250-1

108. Strauss ME, Andresko M, Stryker JC, Wardell JN, Dunkel LD. Methadone maintenance during pregnancy: pregnancy, birth, and neonate characteristics. *Am J Obstet Gynecol*. (1974) 120(7):895–900. doi: 10.1016/0002-9378(74)90335-4

109. Doberczak TM, Kandall SR, Wilets I. Neonatal opiate abstinence syndrome in term and preterm infants. *J Pediatr*. (1991) 118:933–7. doi: 10.1016/S0022-3476(05)82214-0

110. Doberczak TM, Kandall SR, Friedmann P. Relationships between maternal methdone dosage, maternal-neonatal methadone levels, and neonatal withdrawal. *Obstet Gynecol*. (1993) 81(6):936–40. PMID: 8497359.

111. Dashe JS, Sheffield JS, Olscher DA, Todd SJ, Jackson GL, Wendel GD. Relationship between maternal methadone dosage and neonatal withdrawal. *Obstet Gynecol*. (2002) 100(6):1244–9. doi: 10.1016/s0029-7844(02)02387-6

112. Liu AJ, Jones MP, Murray H, Cook CM, Nanan R. Perinatal risk factors for the neonatal abstinence syndrome in infants born to women on methadone maintenance therapy. *Aust N Z J Obstet Gynaecol*. (2010) 50(3):253–8. doi: 10.1111/j.1479-828X.2010.01168.x

113. Brown HL, Britton KA, Mahaffey D, Brizendine E, Hiett AK, Turnquest MA. Methadone maintenance in pregnancy: a reappraisal. *Am J Obstet Gynecol*. (1998) 179:459–63. doi: 10.1016/S0002-9378(98)70379-5

114. Mack G, Thomas D, Giles W, Buchanan N. Methadone levels and neonatal withdrawal. *J Paediatr Child Health*. (1991) 27:96–100. doi: 10.1111/j.1440-1754.1991.tb00360.x

115. Berghella V, Lim PJ, Hill MK, Cherpes J, Chennat J, Kaltenbach K. Maternal methadone dose and neonatal withdrawal. *Am J Obstetr Gynecol*. (2003) 189:312–7. doi: 10.1067/S0002-9378(03)00520-9

116. Kuschel CA, Austerberry L, Cornwall M, Couch R, Rowley RS. Can methadone concentrations predict the severity of withdrawal in infants at risk of neonatal abstinence syndrome? *Arch Dis Child Fetal Neonatal Ed*. (2004) 89(5):F390–F3. doi: 10.1136/adc.2003.036863

117. Seligman NS, Almario CV, Hayes EJ, Dysart KC, Berghella V. Relationship between maternal methadone dose at delivery and neonatal abstinence. *J Pediatr*. (2010) 157:428–33. 33.e1. doi: 10.1016/j.jpeds.2010.03.033

118. Dysart K, Hsieh H, Kaltenbach K, Greenspan JS. Sequela of preterm versus term infants born to mothers on a methadone maintenance program: differential course of neonatal abstinence syndrome. *J Perinat Med*. (2007) 35:344–6. doi: 10.1515/JPM.2007.063

119. Wachman EM, Newby PK, Vreeland J, Byun J, Bonzagni A, Bauchner H, et al. The relationship between maternal opioid agonists and psychiatric medications on length of hospitalization for neonatal abstinence syndrome. *J Addict Med*. (2011) 5(4):293–9. doi: 10.1097/ADM.0b013e3182266a3a

120. Friedman MA, Spitzer AR. Discharge criteria for the term newborn. *Pediatr Clin North Am*. (2004) 51:599–618. doi: 10.1016/j.pcl.2004.01.011

121. Soule AB, Standley K, Copans SA, Davis M. Clinical uses of the brazelton neonatal scale. *Pediatrics*. (1974) 54:583–6. doi: 10.1542/peds.54.5.583

122. Coyle MG, Salisbury AL, Lester B, Jones HE, Lin H, Graf-Rohrmeister K, et al. Neonatal neurobehavior effects following buprenorphine versus methadone exposure. *Addiction*. (2012) 107(Suppl. 1):63–73. doi: 10.1111/j.1360-0443.2012.04040.x

123. Lester BM, Tronick EZ. The neonatal intensive care unit network neurobehavioral scale (NNNS). *Pediatrics*. (2004) 113(Supplement):631–99. doi: 10.1542/peds.113.S2.631

124. Tronick EZ, Olson K, Rosenberg R, Bohne L, Liu J, Lester BM. Normative neurobehavioral performance of healthy infants on the neonatal instensive care unit network neurobehavioral scale. *Pediatrics*. (2004) 113:676–8. doi: 10.1542/peds.113.S2.676

125. Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Eng J Med*. (2010) 363:2320–31. doi: 10.1056/NEJMoa1005359

126. Lejeune C, Simmat-Durand L, Gourarier L, Aubisson S, Groupe d'Etudes Grossesse et A. Prospective multicenter observational study of 260 infants born to 259 opiate-dependent mothers on methadone or high-dose buprenophine substitution. *Drug Alcohol Depend*. (2006) 82(3):250–7. doi: 10.1016/j.drugalcdep.2005.10.001

127. Lacroix I, Berrebi A, Garipuy D, Schmitt L, Hammou Y, Chaumerliac C, et al. Buprenorphine versus methadone in pregnant opioid-dependent women: a prospective multicenter study. *Eur J Clin Pharmacol*. (2011) 67(10):1053–9. doi: 10.1007/s00228-011-1049-9

128. Pritham UA, Paul JA, Hayes MJ. Opioid dependency in pregnancy and length of stay for neonatal abstinence syndrome. *J Obstetr Gynecol Neonatal Nurs*. (2012) 41(2):180–90. doi: 10.1111/j.1552-6909.2011.01330.x

129. Finnegan LP. Treatment issues for opioid-dependent women during the perinatal period. *J Psychoactive Drugs*. (1991) 23(2):191–201. doi: 10.1080/02791072.1991.10472236

130. Brogly SB, Saia K, Hernández-Diaz S, Werler M, Sebastiani P. The comparative safety of buprenorphine versus methadone in pregnancy-what about confounding? *Addiction*. (2016) 111(12):2130–1. doi: 10.1111/add.13551

131. United Nations Office on Drugs and Crime. The World Drug Report (2023). Available at: https://www.unodc.org/unodc/en/data-and-analysis/world-drug-report-2023.html

132. Mackay L, Bach P, Milloy M-J, Zishan C, Kerr T. The relationship between crystal methamphetamine use and methadone retention in a prospective cohort of people who use drugs. *Drug Alcohol Depend*. (2021) 225:1–7. doi: 10.1016/j.drugalcdep.2021.108844

133. Cho AK, Melega WP. Patterns of methamphetamine abuse and their consequences. *J Addict Dis*. (2002) 21(1):21–34. doi: 10.1300/J069v21n01_03

