Cognitive and Behavioral Impact on Children Exposed to Opioids During Pregnancy

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The developmental impact of opioid use during pregnancy is a subject of ongoing debate. Short-term neonatal outcomes, such as lower birth weight and neonatal abstinence syndrome, are the most well-recognized outcomes. However, knowledge gaps exist regarding longer-term neurocognitive and mental health outcomes. In this article, we summarize an expert panel discussion that was held in April 2018 by the Substance Abuse and Mental Health Services Administration and attended by national experts in the field of perinatal opioid exposure and its impact on child development. Despite the challenges with research in this area, there is emerging literature revealing an association between neonates exposed to opioids in utero and longer-term adverse neurocognitive, behavioral, and developmental outcomes. Although adverse sequalae may not be apparent in the neonatal period, they may become more salient as children develop and reach preschool and school age. Multiple variables (genetic, environmental, and biological) result in a highly complex picture. The next steps and strategies to support families impacted by opioid use disorder are explored. Model programs are also considered, including integrated care for the child and mother, parenting supports, and augmentations to home visiting.

Opioid use impacts many facets of our society, with 27 million people in the United States who are using an illicit or prescription opioid on a routine basis.[1] The number of women of childbearing age (15–44 years) who reported past-month heroin use increased to 109 000 in 2013–2014, 31% higher than the number in 2011–2012.[2] In the same demographic, reported past-month misuse of prescription opioids increased 5.3% over that period to 98 000.[2] Overall, the rates of opioid use disorder (OUD) in pregnancy more than doubled between 1998 and 2011 to 4 per 1000 births.[3]

Opioid use during pregnancy results from illicit use, prescription for pain management, or medication-assisted treatment (MAT) for OUD. MAT remains the standard of care for women with OUD.[2] Despite the established benefit of MAT, most pregnant women with OUD receive no treatment at all.[4–6] Addiction is a chronic condition, and the postpartum period is associated with increased vulnerabilities, especially for pharmacotherapy discontinuation, addiction recurrence, and overdose death.[7–9]

The impact of opioid use on the developing fetus and child is a subject of ongoing debate. The most common sequela of opioid use during pregnancy is neonatal abstinence syndrome (NAS), or neonatal opioid withdrawal syndrome (NOWS), a group of physiologic and neurobehavioral signs of withdrawal that

abstract

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Drs Larson and Bada conceptualized, organized, and drafted the manuscript; Drs Graham, Beckwith, Singer, Terplan, and Davis contributed to the writing of sections of the manuscript and reviewed and revised the manuscript; Dr Martinez contributed to the review of the literature and assisted with the drafting of the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: https://doi.org/10.1542/peds.2019-0514

Accepted for publication May 16, 2019

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by the Substance Abuse and Mental Health Services Administration, US Department of Health and Human Services.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

To cite: Larson JJ, Graham DL, Singer LT, et al. Cognitive and Behavioral Impact on Children Exposed to Opioids During Pregnancy. *Pediatrics*. 2019;144(2):e20190514

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may occur in neonates after in utero substance exposure. Approximately 50% to 80% of neonates exposed in utero to opioids will develop NAS.[10] From 2009 to 2012, the number of infants diagnosed with NAS increased from 3.4 to 5.8 per 1000 hospital births; 1 state reported a high rate of 50.6 cases per 1000 births in 2017.[11] NAS results in greater hospital costs and may require prolonged hospitalization and/or pharmacologic intervention.[11,12]

FRAME OF MEETING

Supporting women with OUD and their families is a priority for the Substance Abuse and Mental Health Services Administration (SAMHSA). SAMHSA engages in efforts to support pregnant and postpartum women with mental health and substance use disorders (SUDs), including through clinical guidance for pregnant and parenting women with OUD,[2] a maternal depression tool kit,[13] the National Center for Substance Abuse and Child Welfare,[14] grant programs such as the Pregnant and Postpartum Women pilot grants, and other initiatives.

On April 8 and 9, 2018, SAMHSA convened a meeting entitled Developmental Impacts on Children of Opioid Use During Pregnancy: Pragmatic Approaches to Supporting Children and Families. This meeting included a diverse group of experts, including neonatologists, pediatricians, obstetricians and gynecologists, parents, psychiatrists, SUD providers, nurses, researchers, and federal representatives. The focus of the meeting was to explore long-term cognitive and neurodevelopmental outcomes of opioid use in pregnancy, to identify protective and/or mitigating factors that can diminish negative long-term impacts, and to discuss pragmatic approaches to supporting children and families affected by opioid use during pregnancy. For a description of terms and definitions used throughout this article, see Appendix 1.