134. Ciccarone D. Stimulant abuse: pharmacology, cocaine, methamphetamine, treatment, attempts at pharmacotherapy. *Prim Care*. (2011) 38(1):41–58. doi: 10.1016/j.pop.2010.11.004

135. Rothman RB, Blough BE, Baumann MH. Dual dopamine/serotonin releasers as potential medications for stimulante and alcohol addictions. *AAPS J*. (2007) 9(1):E1–E10. doi: 10.1208/aapsj0901001

136. Lewis B, Hoffman IA, Nixon SJ. Sex differences in drug use among polysubstance users. *Drug Alcohol Depend*. (2014) 145:127–33. doi: 10.1016/j.drugalcdep.2014.10.003

137. Perez FA, Blythe S, Wouldes T, McNamara K, Black KI, Oei JL. Prenatal methamphetamine—impact on the mother and child—a review. *Addiction*. (2021) 117(1):250–60. doi: 10.1111/add.a5509

138. Admon LK, Bart G, Kozhimannil KB, Richardson CR, Dalton VK, Winkelman TNA. Amphetamine- and opioid-affected births: incidence, outcomes, and costs, United States, 2004-2015. *Am J Public Health*. (2019) 109(1):148–54. doi: 10.2105/AJPH.2018.304771

139. Evans K, Wu P, Mamas AM, Irwin C, Kang P, Perlow JH, et al. Substance use in pregnancy and its associaton with cardiovascular events. *JACC: Advances*. (2023) 2(8):100619. doi: 10.1016/j.jacadv.2023.100619

140. Wu M, Lagasse LL, Wouldes TA, Arria AM, Wilcox T, Derauf C, et al. Predictors of inadequate prenatal care in methamphetamine-using mothers in New Zealand and the United States. *Matern Child Health J*. (2013) 17(3):566–75. doi: 10.1007/s10995-012-1033-8

141. Stevens S, Rogers J, Dansereau L, Dellagrotta S, Lester BM, Wouldes TA. A prospective study of service use in the year after birth by women at high risk for antenatal substance use and mental health disorders. *Int J Ment Health Addict*. (2019) 19:1005–18. doi: 10.1007/s11469-019-00207

142. Shah R, Diaz S, Arria A, Lagasse L, Derauf C, Newman E, et al. Prenatal methamphetamine exposure and short-term maternal and infant medical outcomes. *Am J Perinatol*. (2012) 29(05):391–400. doi: 10.1055/s-0032-1304818

143. Plessinger MA. Prenatal exposure to amphetamines. Risks and adverse outcomes in pregnancy. *Obstetr Gynecol Clin N A*. (1998) 25(1):119–38. doi: 10.1016/S0889-8545(05)70361-2

144. Oro AS, Dixon SD. Perinatal cocaine and methamphetamine exposure: maternal and neonatal correlates. *J Pediatr*. (1987) 111:571–8. doi: 10.1016/S0022-3476(87)80125-7

145. Little BB, Snell LM, Gilstrap LD 3rd. Methamphetamine use during pregnancy: outcome and fetal effects. *Obstet Gynecol*. (1988) 72:541–4. PMID: 3419732.

146. Eriksson M, Zetterstrom R. Amphetamine addiction during pregnancy: 10-year follow-up. *Acta Paediatrica Scandanivica*. (1994) 404(November):27–31. doi: 10.1111/j.1651-2227.1994.tb13380.x

147. Billing L, Eriksson M, Larsson G, Zetterstrom R. Amphetamine addiction and pregnancy. III. One year follow-up of the children. Psychosocial and pediatric aspects. *Acta Paediatr*. (1980) 85:204–8. doi: 10.111/j.1651-2227.1980.tb07342.x

148. Wright TE, Schuetter R, Tellei J, Sauvage L. Methamphetamines and pregnancy outcomes. *J Addict Med*. (2015) 9(2):111–7. doi: 10.1097/ADM.0000000000000101

149. Smith LM, LaGasse LL, Derauf C, Grant P, Shah R, Arria A, et al. The infant development, environment, and lifestyle study: effects of prenatal methamphetamine exposure, polydrug exposure, and poverty on intrauterine growth. *Pediatrics*. (2006) 118(3):1149–56. doi: 10.1542/peds.2005-2564

150. Nguyen D, Smith LM, Lagasse LL, Derauf C, Grant P, Shah R, et al. Intrauterine growth of infants exposed to prenatal methamphetamine: results from the infant development, environment, and lifestyle study. *J Pediatr*. (2010) 157(2):337–9. doi: 10.1016/j.jpeds.2010.04.024

151. Abar B, LaGasse LL, Wouldes T, Derauf C, Newman E, Shah R, et al. Cross-national comparison of prenatal methamphetamine exposure on infant and early child physical growth: a natural experiment. *Prev Sci*. (2014) 15(5):767–76. doi: 10.1007/s11121-013-0431-5

152. Smith LM, Diaz S, LaGasse LL, Wouldes TA, Derauf C, Newman E, et al. Developmental and behavioral consequences of prenatal methamphetamine exposure: a review of the infant development, environment and lifestyle (IDEAL) study. *Neurotoxicol Teratol*. (2015) 51:35–44. doi: 10.1016/j.ntt.2015.07.006

153. LaGasse LL, Wouldes T, Newman E, Smith LM, Shah RZ, Derauf C, et al. Prenatal methamphetamine exposure and neonatal neurobehavioral outcome in the USA and New Zealand. *Neurotoxicol Teratol*. (2011) 33:166–75. doi: 10.1016/j.ntt.2010.06.009

154. Evans GW, Dongping L, Whipple SS. Cumulative risk and child development. *Psychol Bull*. (2013) 139(6):1342–96. doi: 10.1037/a0031808

155. Jansson LM, Di Pietro JA, Elko A, Williams EL, Milio L, Velez M. Pregnancies exposed to methadone, methadone and other illicit substances, and poly-drugs without methadone: a comparison of fetal neurobehaviors and infant outcomes. *Drug Alcohol Depend*. (2012) 122(3):213–9. doi: 10.1016/j.drugalcdep.2011.10.003

156. Lester W, Andrews L, Nellhaus EM, Murray S, Loudin S, Davies TH. Symptomology associated with in utero exposures to polysubstance in an Appalachian population. *Marshall J Med*. (2019) 5(2):39. doi: 10.33470/2379-9536.1212

157. Salisbury AL, Ponder KL, Padbury JF, Lester BM. Fetal effects of psychoactive drugs. *Clin Perinatol*. (2009) 36(3):595–619. doi: 10.1016/j.clp.2009.06.002

158. Sanlorenzo LA, Lauren A, Cooper WO, Dudley JA, Stratton S, Maalouf FI, et al. Increased severity of neonatal abstinence syndrome associated with concomitant antenatal opioid and benzodiazepine exposure. *Hosp Pediatr*. (2019) 9(8):569–75. doi: 10.1542/hpeds.2018-0227

159. Seligman NS, Salva N, Hayes EJ, Dysart KC, Pequignot EC, Baxter JK. Predicting length of treatment for neonatal abstinence syndrome in methadone-exposed neonates. *Am J Obstet Gynecol*. (2008) 199(4):396.e1–e7. doi: 10.1016/j.ajog.2008.06.088

160. Loudin S, Murray S, Prunty L, Davies T, Evans J, Werthammer J. An atypical withdrawal syndrome in neonates prenatally exposed to gabapentin and opioids. *J Perinatol*. (2017) 181:286–8. doi: 10.1016/j.peds.2016.11.004

161. Baird RWC, Fox P, Colvin LA. Gabapentinoid abuse in order to potentiate the effect of methadone: a survey among substance misusers. *Eur Addict Res*. (2014) 20(3):115–8. doi: 10.1159/000355268

162. Morris E, Bardsley T, Schulte K, Seidel J, Shakib JH, Buchi KF, et al. Hospital outcomes of infants with neonatal opioid withdrawal syndrome at a tertiary care hospital with high rates of concurrent nonopioid (polysubstance) exposure. *Am J Perinatol*. (2022) 39:387–93. doi: 10.1055/s-0040-1716490

163. Jarlenski MP, Paul NC, Krans EE. Polysubstance use among pregnant women with opioid use disorder in the United States, 2007–2016. *Obstet Gynecol*. (2020) 136(3):556. doi: 10.1097/AOG.0000000000003907

164. Stevens S, Anstice N AC, Goodman L, Rogers J, Wouldes T A. Multiple tools are needed for the detection of prenatal alcohol exposure: findings from a community antenatal setting. *Alcohol Clin Exp Res*. (2020) 44(4):1001–11. doi: 10.1111/acer.14309

165. Oni HT, Buultjens M, Abdel-Latif ME, Islam MM. Barriers to screening pregnant women for alcohol or other drugs: a narrative synthesis. *Women Birth*. (2019) 32(6):479–86. doi: 10.1016/j.wombi.2018.11.009

166. Oni HT, Buultjens M, Davis D, Abdel-latif M, Islam MM. Barriers and facilitators in antenatal settings to screening and referral of pregnant women who use alcohol or other drugs: a qualitative study of midwives' experience. *Midwifery*. (2020) 81:102595. doi: 10.1016/j.midw.2019.102595

167. Wouldes TA. What health professionals know and do about alcohol and other drug use during pregnancy. Alcohol Healthwatch (2009). Available at: http://www.ahw.org.nz/

168. Sivak L, Reilly R, Lockton J, Treloar C, Roe Y, McKetin R, et al. Psychosocial stress and methamphetamine use: a mixed-methods study of intersectional stigma and aboriginal and torres strait islander methamphetamine use. *Int J Drug Policy*. (2023) 121. doi: 10.1016/j.drugpo.2023.104189

169. Choi S, Ryan JP. Co-occurring problems for substance abusing mothers in child welfare: matching services to improve family reunification. *Child Youth Service Review*. (2007) 29:1395–410. doi: 10.1016/j.childyouth.2007.05.013

170. Verstegen RHJ, Anderson PO, Ito S. Infant drug exposure via breast milk. *Br J Clin Pharmacol*. (2022) 88(10):4311–27. doi: 10.1111/bcp.14538

171. Bartholomew M, Lee M-J. Substance use in the breastfeeding woman. *Contemp Ob Gyn*. (2019) 64(9):22–6.

172. Finnegan LP, Kron RE, Connaughton JF, Emich JP. Neonatal abstinence syndrome: assessment and management. *Addict Dis*. (1975) 2(1):141–58. PMID: 1163358.

173. Gomez-Pomar E, Christian A, Devlin L, Ibonia KT, Concina VA, Bada H, et al. Analysis of the factors that influence the finnegan neonatal abstinence scoring system. *J Perinatol*. (2017) 37(7):814–7. doi: 10.1038/jp.2017.40

174. Velez M, Jansson LM. The opioid dependent mother and newborn dyad: nonpharmacologic care. *J Addict Med*. (2008) 2(3):113–20. doi: 10.1097/ADM.0b013e31817e6105

175. Grossman MR, Berkwitt AK, Osborn RR, Xu Y, Esserman DA, Shapiro ED, et al. An initiative to improve the quality of care of infants with neonatal abstinence syndrome. *Pediatrics*. (2017) 139(6). doi: 10.1542/peds.2016-3360

176. Jansson LM, Velez ML. Optimal care for NAS: are we moving in the wrong direction? *Hosp Pediatr*. (2019) 9(8):655–8. doi: 10.1542/hpeds.2019-0119

177. Young LW, Ounpraseuth ST, Merhar SL, Hu Z, Simon AE, Bremer AA, et al. Eat, sleep, console approach or usual care for neonatal opioid withdrawal. *N Engl J Med*. (2023) 388(25):2326–37. doi: 10.1056/NEJMoa2214470

178. Conradt E, Flannery T, Aschner JL, Annett RD, Croen LA, Duarte CS, et al. Prenatal opioid exposure: neurodevelopmental consequences and future research priorities. *Pediatrics*. (2019) 144(3):e20190128. doi: 10.1542/peds.2019-0128

179. Liu J, Bann C, Lester B, Tronick E, Das A, Lagasse L, et al. Neonatal neurobehavior predicts medical and behavioral outcome. *Pediatrics*. (2010) 125(1):e90–e8. doi: 10.1542/peds.2009-0204

180. Smith B, Knox S, Benjamin DK. Coordination of the environmental influences on child health outcomes program. *Curr Opin Pediatr*. (2018) 30(2):263–8. doi: 10.1097/MOP.0000000000000598

181. Blackwell CK, Wakschlag LS, Gershon RC, Cella D. Measurement framework for the environmental influences on child health outcomes research program. *Curr Opin Pediatr*. (2018) 30(2):276–84. doi: 10.1097/MOP.0000000000000606

182. Miele K, Kim SY, Jones R, Rembert JH, Wachman EM, Shrestha H, et al. Medication for opioid use disorder during pregnancy — maternal and infant network to understand outcomes associated with use of medication for opioid use disorder during pregnancy (MAT-LINK), 2014–2021. *MMWR Surveill Summ*. (2023) 72(3):1–14. doi: 10.15585/mmwr.ss7203a1

183. Tran EL, Kim SY, England LJ, Green C, Dang EP, Broussard CS, et al. The MATernaL and infant NetworK to understand outcomes associated with treatment of opioid use disorder during pregnancy (MAT-LINK): surveillance opportunity. *J Women's Health*. (2020) 29(12):1491–9. doi: 10.1089/jwh.2020.8848

frontiers | Frontiers in Pediatrics

TYPE Review
PUBLISHED 21 December 2023
DOI 10.3389/fped.2023.1316583

Check for updates

OPEN ACCESS

EDITED BY
Oscar Garcia-Algar,
Hospital Clinic of Barcelona, Spain

REVIEWED BY
Simona Pichini,
National Institute of Health (ISS), Italy
Mathangi Gopalakrishnan,
University of Maryland, United States