APPROACHES TO TREATMENT DURING PREGNANCY

Similar to other chronic health conditions, the principle of "healthy mother equals healthy baby" also applies to OUD.[15] The use of MAT for OUD during pregnancy is supported by a broad range of professional societies and public health agencies.[16–19] Pregnant women receiving treatment have improved outcomes, including decreased rates of low birth weight and prematurity, when compared with pregnant women with OUD not in treatment.[20] Literature from the 1970s discussed comprehensive care models for pregnant women with OUD and found similar birth outcomes between pregnant women without OUD and those with OUD who received both pharmacotherapy and prenatal care.[21,22]

Significant stigma is associated with OUD and MAT in the pregnant population[23] and is 1 of many barriers to accessing treatment.[24] Discussing the impact of opioids on the developing fetus may contribute to this stigma. MAT has been perceived negatively by some in treatment as not being "drug-free" or as "trading one drug for another."[25] Furthermore, criminalization of SUDs in pregnancy with resultant incarceration and removal of the child from mother's care can deter women from seeking prenatal care.[26,27]

Because of concerns about the impact of opioid use in pregnancy, detoxification during pregnancy has been reexamined.[28,29] For the majority of women, research suggests that the risk of relapse outweighs any benefit of detoxification.[5] It is not clear, however, whether there are subgroups of women who may benefit from detoxification.

DEVELOPMENTAL SEQUELAE OF IN UTERO OPIATE EXPOSURE

Historically, research on the impact of prenatal opioid use on childhood development was focused primarily on examining outcomes during the immediate neonatal period such as premature delivery,[30,31] length of hospital stay,[32,33] birth weight,[34] and rates of NAS.[35]

Congenital heart defects, hydrocephaly, and neural tube defects are conditions that have been reported to be increased after prenatal opioid exposure.[36,37] Prenatal opioid exposure has also been associated with small fetal head circumference[38] and decreased cerebral volume.[39] Postmortem studies and quantitative MRI reveal small brains and decreased brain volume among neonates born to users of heroin, although concerns have been raised about the absence of masking.[39] Other studies have reported higher rates of preterm birth and low birth weight.[40]

Less is known regarding outcomes after discharge. Authors of most studies have examined short-term outcomes such as the severity of NAS, need for treatment, and length of hospital stay. Because NAS is an expected outcome for many infants with any type of in utero opiate exposure, perhaps less important than the presence or absence of NAS is how the duration and severity correlate with future outcomes in different infants.

Despite the challenges with research in this area and the scarcity of longitudinal research, there is emerging literature revealing an association between fetal exposure to opioids in utero and adverse neurocognitive, behavioral, and developmental outcomes.

To have a comprehensive appraisal of the extant literature for the panelists, an annotated bibliography was prepared. Appendix 2 includes the databases and search terms used. This article is not intended as a full systematic review; articles were included if they pertained to the topic of interest, had historical importance, or were important to the field. When additional information on a topic was

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needed, a biomedical librarian conducted additional searches and provided the search terms and results.

A number of issues have been raised regarding this area of research, including concerns about the heterogeneity of the population of children with NAS, problems with matching of patients and controls, absent masking, and the detection of small effects in large data sets as well as concerns about the "single cause fallacy" of research, that is, attributing all differences to opioid exposure.[41] The experience from the 1980 crack-cocaine–exposure research cautions against the potential harm of stigmatization, discouraging women to choose MAT, criminalization of pregnant women with OUD, or other harms when implying causality to opioid exposure in pregnancy. An important distinction between the crack-cocaine narrative and the impact of opiates in utero on development is that opiates themselves are the treatment of OUD, further complicating the risk/benefit discussion.