*CORRESPONDENCE
John J. McCarthy
✉ Drjackmac9@gmail.com

RECEIVED 10 October 2023
ACCEPTED 27 November 2023
PUBLISHED 21 December 2023

CITATION
McCarthy JJ and Finnegan LP (2023) Methadone and neonatal abstinence syndrome (NAS): what we think we know, but do not. Front. Pediatr. 11:1316583. doi: 10.3389/fped.2023.1316583

COPYRIGHT
© 2023 McCarthy and Finnegan. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Methadone and neonatal abstinence syndrome (NAS): what we think we know, but do not

John J. McCarthy[1]* and Loretta P. Finnegan[2]

[1]Department of Psychiatry, University of California, Davis, CA, United States, [2]Finnegan Consulting LLC, Avalon, NJ, United States

Since the first use of methadone to treat OUD in pregnancy in the 1970s, there has been a long, controversial, and confusing history of studies, regulatory actions, and practice changes that have clouded an accurate perception of methadone's use in pregnancy. This review will trace this history with a focus on the effect of methadone exposure during pregnancy on neonatal abstinence syndrome (NAS). A new laboratory measure, the serum methadone/metabolite ratio (MMR), has provided a tool for documenting the profoundly dynamic nature of perinatal metabolism. Continuous induction of metabolic enzymes during pregnancy requires dose adjustments and dose frequency changes. The concept of "fetal methadone dosing" emphasizes that relative stability of methadone levels in the fetus is an important consideration for methadone dosing in pregnancy. Finally, the effects of the societal "war on drugs" on pediatric management of neonatal withdrawal risks will be discussed, as well as the importance of comprehensive services for mother and child including the "rooming-in" approach of neonatal care which has considerably replaced the older NICU care model of maternal/infant separation.

KEYWORDS

neonatal abstinence syndrome, opioid use disorder, pregnancy, split dosing, rooming-in, methadone metabolism

Introduction

A century ago, infants with signs of abstinence were given the diagnosis of congenital morphism (1); they were not provided medication, resulting in an extremely high mortality. It was in the1970's that the infants with *in utero* opioid exposure were given the diagnosis of NAS. Desmond and Wilson described the basics of NAS, what effects onset, the various courses of the syndrome and persistent signs (2). Further, it also became clear that NAS was a potentially a serious medical condition in the newborn since it effected feeding with metabolic complications, inability to sleep, manifestations that led to a comprehensive supportive care approach to mother/fetal/infant unit. Infants were monitored closely for intake and weight gain, fed by gavage if needed, had minimal environmental stimuli (light and noise) and decreased handling, and provided supportive neonatal nursing care (3).

Although Methadone was approved for use in adults with OUD as early as 1946, it was not until a few decades later, in the 1960's that methadone began to be used for pregnant women who had OUD (4). At that time maternal treatment with methadone was thought to be the best approach for treatment of pregnant women with OUD since it was associated with increased prenatal care visits, compliance with program treatment requirements, less risk for medical complications, and was also thought to mitigate the signs of NAS. If the signs became severe, treatment with medication was provided, usually

an opioid or sedative or both, and the infant was transferred to the NICU for close monitoring. The assessment of NAS severity required a systematic approach and scoring systems began to be developed and were being used as in adults, in infants with withdrawal signs from prenatal exposure to heroin and/or methadone treatment during pregnancy (5–7). The assessment also helped to identify the infants who needed pharmacologic treatment. Since pharmacologic treatment involved close monitoring of infants in intensive care units resulting in the separation of maternal-infant dyad, the prolonged hospitalization and other side effects of severe NAS fostered the assumption that NAS severity was associated with high methadone doses compared to buprenorphine that was thought to have lesser risk of NAS.

But, does buprenorphine actually cause less neonatal abstinence than methadone? Studies that purport to demonstrate such outcomes suffer from significant limitations. These data are frequently based on hospital records associating methadone dose at delivery to NAS severity and length of hospitalization. Usually, nothing is reported about the actual specifics of treatment with methadone, nor are hospital policies for managing NAS reported beyond morphine dose used to treat NAS, length of hospitalization, and methadone dose at delivery. This review re-assesses what is known about methadone and NAS risk.

Pharmacokinetics and consequences of maternal/fetal methadone mis-dosing

Missing from virtually all studies are measures of actual fetal methadone exposure as measured by maternal trough serum levels, and absence of any mention of how the medication was taken (i.e., single vs. multiple doses). The fetus is not exposed to the maternal dose, as most outcome studies presume. It is only exposed to the maternal serum level which is reduced by significantly increased metabolic activity due to the continuous induction of CYP450 enzymes by pregnancy hormones (8). Trough serum levels provide the most accurate proxy for fetal exposure. Further, levels maintained within an established therapeutic range (150–600 ng/ml) (9) have been validated as safe and effective in a pregnancy population where all patients were on split doses (10).

Since methadone is converted to an inactive metabolite, maternal and fetal levels of exposure to the active medication can be significantly decreased relative to a non-pregnant population. This metabolic induction begins at conception, and patients conceiving on methadone often report experiencing withdrawal before they realize they are pregnant. The evolutionary goal of this metabolic acceleration is to protect the fetus from toxins. The metabolism of methadone, as well as many other medications, is significantly altered as a result. This requires adaptive dosing strategies, and especially divided dosing.

Historically, however, most pregnant patients have been required to take methadone as a single dose, which exposes both mother and fetus to problematic oscillating serum levels and daily episodes of maternal and fetal withdrawal. The effects of this serum cycling on maternal/fetal stability and NAS have been ignored in virtually all outcome studies. Westermeyer et al. showed that rapid metabolizing patients cannot be effectively stabilized on single methadone doses despite dose increases (11). Use of single doses causes over sedation at the peak serum level (4–6 h after the AM dose) which, because of accelerated metabolism, results in a rapid reduction of serum concentration at the mu receptor, causing withdrawal in the evening and night. This process was documented by ultrasound demonstrating fetal hypomotility at the peak and hypermotility at the trough (12). On divided doses, this physiologic abnormality resolved. Janssen et al. demonstrated fetal cardiac rhythm abnormalities on single doses that also improved on split doses (13).