MOTOR AND COGNITIVE DEVELOPMENT

Most studies on early childhood outcomes involved children whose mothers were treated with methadone during pregnancy. Several earlier follow-up studies of infants who were exposed revealed delays in psychomotor development.[42–44] In 2008, Hunt et al[45] examined outcomes at 18 to 36 months in 133 children born to mothers who were adherent with their methadone treatment. The Bayley Scales of Infant Development psychomotor index scores did not differ significantly between the children who were exposed and controls who were not exposed.[45] A recent study revealed that neurodevelopmental outcomes of infants born to mothers on MAT at 3 to 8 months of age did not differ those of from healthy controls, treatment of opioid withdrawal notwithstanding. However, compared with healthy controls, a higher proportion of neonates born to mothers on MAT had negative affect and self-regulation, and fewer demonstrated typical performance in the sensation-seeking scale.[46] Beckwith and Burke[42] compared 28 infants with in utero opioid exposure with a historical control and found significant differences in the Bayley Scales of Infant and Toddler Development, Third Edition cognitive, language, and motor subscales. The authors of another study examined the outcomes of children whose mothers had received methadone and buprenorphine in pregnancy and found that at 36 months, the children were within normal range on multiple instruments in cognition, sensory processing, and behavior, although there was no control group.[47]

Researchers have examined cognitive differences between children prenatally exposed to opioids and controls. Several studies revealed lower performance scores in infants who were prenatally exposed compared with controls.[44,45,48] Bauman and Levine[49] found that children 3 to 6 years of age who were exposed had significantly lower IQ scores, including verbal-, performance-, and full-scale scores, than controls. Children who were exposed also scored lower in their sense of well-being, responsibility, self-control, psychological mindedness, empathy, and social maturity index.

Davis and Templer[50] explored cognitive function in a group of school-aged children 6 to 15 years of age with prenatal methadone exposure and found lower performance- and full-scale IQ scores compared with those of controls. Soepatmi[51] reported that children with prenatal opioid exposure had lower IQ scores, higher total behavioral problem scores, and a higher proportion of school problems at 6 years of age compared with controls. In another study, in utero exposure to heroin or methadone was associated with lower IQ scores compared with cannabis or tobacco exposure alone in a group of children with similar risk factors.[52] Results from a 2015 meta-analysis also revealed impairment in verbal working memory, cognitive impulsivity, and cognitive flexibility in preschool-aged children with in utero opioid exposure compared with children without opioid exposure.[53]

Attention and executive functioning are significant areas of concern. In 1 study, children exposed to methadone in utero were found on neuropsychological testing to demonstrate deficits in executive function (cognitive flexibility, strategic planning, and decision-making) compared with controls who were not exposed.[53] Children exposed to either methadone or buprenorphine in utero scored more poorly on tasks of short-term memory and inhibition than peers who were not exposed.[54]

EDUCATIONAL PERFORMANCE AND BEHAVIOR

Adding complexity to studies of neurocognitive deficits after in utero drug exposure is a potential lag between birth and when deficits manifest later in childhood. Authors of an Australian study compared 2234 children with a history of NAS with a matched control group (n = 4330) and all other children in the region (N = 598 265). Mean academic test scores were significantly lower for children with NAS in every grade and domain of testing compared with children in the other 2 groups. Moreover, children with NAS had lower scores in grade 7 than control children in grade 5,[55] although other authors raised the limitation that controls were not appropriately matched on important variables.[56] Another report revealed that children with NAS were significantly more likely to be referred for a disability, to meet criteria for a disability, or to require classroom therapies or services. Developmental delay and speech and/or language impairments were common among these children, and speech therapy was more likely to be

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needed. These findings remained significant after controlling for maternal tobacco use, maternal education status, birth weight, gestational age, and/or NICU admission.[57]

In addition, as noted in a cohort study comparing 72 participants with opioid and polysubstance exposure with 58 participants without any established prenatal risk at 1, 2, 3, 4.5, and 8.5 years, IQ differences between groups were noted to widen with age.[58] When cognitive performance was measured over time after exposure, boys had consistently lower scores than girls. Girls who were exposed also had lower scores than controls, but the differences between their IQ scores widened in later years. Cognitive functioning was lower in all children with opioid exposure than in controls, even after controlling for socioeconomic status, adoption and foster care placement, gestational age, and birth weight.

Using MarketScan data, Sherman et al[59] found that children with a diagnosis of NAS were twice as likely to be diagnosed with disorders of conduct, attention-deficit/hyperactivity, adjustment, and intellectual disabilities. They were also 1.5 times more likely to be diagnosed with development delays, anxiety, emotional disturbances, and autistic disorders compared with children of all other births.[59] These findings support an earlier report on children with methadone exposure who were found to exhibit greater anxiety, aggression, and rejection behaviors than controls.[60] A study limitation was the inability to control for environmental factors, socioeconomic status, or other confounding variables.