Women who report breakthrough withdrawal on methadone clearly identify fetal hyperactivity as simultaneously present and which they rate as severe (10). There is animal evidence that, in the fetus, withdrawal activates a catecholamine response that the mother may not mount, suggesting that the fetus may be more sensitive to the adverse effects of withdrawal (14). A study by Rothwell et al, using rodents, found that, in opioid-dependent animals, intermittent opioid exposure (stopping or skipping doses) and related intermittent withdrawal have a role in promoting a modification of brain function and behavior called "psychomotor sensitization" (15). This study used acoustic startle reflexes as a proxy for withdrawal-related stress. Startle potentiation occurred predictably during withdrawal periods. The authors conclude that events that occur during the offset of drug action (i.e., acute withdrawal) may have a pervasive role in adverse effects of opioid exposure. Use of single dose methadone mimics the Rothwell study protocol of frequent on/off receptor occupancy. This process may partly explain why many studies find an association between high methadone dose and NAS severity under conditions where all mothers are maintained on single doses. However, pregnant patients requiring unusually high methadone doses, in the 200–400 mg/day range, have been shown to have serum levels in the therapeutic range and to not have increased NAS risk, provided they are given methadone in multiple divided doses (10). Therefore, rather than dose amount, it may be the single dose regimen, to which most pregnant women have been exposed, that "sensitizes" the fetal brain and potentiates the post-delivery withdrawal response called NAS.

There is further evidence indicating that prenatal fetal stress can alter later hypothalamic-pituitary-adrenal function, behavior, and neurotransmission (14, 16, 17). Recurrent prenatal withdrawal is a type of biologic stress that has been associated with a prolonged surge of corticosteroids (18). Withdrawal is only one of a variety of maternal stressors (physiologic and psychologic) that can adversely affect fetal development via epigenetic alterations of fetal gene expression (19). There is reason for concern that babies exposed to intrauterine withdrawal by single doses, or low dosing practices, or forced or planned withdrawals, may have long term outcomes adversely effected by such intrauterine stress.

Not all mothers on methadone are necessarily rapid metabolizers. A small number have poor genetic loading for metabolic enzymes such that pregnancy induction of metabolism

may not affect them or may just move them from poor metabolizers to normal metabolizers. They may feel fine on single doses. However, a strong case can still be made that the fetus needs methadone in divided doses to avoid the physiologic abnormalities associated with single doses.

Regulatory and administrative barriers to appropriate dosing

There were studies as early as 1985 documenting accelerated methadone metabolism in pregnancy (20) and improved outcomes using divided doses of methadone (21). These had little impact on actual dosing of most pregnant women who continued to be prescribed methadone as a single dose. Until recently, Federal regulations required an exception to provide methadone using a divided dose regimen. This was not often used because programs were discouraged from giving daily take home doses because of exaggerated fears of diversion. For decades, therefore, most pregnant women have been dosed without regard for their unique metabolic state and without awareness of adverse effects of incorrect dosing on the fetus. This continues to be a serious problem in the highly regulated methadone treatment system.

The fact that these early studies on the need and benefit of split dosing were largely ignored speaks of how effective and safe provision of methadone during pregnancy has been discouraged by Federal regulations posing barriers to divided dosing, and further undermined by the view of the mother as someone who cannot be trusted with take home doses. Programs still refuse to split-dose pregnant women because they do not trust the mother not to divert the medication. Mis-dosing mother and fetus is therefore justified as preventing hypothetical diversion. This is a myth based on the view of the mother as someone who does not care for the wellbeing of her baby and who would sell the methadone, which she knows is critical to keeping her baby out of withdrawal. These mothers have normal protective concerns about the safety of the baby and, therefore, are highly motivated to recover. However, conception often occurs during a period of use and dependence, and women can suffer temporary impairments in judgement and face significant barriers to accessing care. However, once in appropriate care, they are as motivated and able to have a healthy pregnancy as any other mother. They would not deliberately put their baby in withdrawal by diverting their methadone. Yet program biases about maternal "untrustworthiness" are still allowed to interfere with appropriate prescribing of methadone.

A study of the Subjective Opioid Withdrawal Scale (SOWS) augmented with two pregnancy-related items (uterine cramping and fetal hyperactivity) demonstrated that mothers are very aware of fetal hyperactivity when they themselves are experiencing withdrawal (10). When the pregnant women are inappropriately dosed, they feel compelled to use illicit opioids to treat their own and their baby's withdrawal. It reflects a serious failure of the methadone system when inappropriate dosing drives drug use rather than resolving it. It illustrates just one reason why mothers should have options for methadone treatment outside the clinic system, which often prioritizes administrative polices over proper medical care. NIDA director, Dr. Nora Volkow, has recently called for trained physician prescribing of methadone under a new regulatory system. Patients would then have options in choosing their care, options they do not have now. Addiction trained family medicine and obstetrical physicians would be an important starting point in this process of expanding access to methadone (22). A new SAMHSA ruling (April 28, 2022) has eliminated the need for special exceptions and all pregnant patients in the methadone system can now receive proper dosing solely at physician discretion. This will, hopefully, lead to changes at the level of State regulatory agencies and especially programs themselves whose risk management practices often prevent take home doses as a "program risk" that outweighs the medical needs of the mother and baby.

Laboratory advances and dosing decisions

A newly available laboratory measure of metabolic activity is the serum methadone/metabolite ratio (MMR). This simple numeric ratio measures the speed of metabolism of the parent drug, methadone, to its inactive metabolite (23). Two studies have found a mean MMR of approximately 12 in a random population of methadone-maintained patients (24, 25). "Normal" metabolizing patients would have an MMR clustered around a mean of roughly 12 molecules of methadone to one of metabolite, within a "normal MMR range" of 8–16. Rapid metabolizers will have lower MMRs, and slow metabolizers will have higher ones. Eap et al. found a seventeen-fold variability in human metabolism of methadone (26). A study of 1,700 patients found an MMR range from 2 to 26, corroborating this wide range of methadone metabolism (23).

A study of the MMR in pregnancy demonstrated accelerated metabolism starting in the first trimester (mean MMR of 7. 2) which decreased to 5.9 in the second trimester, and then further decreased to 5.1 in the third trimester. The MMR then rose to 7.2 in the first two weeks post-partum, documenting a rapid reversal of metabolic induction (8). When the MMR is performed serially during the pregnancy, both physician and mother can monitor the changes in her metabolic rate and the effect on serum levels and on fetal exposure. Mothers are always concerned when high doses are needed. Therefore, laboratory data are important to discuss as part of physician counseling.

Dose increases are done to manage breakthrough withdrawal within the limits of the therapeutic serum range of 150–600 ng/ml, and the dose regimen is increased from an initial twice daily dosing on induction, to doses divided 3–4 times a day, roughly proportionate to the speed of metabolism (i.e., the lower the MMR the more frequent the dosing regimen). Patients with low MMRs (in the 3–6 range), especially in the third trimester, usually require 4–6 doses for optimal stability. Further, increasing the frequency of dosing may minimize the need for increased doses by providing the medicine more effectively. Finally, it is

unknown what effect high level fentanyl dependence has on the efficacy of this serum level range, which was an effective guide for heroin and opioid pill dependence. The current therapeutic range needs further study and perhaps modification.