IMPACT OF COEXISTENT VARIABLES

Studying the impact of prenatal opioid exposure is complicated by a number of coexistent variables that are complex, are difficult to control, and may significantly influence outcome. These variables include the following: (1) specific opioid exposure in pregnancy or during NAS treatment, (2) exposure to other substances, (3) genetic and environmental interactions, and (4) caregiving environment (biological or adoptive home setting as well as other environmental determinants, including parenting behaviors, exposure to trauma, inadequate nutrition, and other factors).

SPECIFIC OPIOID EXPOSURE AND NAS

Studies comparing the impacts of prenatal buprenorphine and methadone exposure are still at relatively early stages of follow-up. Buprenorphine was associated with a lower risk of low birth weight, smaller head circumference, and more preterm birth compared with methadone.[61] As for behavioral outcomes, neonates exposed to buprenorphine exhibited fewer signs of stress, were less excitable and less hypertonic, and displayed better self-regulation compared with neonates exposed to methadone.[62] The authors of 1 meta-analysis used to compare both drugs concluded that buprenorphine was associated with lower rates of treatment of NAS and shorter hospital stays but cautioned about bias, such as confounding by indication, impacting the findings.[63] One study revealed that a methadone dose of >60 mg/day significantly increased the odds for pharmacotherapy for NAS.[64] Kaltenbach et al[47] evaluated 96 children whose mothers participated in a randomized trial of pharmacotherapy during pregnancy. Outcomes of neonates whose mothers received methadone differed in only 2 of 27 variables from those of neonates whose mothers received buprenorphine.[47]

Another question of interest is whether heroin or other illicit opioid exposure in utero, compared with MAT or another prescribed opioid, has different developmental effects. Certainly, multiple confounding variables exist in the context of heroin use in pregnancy that could impact development. There have been a number of studies in the 1970s and 1980s that have attempted to compare neurocognitive development among infants exposed to methadone versus heroin, but these studies were small and had methodologic challenges. Although several studies from this period revealed little difference between the groups exposed to methadone and heroin on neurodevelopmental and cognitive testing,[65–67] other studies revealed that the group exposed to methadone actually performed more poorly on subsequent neurocognitive testing.[50,68] Authors of a more recent study conducted a subanalysis of 72 children with prenatal opioid exposure and found that heroin exposure resulted in similar cognitive development compared with exposure to other opioids.[58] There has been little research comparing the longitudinal neurodevelopmental impacts of in utero heroin versus buprenorphine exposure. As described previously, MAT is the recommended treatment of OUD in pregnancy because of the risk of relapse and adverse health effects.

Another variable is the type of treatment the neonate receives for NAS, which ranges from a nonpharmacologic approach to various pharmacologic treatments, including the specific agent, differences in titration schedule, dosing, and triggers for intervention. One study revealed that neonatal outcomes were affected by the type of pharmacologic treatment of NAS, with a significantly lower mean cognitive composite score in neonates treated with methadone than that in those treated with morphine (although this was a retrospective study).[43] Authors of other studies have examined specific variables in the treatment of NAS, including the use of rooming-in approaches, variation in dosing and titration schedules, and differences in assessment tools, which have resulted in group difference in proximal

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outcomes such as hospital costs and length of stay.[69,70] More research is needed to better understand the role of treatment of NAS beyond length of stay and hospital costs. In addition, it is not clear if reducing length of stay necessarily results in better developmental outcomes.

POLYSUBSTANCE EXPOSURE

Co-exposures to other substances (licit or illicit) are often seen in women with OUD. Studies of people with OUD of the late 1970s and early 1980s identified alcohol, cannabis, and tobacco use as common correlates in pregnant women treated with methadone.[68] Since that time, a host of other prescribed drugs in conjunction with opioids have been increasingly used during pregnancy, including amphetamines, antidepressants, benzodiazepines, gabapentin, and nonbenzodiazepine hypnotics.[71] In an observational study, the use of opioids with psychotropic medications during pregnancy significantly increased the risk of NAS compared with opioid use alone.[72] Finally, an estimated 95% of pregnant women with OUD smoke cigarettes.[73]

Although a number of these substances have been shown to have effects on child cognitive, physical, and behavioral outcomes, their potential interactions with opioid exposure need more study. The additive or synergistic effects of these other substances may lead to differing outcomes from those of opioids alone.

GENETIC AND EPIGENETIC FACTORS

Genetic and epigenetic factors may also play a role in determining the impact of opioid exposure. Significant variability has been observed in the incidence and severity of NAS in neonates exposed to antenatal opioids. Precision medicine approaches increase the probability of discovering genomic variants that could better explain the development of NAS and facilitate new therapeutic approaches.[74] Previous studies in small cohorts have revealed an association with genetic variants (eg, single-nucleotide polymorphisms) in the *OPRM1*, *COMT*, and *PNOC* genes, with a shorter length of hospital stay and less need for treatment in newborn infants exposed to opioids in utero.[75,76] Epigenetic regulation of genes associated with maternal, fetal, and placental drug metabolism may also contribute to disease severity.[77] Additional larger studies are needed to establish more definitive links.

ENVIRONMENT AND NAS OUTCOMES

Differences in environments among children exposed to opioids in utero and those not exposed to opioids are likely to play a significant role in mental development and behavior and confound many studies in which the effect of opioid exposures is examined.[78] A recent retrospective, repeated cross-sectional study revealed that counties with long-term unemployment and shortages of mental health clinicians had higher rates of NAS, highlighting the fact that many social determinants of health impacting developmental outcomes are co-occurring with NAS.[79]

The authors of a prospective cohort study of 35 children exposed to methadone or buprenorphine examined whether a child's behavior resulted primarily from prenatal opioid exposure or from a contribution of other factors. Three risk models were investigated: the teratogenic risk model, the maternal risk model, and a combined risk model. Results supported both the maternal risk and combined models, with the combined model being most predictive of a child's developing internalizing and externalizing behavior problems.[80]

Many more factors beyond the scope of this review (such as maternal emotion regulation, attachment behaviors, parenting stress, and maternal and parental parenting behavior) may also play a role in childhood developmental outcomes and are difficult to detangle from risk of drug use. Studies suggest an interaction between stress and substance use.[81] A cause and consequence of stress is maternal emotional dysregulation, which may be transmitted through epigenetics and may impact the child's environment.[82] Additionally, fetal exposure to high levels of prenatal maternal stress could lead to "programming effects" on the fetal-stress response system.[82]

MITIGATING FACTORS

The discharge of neonates with in utero drug exposure is often made in conjunction with local child welfare departments to ensure a plan for safe care. In families affected by substance use, children may grow up with exposure to adverse experiences. Factors such as parental separation or divorce; household substance use; incarceration of a household member; physical, sexual, or emotional abuse; physical or emotional neglect; domestic violence; and household mental illness are traumatic or adverse experiences for young children. Cumulative exposure to these adverse childhood experiences is associated with increased odds of later adult risky behavior, heart disease, cancer, chronic lung disease, and a shortened life span.[83] Supporting optimal neurodevelopment in early childhood can decrease the likelihood of developing long-term medical and psychological disorders. In a longitudinal follow-up study of children exposed to cocaine and/or opiates through adolescence, the balance of risk and protective factors predicted the trajectory of behavior problems.[84] In the presence of protective factors among those with in utero drug exposure, behavior problem scores decreased over time, mitigating the effect of prenatal drug exposure. It is therefore vital that in the neurodevelopmental assessment of infants with NAS, the balance of risks and protective factors is evaluated to design interventions to promote optimal outcomes.

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TABLE 1 Strategies and Next Steps

Category	Next Step
Research	Support quality longitudinal studies. Of note, 2 promising initiatives, the ECHO study and the Trans-NIH bBCD study, will direct efforts toward outcomes of longitudinal NAS cohorts by establishing a large cohort of pregnant women and their offspring who will be followed throughout childhood to better understand the impact of specific exposures.
	Further develop genomics research to understand who is at highest risk for adverse outcomes. Decreasing genomic sequencing costs and innovative approaches to investigate variant function should facilitate discovery of genomic variants and gene pathways associated with differences in maternal, fetal, and placental opioid pharmacokinetics and pharmacodynamics. A better delineation of the risk will allow investigators to (1) establish high-risk genetic profiles so opioid exposure could be limited, (2) establish low-risk genetic profiles and safely wean the mother off MAT without an increased risk of relapse, (3) identify high-risk profiles in pregnant women and modify risk factors such as cigarette smoking and polypharmacy, (4) identify high-risk neonates and start low-dose opioid treatment immediately after birth to limit the development and severity of NAS, (5) identify lower risk newborns for early discharge with careful follow-up (a significant cost savings), and (6) combine clinical and demographic variables with genetic profiles and develop graded risk-assessment models to determine the likelihood of addiction after opioid exposure.
	Deepen an understanding of the role of alcohol, polysubstance, and polypharmacy use on the impact of in utero opioid exposure despite the fact that polysubstance use is extremely common yet currently understudied.
	Clarify optimal maternal pharmacology, including dosage and alternative medication options, and its impact on the developing fetus. Study the effects of alternative medications such as naltrexone.
	Study the potential role of detoxification in the treatment of specific subgroups of women.
	Improve on existing animal models to encompass all stages of brain development and to delineate underlying circuits and mechanisms. Opioids, specifically heroin and morphine, are used in developmental animal models to study the short- and long-term consequences of prenatal exposure.[85,86] However, there are challenges with extrapolating the animal studies to humans, including differences in placental transmission,[87,88] dose equivalences, and variations in metabolism as well as differences in fetal development.[89–93]
	Include fathers as well as mothers when looking at risk and protective factors.
	Study appropriate program models to better understand optimal service delivery for families impacted by opiate exposure.
	Follow outcomes beyond postpartum length of stay. Length of stay is a problematic primary outcome measure that may be influenced by other medical and social issues and may not correlate with long-term outcomes.
Programmatic	Within SUD treatment programs, consider the caregiving role of adults receiving services and offer programming to support positive and healthy parenting.
	Support family planning and access to contraceptives for women of childbearing age who are experiencing OUD.
	SUD treatment providers as well as clinicians serving both parents and children should attend to attachment behaviors and positive parenting among mothers and fathers, beginning prenatally and continuing postpartum, to potentially mitigate adverse outcomes.
	Given the complex needs of many impacted families, make case-management services available to coordinate medical and behavioral health services for parents and children.
	All neonates with prenatal opioid exposure should access early intervention and screening. Current criteria for early intervention in many states may not enable children with opioid exposure to access these services, especially if developmental issues arise beyond the age of 3 y, when children are transitioned to school services. With additional funding, the Individuals with Disabilities in Education Act, part C would be able to accommodate and sustain early intervention services for children with prenatal opioid exposure.
	Support models that include peers who can support both parenting and recovery.
	Provide education about potential childhood developmental and neurocognitive risks to health systems such as early intervention services; Head Start; the Mother, Infant, and Early Childhood Home Visiting Program; day care centers; WIC; and school settings.
	Expand home-visiting models for early identification of children impacted by opioid exposure and at risk for neurodevelopmental issues.
	Encourage family-centered approaches and consideration of the needs of all family members, including children, in settings such as family drug courts.
Communication and tracking	Standardize record keeping so that in utero exposures can be communicated across systems.
	Promote record sharing among providers (prenatal and obstetric, maternal mental health and MAT, and child's primary care).
	Develop tracking systems and databases to better monitor outcomes. A national registry of data could include common data elements and terminology, with consensus on variables to track and well-defined, appropriate outcome measures. Outcomes should be value based and should include aspects of healthy child development and school readiness. To the extent possible, information on parents and their mental health and children's health records should be linked.
	Promote the use of common definitions of NAS and NOWS. Criteria to diagnosis NAS vary between hospitals, ranging from inclusion of any infant known to be exposed to opioids in utero to only infants requiring pharmacotherapy. The lack of consensus regarding diagnosis complicates tracking efforts.

bBCD, baby Brain Cognitive Development; ECHO, Environmental Influences on Child Health Outcomes; NIH, National Institutes of Health; WIC, Special Supplemental Nutrition Program for Women, Infant and Children.

STRATEGIES AND NEXT STEPS

There are a number of important next steps, both in the area of future research and program development, which are presented in Table 1.

Future research should be focused on the role of genetics and epigenetics and the effects of polysubstance use and psychosocial and environmental factors on child outcomes and should include outcomes that go beyond NAS and length of hospital stay after birth. Importantly, the distinction between opioid exposure in the context of OUD and opioid exposure in the context of treatment for OUD (eg, buprenorphine or methadone) or for chronic pain, for

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TABLE 2 Examples of Promising Programs and Models