Compassionate, supportive care of the mother

The stress on a pregnant woman who is opioid dependent can be quite severe, encompassing anxiety and guilt about effects of their drug use on the baby, confusion about the medication and possible adverse effects on the baby (especially NAS), family pressures to stop the medication, and the need to conceal use of methadone treatment for fear of condemnation by family and friends. It is a very lonely experience that is best overcome by a close on-going supportive relationship using a pregnancy team approach with a pregnancy-trained counselor, a nurse practitioner or physician assistant who usually manages acute care, and regular supportive meetings with the prescribing physician. This approach of comprehensive care of the pregnant woman with SUD was described forty years ago (27). Frequent contacts with the physician are needed, not only to manage changing dosing needs, but also to discuss issues such as hospital care, NAS risks, breastfeeding, dose reductions post-partum, potential interactions with child protective services, and concurrent mental health issues which are ideally but rarely managed within the methadone program.

High anxiety and stress states are associated with adverse outcomes independent of substance use (19). Yet maternal stress is rarely considered as a factor in poor outcomes to be addressed as a component of good methadone care. Methadone programs promote "non-medical counseling" as what they offer to help recovery. They do not mention close physician/patient contact because that is not the usual methadone model. While it is not possible to quantitate the effect of these factors in fetal outcomes, it is reasonable to expect that supportive physician interventions can mitigate stress. Knowing that the physician prescribing methadone is available and willing to confer with obstetricians and neonatologists on the patient's behalf can significantly reduce adverse effects of stress on the birthing process and improve outcomes. Such "medical counseling" would be ideally done by trained obstetricians or family medicine physicians, if they were allowed to use methadone, as they are allowed to use buprenorphine.

There is an urgent need to change Federal regulations that limit access to methadone to clinics that meet only 10%–15% of the national need and impose burdens of excessive attendance that interferes with job, school, childcare, and family obligations, in addition to increasing risks of exposure to viral infections in overcrowded clinics. Proposals for physician prescribing, pharmacy dispensing of methadone and ending the clinic monopoly on care are currently under consideration and are urgently needed to address the opioid overdose crisis (28). This urgency is illustrated by situations where pregnant patients are prescribed methadone as a single dose by programs unaware of current science and the availability of exception process. Pregnant patients in the clinic system can be significantly over-sedated on single doses and yet are denied appropriate dosing, even when it threatens their ability to care for their children.

Maternal infant separation policies and criminalization of NAS

Time has also clarified the actual factor responsible for the severity of NAS in methadone exposed neonates described repeatedly in the media and in medical literature. Separation of mother and neonate and overuse of NICUs has been shown to contribute to the expression of NAS and prolonged hospitalizations. Once neonatologists and obstetricians stopped separating mothers and babies, the rates of NAS treatment and length of stay in hospital fell dramatically (29–31). Numerous reports have also clarified the other issues that affect the expression of neonatal abstinence, including, breastfeeding (32), genetics (33), pharmacokinetics (8), smoking (34), gestational age (2) and others. The signs of NAS can mimic those of other serious diseases such as, sepsis, cerebral hemorrhage, hypoglycemia and hypocalcemia; these disorders will need to be ruled out. The seminal paper on NAS by Finnegan et al. did not mandate NICU care and used the term "comprehensive care" for the needs of the maternal/fetal dyad (27). This term was only "rediscovered" recently as part of the recognition of the critical importance of compassionate care and the importance of the mother in the amelioration of NAS (5).

The idea that NAS was so severe that NICU care was virtually mandatory evolved during the era of drug war polemics. Since drug users were labelled as criminals, and pregnant drug users were labelled "child abusers", then the NICU was a way of protecting the newborn from an inadequate mother. It was as much a social punishment as a medical intervention. However, in the early years when opioid withdrawal was a new diagnosis with a high mortality, medical protection of the baby was important and nurses with the best training were in NICU's.

However, separation of the mother from her newborn involved ignoring what is known scientifically about the critical importance of early maternal/infant skin-to-skin contact, which promotes reciprocal hormonal interactions critical to attachment and to managing the physiology of NAS. NICU care made breastfeeding very difficult, yet breastfeeding was shown to mitigate NAS (32). The two neurohormones that are especially critical are endorphin and oxytocin, which are stimulated by nursing and skin-to-skin contact. To deprive the newborn of this critical process by placing the baby in a NICU reflects how the social anti-drug milieu affected medical judgement. And this bias was what created the nationwide epidemic of "severe NAS" which made headlines in every newspaper across the country, and for which methadone was widely blamed.

The State of Tennessee went so far as to criminalize having a baby who had NAS, resulting in women being coerced into attempting rapid methadone withdrawal. An outcome study of this process was published purporting to find that an ultra-rapid

withdrawal was "not harmful" because there were no "apparent complications" beyond two fetal deaths during jail withdrawals (35). Minimal monitoring of maternal and fetal stress was done and there was no long-term follow up of the mother or baby. This attempt to put pregnant women through a potentially life-threatening opioid withdrawal without intensive maternal/fetal monitoring has been called "stressing the fetal brain" (36). Pregnant incarcerated women are often forced through abrupt opioid withdrawal, some of whom predictably experience miscarriages. These fetal deaths are a direct result of law enforcement bias against methadone and their refusal to allow women to access it. They see their role as punishing mothers even though it is traumatic to the fetal brain, can cause epigenetic modifications and long-term developmental problems, and can result in fetal death (17, 18).

Ending the inadequate mother model

The first change in the separation model of NAS management came from England where Saiki et al. reported on a hospital policy change that mandated the maternal/neonatal dyad should be kept together on the regular maternity unit (29). This resulted in an 11% rate of treatment for NAS and a reduction of duration of hospital care from 12.7 to 7.3 days. In the US, Holmes et al. introduced the term "rooming-in" for the new model of care relying primarily on the mother to mitigate symptoms and found similar reductions in number of neonates treated, length of stay, and cumulative morphine doses in both methadone and buprenorphine exposed neonates (30). These authors concluded that "the environment of care is likely more important than the medication used for treatment". Grossman et al. furthered this rooming-in approach with a new NAS assessment tool termed "Eat, Sleep, and Console" (ESC), simplifying target symptoms for medication usage (appropriate eating, sleeping, and control of distress) (37). Over a 5-year period this model reduced the use of any morphine from 98% to 12% and reduced the length of stay from 22.5 to 5.9 days. Eighty percent of patients in this cohort were on methadone. In a recent cluster trial, the ESC approach was associated with shortened length of stay and duration of treatment (38). Results are indeed in support of the importance of the environment in the management of the mother-infant dyad but the study awaits long-term follow-up (39).

Summary

Aspects of methadone use in pregnancy that reduce risks for NAS symptoms include the systematic use of methadone serum levels, especially trough levels and MMRs, to guide dosing during the metabolically dynamic perinatal period. This includes routine use of split-dosing to minimize adverse fluctuations of serum levels associated with withdrawal and fetal side effects. Dosing decisions should be discussed with the mother in the context of regular physician counseling, education, and stress management. Post-partum hospital care relying primarily on normal mother/infant comforting and nurturing interactions for control of withdrawal symptoms will further minimize NAS symptoms.

Studies to date have compared single daily maternal dosing with methadone and daily dosing of buprenorphine regarding the amount of morphine needed to treat NAS, duration of treatment for NAS and length of stay. Former studies demonstrated a significant difference between methadone and buprenorphine regarding the three outcomes listed above. The question is did these differences occur because of a real difference between the two medications or was the single dosing of methadone the main issue. Future studies need to be directed to comparing the effects of split versus single dosing of methadone and buprenorphine regarding newborn outcomes including the same parameters as evaluated in the initial studies (40). Studies should describe not only the actual methadone treatment practices including dosing practices and serum levels, but also the availability and nature of physician support, and hospital practices for NAS management so that outcomes are not skewed by the adverse effects of either unphysiological dosing, lack of physician support, or maternal/infant separation. This should establish more accurately the real risks of NAS under these optimal methadone dosing conditions.

Furthermore, methadone, a full agonist, is pharmacologically, a more appropriate medication for use in medication induction in pregnancy during the current epidemic of fentanyl-dependent pregnant women. Methadone avoids the risks to the fetus of harm from precipitated buprenorphine withdrawal and the need for polypharmacy to manage such withdrawal (41–43). This emphasizes the critical importance of changing Federal regulations that prevent physicians, especially obstetricians and family medicine doctors trained in addiction medicine, from using a safer and more effective medication to manage severe dependence.

Author contributions

JM: Conceptualization, Writing – original draft, Writing – review & editing. LF: Conceptualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

Author LF was employed by Finnegan Consulting LLC. Dr. Finnegan declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Pettey GE. Congenital morphism, with report of cases. *South Med J*. (1912) 5 (1):25–7. doi: 10.1097/00007611-191202000-00006

2. Desmond MM, Wilson GS. Neonatal abstinence syndrome: recognition and diagnosis. *Addict Dis*. (1975) 2(1-2):113–21.

3. Finnegan LP, MacNew BA. Care of the addicted infant. *Am J Nurs*. (1974) 74 (4):685–93.

4. Dole VP, Nyswander M. A medical treatment for diacetylmorphine (heroin) addiction. A clinical trial with methadone hydrochloride. *JAMA*. (1965) 193:646–50. doi: 10.1001/jama.1965.03090080008002

5. Finnegan LP, Connaughton JF Jr, Kron RE, Emich JP. Neonatal abstinence syndrome: assessment and management. *Addict Dis*. (1975) 2(1-2):141–58.

6. Kolb L, Himmelsbach CK. Clinical studies of drug addiction, III: a critical review of the withdrawal treatments with method of evaluating abstinence syndromes. *Am J Psychiatr*. (1938) 94(4):759–99. doi: 10.1176/ajp.94.4.759

7. Himmelsbach CK. The morphine abstinence syndrome, its nature and treatment. *Ann Intern Med*. (1941) 15(5):829–39. doi: 10.7326/0003-4819-15-5-829

8. McCarthy JJ, Vasti EJ, Leamon MH, Graas J, Ward C, Fassbender C. The use of serum methadone/metabolite ratios to monitor changing perinatal pharmacokinetics. *J Addict Med*. (2018) 12(3):241–6. doi: 10.1097/ADM.0000000000000398

9. Dole VP. Implications of methadone maintenance for theories of narcotic addiction. *JAMA*. (1988) 260(20):3025–9. doi: 10.1001/jama.1988.03410200081030

10. McCarthy JJ, Leamon MH, Willits NH, Salo R. The effect of methadone dose regimen on neonatal abstinence syndrome. *J Addict Med*. (2015) 9(2):105–10. doi: 10.1097/ADM.0000000000000099

11. Westermeyer J, Yoon G, Thuras P, Batres-y-Carr T, Dickmann P. Pharmacotherapy in methadone maintenance: clinical utility of peak-trough blood levels. *Addict Disord Their Treat*. (2016) 15(4):157–64. doi: 10.1097/ADT.0000000000000093

12. Wittmann BK, Segal S. A comparison of the effects of single- and split-dose methadone administration on the fetus: ultrasound evaluation. *Int J Addict*. (1991) 26(2):213–8. doi: 10.3109/10826089109053183

13. Jansson LM, Dipietro JA, Velez M, Elko A, Knauer H, Kivlighan KT. Maternal methadone dosing schedule and fetal neurobehaviour. *J Matern Fetal Neonatal Med*. (2009) 22(1):29–35. doi: 10.1080/14767050802452291

14. Schrott LM, Baumgart MI, Zhang X, Sparber SB. Prenatal opiate withdrawal activates the chick embryo hypothalamic pituitary-adrenal axis and dilates vitelline blood vessels via serotonin(2) receptors. *J Pharmacol Exp Ther*. (2002) 303 (1):257–64. doi: 10.1124/jpet.102.037044

15. Rothwell PE, Gewirtz JC, Thomas MJ. Episodic withdrawal promotes psychomotor sensitization to morphine. *Neuropsychopharmacology*. (2010) 35 (13):2579–89. doi: 10.1038/npp.2010.134

16. McCarthy JJ. Intrauterine abstinence syndrome (IAS) during buprenorphine inductions and methadone tapers: can we assure the safety of the fetus? *J Matern Fetal Neonatal Med*. (2012) 25(2):109–12. doi: 10.3109/14767058.2011.600371

17. Stevenson DK, Sunshine P, Benitz WE. *Fetal and neonatal brain injury*. 3rd ed: Cambridge: Cambridge University Press; 2005.

18. McCarthy JJ, Leamon MH, Finnegan LP, Fassbender C. Opioid dependence and pregnancy: minimizing stress on the fetal brain. *Am J Obstet Gynecol*. (2017) 216 (3):226–31. doi: 10.1016/j.ajog.2016.10.003

19. Kapoor A, Dunn E, Kostaki A, Andrews MH, Matthews SG. Fetal programming of hypothalamo-pituitary-adrenal function: prenatal stress and glucocorticoids. *J Physiol*. (2006) 572(Pt 1):31–44. doi: 10.1113/jphysiol.2006.105254

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

21. Swift RM, Dudley M, DePetrillo P, Camara P, Griffiths W. Altered methadone pharmacokinetics in pregnancy: implications for dosing. *J Subst Abuse*. (1989) 1 (4):453–60. doi: 10.1016/S0899-3289(20)30008-0

22. McCarthy JJ. Buprenorphine versus methadone in pregnancy. *N Engl J Med*. (2023) 388(10):957. doi: 10.1056/NEJMc2300439

23. McCarthy JJ, Graas J, Leamon MH, Ward C, Vasti EJ, Fassbender C. The use of the methadone/metabolite ratio (MMR) to identify an individual metabolic phenotype and assess risks of poor response and adverse effects: towards scientific methadone dosing. *J Addict Med*. (2020) 14(5):431–6. doi: 10.1097/ADM.0000000000000620

24. Diong SH, Mohd Yusoff NS, Sim MS, Raja Aziddin RE, Chik Z, Rajan P, et al. Quantitation of methadone and metabolite in patients under maintenance treatment. *J Anal Toxicol*. (2014) 38(9):660–6. doi: 10.1093/jat/bku096

25. Alburges ME, Huang W, Foltz RL, Moody DE. Determination of methadone and its N-demethylation metabolites in biological specimens by GC-PICI-MS. *J Anal Toxicol*. (1996) 20(6):362–8. doi: 10.1093/jat/20.6.362

26. Eap CB, Buclin T, Baumann P. Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. *Clin Pharmacokinet*. (2002) 41(14):1153–93. doi: 10.2165/00003088-200241140-00003

27. Finnegan LP, Connaughton JF, Emich JP, Weiland WF. Comprehensive care of the pregnanct addict and its effects on maternal and infant outcomes. *Contemp Drug Probl*. (1973) 1:795–809.