Program or Model	Service Description	Web Site Link	State
Project Respect	Obstetric and SUD treatment, case management, and peer support	http://www.bumc.bu.edu/obgyn/special-programs/project-respect/	Massachusetts
MTP	Relapse prevention, developmental therapy, anger management, spirituality and recovery, family nurturing, and pathways to reunification	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2802496/	Connecticut
The Bridging Program	Home visiting, wraparound planning, occupational and physical therapy, developmental therapy, family support services, parent education, and case management	https://www.cccmaine.org/services-programs/bridging/	Minnesota
CAP	Substance-abuse treatment, family planning, case management, housing, transportation, primary care, integrative services, education, and parenting support	https://www.hopkinsmedicine.org/psychiatry/patient_information/bayview/medical_services/substance_abuse/center_addiction_pregnancy.html	Maryland
REACH	Case management, recovery coaching, peer support, and parental education	https://www.ct.gov/dmhas/cwp/view.asp?a2902&q=607228	Connecticut
PATHWAYS	Peer support, buprenorphine treatment, education, legal support, prenatal and postnatal health services, developmental therapy, case management, and integrative services	https://med.uky.edu/news/pathways-program-demonstrates-success-evidence-based-collaborative-approaches-perinatal-opioid	Kentucky
MOTHER	Education, counseling, developmental therapy, case management, and parenting support	https://www.northlandtreatment.com/m-o-t-h-e-r-program/	Ohio
MOMS	Case management, buprenorphine treatment, counseling, social services, and education	https://www.stonybrookmedicine.edu/patientcare/obgyn/MOMS	New York

CAP, Johns Hopkins Center for Addiction and Pregnancy; MOMS, Maternal Opioid Management Support; MOTHER, Maternal Opiate Treatment and Healthy Educational Resources; MTP, Mothers and Toddlers Program; PATHWAYS, Perinatal Assistance and Treatment Home; REACH, Recovery, Engagement, Access, Coaching, and Healing.

which opiates are prescribed, is a distinction that requires ongoing clarification and research. Given the fact that many environmental risk factors are more likely to occur in the context of illicit heroin use, it is certainly important to stabilize individuals with OUD through evidence-based treatments, such as MAT, even in the face of possible teratogenicity. Several systematic reviews have revealed that detoxification is associated with high relapse rates,[28,29] although the research to date is limited and is an important area of ongoing inquiry. In addition, it is important to examine the factors that result in different developmental trajectories for infants with similar opioid exposures and similar NAS presentations.

Given the challenges of differentiating the many variables that may impact outcomes of infants who have experienced opiate exposure in utero, a practical approach is to intervene when it is most likely to result in a more positive outcome. There are a number of strategies that have the potential to mitigate the negative impacts of OUDs in pregnancy. Such strategies involve interventions to support the parenting among families impacted by OUD, to provide greater coordination and access to care for parents and children, and to increase the likelihood of follow-up to care by integrating services and enhancing care management.

There are already a number of promising program models to support families impacted by OUD (see Table 2). Many have common elements, including care that uses a dyadic family-based approach, support for positive parenting behaviors, focus on maternal physical and emotional wellness, integrated pediatric and maternal health care, early intervention, and the integration of peer support.[94] A number of programs provide MAT to parents, when necessary, while also providing health care for the child. Several innovative programs have employed peers to support mothers in recovery and in the challenges of parenting a neonate. Peer-to-peer support helps women connect with services, prepare for pregnancy, and access MAT when indicated.[27] Programs that support families in the community are potentially helpful in this population. Home-visiting programs can help parents navigate systems of care and provide long-term solutions and adaptation. Home visiting may also allow for earlier identification of any developmental issues.

Communication among integrated systems will improve quality of care and minimize gaps in health care delivery to the dyads and families. Programs and policies must include models of care that will increase access to maternal treatment while ensuring optimal child health and developmental outcomes.

CONCLUSIONS

The adverse developmental outcomes that occur in children prenatally exposed to opioids are well documented and are likely to be the result of a combination of factors (including biological, genetic, and

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environmental causes) that represent a cumulative risk. Given the co-occurrence of environmental risk with biological risk, it is important to support parents and children through access to appropriate treatment, screening and early identification, care coordination, and other supports. It is also important to note that adverse sequelae for children prenatally exposed to opioids may also not be obvious in the neonatal period but may become more important into the preschool- and school-aged years. Attributing causality is difficult in such a highly complex system, with a myriad of genetic, environmental, and biological variables.

In general, children have the greatest potential for success when their mothers are healthy and supported. Given the increasing numbers of children exposed to opiates, it is important to advocate for increasing access to treatment of women with OUD and for postdelivery programs that integrate interventions for the parent-child unit to mitigate any impact of prenatal opioid exposure through every stage of child development.

APPENDIX 1: TERMINOLOGY

Neonatal abstinence syndrome (NAS): A group of physiologic and neurobehavioral signs of withdrawal that may occur in a newborn who was exposed to psychotropic substances in utero and may require pharmacotherapy. NAS is also a nonspecific term assigned to a type of presentation that exhibits signs of physiologic withdrawal from substances after birth in the newborn. NAS is a result of the sudden discontinuation of fetal exposure to substances that were used or abused by the mother during pregnancy.[95]

Neonatal opioid withdrawal syndrome (NOWS): The pattern of physiologic manifestations of withdrawal explicitly attributable to opioids seen in newborns, and the term is becoming more widely used. Opioid exposure in utero leads to a well-described complex of withdrawal signs and symptoms that can be described as NOWS.[96]

Medication-assisted treatment (MAT): The use of medications in combination with counseling and behavioral therapies for the treatment of SUDs. Most patients with OUD require pharmacotherapy for effective treatment. The most frequent medications used in this treatment are methadone and buprenorphine. Currently, 3 medications are approved by the US Food and Drug Administration for treating opioid addiction. Classified by their underlying mechanisms, these medications include agonist (methadone), partial agonist (buprenorphine), and antagonist (naltrexone) agents.[97]

APPENDIX 2: METHODOLOGY OF THE DEVELOPMENT OF THE ANNOTATED BIBLIOGRAPHY USED TO INFORM THE PANEL AND ARTICLE

The literature search identified studies published in peer-reviewed journals. Databases searched included the Journal of the American Medical Association Network, ScienceDirect, PubMed, Wiley Online Library, the US National Library of Medicine, Medline (via EBSCO), Embase, Web of Science, PsycINFO, and the Cumulative Index to Nursing and Allied Health Literature.

Inclusion criteria included the following:

- case-controlled or well-designed longitudinal studies;
- longitudinal animal studies with respect to brain and behavior development (primates preferred);
- published in the English language;
- published between 1966 and November 30, 2017; and
- relevance to the purpose (eg, any opioid use and information on longitudinal animal studies [preferably primates] with respect to brain and behavior development).

Search terms for this search included, but were not limited to, the following:

- Buprenorphine, naltrexone, probuphine, (buprenorphine AND implant*), methadone, "medication-assisted treatment," "medication-assisted recovery," "medication assisted treatment," "agonist therapy," "agonist treatment";
- Opioid*, opiate*, oxycodone, hydrocodone, morphine, fentanyl, hydromorphone, meperidine; and
- Pregnan*, fetal, fetus*, embryo*, neonat*, utero, child*, prenatal, infant*, "child* development*," "child behavior," "development* consequences," cognit*, "brain development*," neuropath*.

Key search terms were further delineated and identified as needed to obtain relevant research findings. Abstracts were collected, catalogued, and reviewed on the basis of inclusion and exclusion criteria. Articles were selected on the basis of the applicability of the abstract and review of the full text. Only articles that met the inclusion criteria were included in the annotated bibliography.

UNPUBLISHED/"GRAY" LITERATURE

Because of the limited amount of published literature on this topic, the literature search process also included a search of unpublished materials related to various aspects of the topic. Unpublished documents that were explored included the following:

- technical reports and other publications from US Government agencies;
- technical reports and other publications from state agencies;
- white papers, monographs, and recommendations from medical professional organizations; and
- guidelines, publications, and recommendations from national and international organizations.

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ACKNOWLEDGMENTS

We thank the Assistant Secretary for Mental Health and Substance Use, Dr Elinore F. McCance-Katz for guidance and direction in preparation of this article. We also thank the group of subject-matter experts from the expert panel meeting that took place on April 10, 2018, in Rockville, Maryland. We also acknowledge Joseph Perpich, Anne Leopold, Erika Capinguian, and Susan Hayashi for their assistance in preparing the annotated bibliography that informed the panel and subsequent article as well as Alicia Livinski, National Institutes of Health librarian, for her assistance with literature searches.

ABBREVIATIONS

MAT: medication-assisted treatment
NAS: neonatal abstinence syndrome
NOWS: neonatal opioid withdrawal syndrome
OUD: opioid use disorder
SAMHSA: Substance Abuse and Mental Health Services Administration
SUD: substance use disorder

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Pediatrics 2019;144;
DOI: 10.1542/peds.2019-0514 originally published online July 18, 2019;

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