28. Joudrey PJ, Edelman EJ, Wang EA. Methadone for opioid use disorder-decades of effectiveness but still miles away in the US. *JAMA Psychiatry*. (2020) 77(11):1105–6. doi: 10.1001/jamapsychiatry.2020.1511

29. Saiki T, Lee S, Hannam S, Greenough A. Neonatal abstinence syndrome–postnatal ward versus neonatal unit management. *Eur J Pediatr*. (2010) 169(1):95–8. doi: 10.1007/s00431-009-0994-0

30. Holmes AV, Atwood EC, Whalen B, Beliveau J, Jarvis JD, Matulis JC, et al. Rooming-in to treat neonatal abstinence syndrome: improved family-centered care at lower cost. *Pediatrics*. (2016) 137(6):e20152929. doi: 10.1542/peds.2015-2929

31. Grossman MR, Berkwitt AK, Osborn RR, Xu Y, Esserman DA, Shapiro ED, et al. An initiative to improve the quality of care of infants with neonatal abstinence syndrome. *Pediatrics*. (2017) 139(6):e20163360. doi: 10.1542/peds.2016-3360

32. Welle-Strand GK, Skurtveit S, Jansson LM, Bakstad B, Bjarko L, Ravndal E. Breastfeeding reduces the need for withdrawal treatment in opioid-exposed infants. *Acta Paediatr*. (2013) 102(11):1060–6. doi: 10.1111/apa.12378

33. Wachman EM, Hayes MJ, Brown MS, Paul J, Harvey-Wilkes K, Terrin N, et al. Association of OPRM1 and COMT single-nucleotide polymorphisms with hospital length of stay and treatment of neonatal abstinence syndrome. *JAMA*. (2013) 309 (17):1821–7. doi: 10.1001/jama.2013.3411

34. Jones HE, Heil SH, Tuten M, Chisolm MS, Foster JM, O'Grady KE, et al. Cigarette smoking in opioid-dependent pregnant women: neonatal and maternal outcomes. *Drug Alcohol Depend*. (2013) 131(3):271–7. doi: 10.1016/j.drugalcdep.2012.11.019

35. Bell J, Towers CV, Hennessy MD, Heitzman C, Smith B, Chattin K. Detoxification from opiate drugs during pregnancy. *Am J Obstet Gynecol*. (2016) 215(3):374 e1–6. doi: 10.1016/j.ajog.2016.03.015

36. McCarthy JJ, Terplan M. Detoxification from opiates during pregnancy: stressing the fetal brain. *Am J Obstet Gynecol*. (2016) 215(5):670 e1–e2. doi: 10.1016/j.ajog.2016.05.041

37. Grossman MR, Lipshaw MJ, Osborn RR, Berkwitt AK. A novel approach to assessing infants with neonatal abstinence syndrome. *Hosp Pediatr*. (2018) 8(1):1–6. doi: 10.1542/hpeds.2017-0128

38. Young LW, Ounpraseuth ST, Merhar SL, Hu Z, Simon AE, Bremer AA, et al. Eat, sleep, console approach or usual care for neonatal opioid withdrawal. *N Engl J Med*. (2023) 388(25):2326–37. doi: 10.1056/NEJMoa2214470

39. Pomar E G. A mini review of what matters in the management of NAS, is ESC the best care? *Front Pediatr*. (2023) 11:1239107. doi: 10.3389/fped.2023.1239107

40. Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med*. (2010) 363(24):2320–21. doi: 10.1056/NEJMoa1005359

41. Spadaro A, Faude S, Perrone J, Thakrar AP, Lowenstein M, Delgado MK, et al. Precipitated opioid withdrawal after buprenorphine administration in patients presenting to the emergency department: a case series. *J Am Coll Emerg Physicians Open*. (2023) 4(1):e12880. doi: 10.1002/emp2.12880

42. Holbrook AM, Jones HE, Heil SH, Martin PR, Stine SM, Fischer G, et al. Induction of pregnant women onto opioid-agonist maintenance medication: an analysis of withdrawal symptoms and study retention. *Drug Alcohol Depend*. (2013) 132(1–2):329–34. doi: 10.1016/j.drugalcdep.2013.02.031

43. Whitley SD, Sohler NL, Kunins HV, Giovanniello A, Li X, Sacajiu G, et al. Factors associated with complicated buprenorphine inductions. *J Subst Abuse Treat*. (2010) 39(1):51–7. doi: 10.1016/j.jsat.2010.04.001

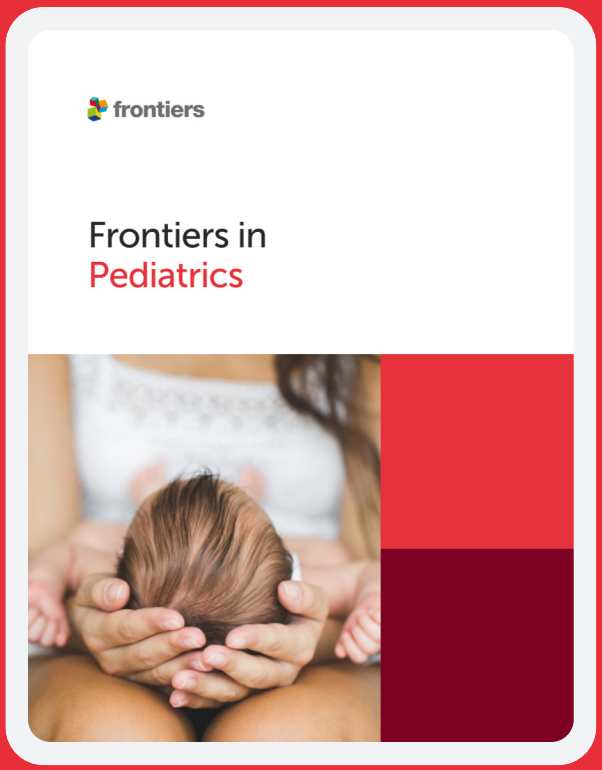
Frontiers in Pediatrics

Addresses ongoing challenges in child health and patient care

Explores research that meets ongoing challenges in pediatric patient care and child health, from neonatal screening to adolescent development.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact