Long-Term Outcomes of Infants with Neonatal Abstinence Syndrome

Denise J. Maguire, PhD, RN, CNL
Susan Taylor, MSW, LCSW-C, CMA
Kathleen Armstrong, PhD
Emily Shaffer-Hudkins, PhD
Aaron M. Germain, MD
Sandra S. Brooks, MD, MPH
Genieveve J. Cline, DNP, ARNP, NNP-BC, CNE, RN-BC
Leah Clark

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Abstract

Parents of infants with neonatal abstinence syndrome (NAS) in the NICU may have questions about the long-term consequences of prenatal exposure to methadone, both asked and unasked. Although the signs of withdrawal will abate relatively quickly, parents should be aware of potential vision, motor, and behavioral/cognitive problems, as well as sleeping disturbances and ear infections so their infants can be followed closely and monitored by their pediatrician with appropriate referrals made. Furthermore, this knowledge may inspire parents to enroll their infants in an early intervention program to help optimize their outcomes. There are still many unanswered questions about epigenetic consequences, risk for child abuse/neglect, and risk of future substance abuse in this population.

Keywords: abstinence; withdrawal; outcomes; long term; neonatal

Every hour, a baby is born with neonatal abstinence syndrome (NAS), totaling >10,000 annually.[1] Aside from the effect of prenatal drug exposure on the developing nervous system, these infants may face additional postnatal threats including inconsistent caregiving, family instability, out-of-home placements, chronic stress, and poverty, all of which affect health and development. Although there is an initial financial burden on the health care system because of the needed neonatal intensive care, infants with NAS may require additional long-term supports including health care and special education. Patients in this population are difficult to study long term because of their transient lifestyle, mistrust of health care professionals, and often-difficult home life. Although all of these issues make it challenging to study long-term outcomes of prenatal opioid exposure, there is evidence that prenatal opioid exposure has a long-lasting impact on many infants.

Short-term outcomes of opioid exposure have been well documented for methadone, buprenorphine, and many illicit substances. The most well-known outcome of any opioid exposure is NAS, reported to occur in 75–90 percent of exposed infants.[2] The severity of withdrawal does not seem to be associated with maternal methadone dose or length of treatment.[3] Onset of signs of withdrawal is usually between 24 and 48 hours after birth, but those exposed to polydrug abuse require treatment earlier.[4] Withdrawal scores peak between 34 and 50 hours of

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life.[5] The majority (95 percent) of infants with NAS can be identified by Day 5 of life.[4] Those who develop NAS demonstrate varying signs of central nervous system irritability, autonomic overreactivity, and gastrointestinal distress.[2] The signs of withdrawal include excessive, high-pitched crying, sleeplessness, hyperactive reflexes, tremors, increased muscle tone, excoriation, sweating, fever, mottling, nasal stuffiness and flaring, tachypnea, poor feeding, regurgitation, projectile vomiting, and, in the worst cases, seizures.[6] Infants are first managed with nonpharmacologic interventions designed to reduce external stimuli,[7] such as tight swaddling in a dark and quiet environment. Signs of withdrawal are managed with opioids until they are well controlled, and then the doses are slowly tapered.[2] Depending on the severity of withdrawal signs, treatment can be expected to last four to six weeks.[2] Infants exposed to buprenorphine have a later onset of withdrawal and require less morphine and shorter duration of treatment than those exposed to methadone.[8,9]

The incidence of NAS in preterm infants has been reported to be less severe,[10–12] but it is very likely that the assessment scales developed for full-term infants are not sensitive enough to identify withdrawal in preterm infants. Ruwanpathirana and colleagues[10] recently concluded that prematurity reduced the severity and need for treatment for NAS, but they used a scale developed for full-term infants, infants were not regularly assessed, and there was no information about how nurses were trained or how interrater reliability was established or maintained. It is well known that premature infants have much less robust behaviors than full-term infants, so it is not unreasonable to expect signs associated with NAS would be much more subtle also.

Most infants are managed in the NICU until they have fully recovered, but there are reports of infant opioid management at home.[4] There are probably many more opiate-exposed infants who are not assessed and treated, because many pregnant women are not routinely screened for substance abuse despite guidelines from the American College of Obstetricians and Gynecologists.[13] The purpose of this article is to review the long-term outcomes of infants with NAS beyond the neonatal period.

LITERATURE REVIEW

A systematic literature search of published research studies was conducted in Scopus, MEDLINE, PsycINFO, and PubMed using the key words "neonatal abstinence syndrome" and "long-term outcomes." In addition, the reference lists from the studies were reviewed for potential articles. Although we hoped to find randomized clinical trials, the strongest level of evidence available was case-control studies (except for Wachman and colleagues,[14–17] who conducted genetic studies). We also included descriptive studies that were mostly medical record review. Citations that were not primary sources of studies or were not related to opioid dependency were not included for review. We did not limit the search by date because older studies included reports of heroin, which is currently experiencing a resurgence. A total of 23 research papers were included in this review (Table 1). Systematic reviews were included only to support conclusions. Fourteen papers were published since 2001, and seven papers were published between 1979 and 1987. Areas of concern included epigenetic consequences, vision problems, motor problems, behavioral/cognitive problems, otitis media, child abuse/neglect, sudden infant death syndrome (SIDS), and risk of future substance abuse. We begin the review with epigenetic consequences because this is a new area of research in this population that may provide context in which to understand some of the long-term outcomes of prenatal opioid exposure.

Epigenetic Consequences

Epigenetics is the study of heritable changes in gene expression without changes to DNA. Epigenetic change occurs regularly and is influenced by factors such as age, environment, and lifestyle.[18] Certain circumstances can cause genes to be turned off (silenced) or on (expressed). Substance abuse itself is postulated to be dependent on both genetics and the environment.[18] There are numerous animal studies examining the transgenerational effects of environmental toxins on offspring, both prenatally and preconception. In fact, research has demonstrated that animals that have been given morphine during adolescence have epigenetic changes that are expressed in future generations,[18] which clearly demonstrates epigenetic influences. Byrnes and colleagues[19] reported that the male offspring of female rats exposed to morphine during adolescence had increased sensitivity to the analgesic effects of acute morphine and developed tolerance more rapidly than male offspring exposed to saline. In another study, the authors also described increased anxiety-like behavior in female offspring of morphine-exposed dams.[20] Lu and colleagues[21] reported that heroin use during pregnancy significantly reduced neuronal dendritic branching and length, which resulted in impaired short-term spatial memory in the adult offspring of mice.

Although no studies could be found involving humans when either parent used opioids prior to conception and stopped during pregnancy, there are several reports of epigenetic changes in newborns who were exposed to opioid during pregnancy. Wachman and colleagues[15] first identified that infants who were carriers of the mu-opioid receptor (MOR) G allele had less severe withdrawal and a shorter length of stay than infants without the G allele. In a follow-up study of 86 infants from four hospitals who were chronically exposed to opioids in utero, the authors demonstrated epigenetic changes in the MOR gene that correlated with short-term NAS outcome measures.[16] Specifically, infants with increased methylation of the MOR gene had significantly worse NAS symptoms, consistent with silencing of the gene. Infants without the methylation required significantly less pharmacologic

TABLE 1 ■ Summary of Study Outcomes in Response to Prenatal Exposure

Authors	Sample Size Exposed/Control*	Exposure(s) Identified	Outcomes
Beckwith & Burke, 2015	28	Opiates	Language, motor, cognition
Chasnoff and colleagues, 1984	58/27	Methadone	Growth
Gill and colleagues, 2003	49	Opiates	Strabismus
Hamilton and colleagues, 2010	20	Methadone	Ophthalmic abnormalities
Hunt and colleagues, 2008	133/103	Opiates	Neurodevelopmental
Johnson and colleagues, 1984	61/32	Methadone	Neurobehavioral
Kahila and colleagues, 2007	67	Buprenorphine	SIDS
Kaltenbach and colleagues, 1987	105/63	Methadone	Developmental
McGlone and colleagues, 2014	81/26	Methadone	Nystagmus
Mulvihill and colleagues, 2007	14	Opiates	Nystagmus
Ornoy and colleagues, 2001	65/62	Heroin	Developmental/cognitive
Ornoy, 2003	93/87	Heroin	Developmental, behavioral
Rosen & Johnson, 1982	38/23	Methadone	Neurologic, motor, otitis media, vision/behavioral/cognitive
Sandtorv and colleagues, 2009	15	Polysubstances	SIDS
Spiteri Cornish and colleagues, 2013	301/7,887	Polyoioids	Nystagmus, strabismus
Strauss and colleagues, 1976	60/53	Methadone	Behavioral/motor
Sundelin Wahlsten & Sarman, 2013	28	Buprenorphine	Neurobehavioral/attention
Wachman and colleagues, 2013†	86	Methadone	Hospital stay
Wachman and colleagues, 2014†	86	Methadone	Gene variation
Wachman and colleagues, 2015†	86	Methadone	Gene variation
Walhovd and colleagues, 2015	23/24	Detoxified opioid and polysubstance	Visual acuity
Wilson and colleagues, 1979	22/20	Heroin	Growth/cognitive
Wilson and colleagues, 1981	69/58	Narcotics or methadone	Health, developmental

Abbreviation: SIDS = sudden infant death syndrome.
*Studies with a control group were case control designs; other designs were descriptive.
†Studies using genetic markers.

treatment, if any. Most recently, these investigators added to these findings by reporting an additional association of worsened NAS symptoms when single nucleotide polymorphisms (SNPs) were present in the prepronociceptin (PNOC) genes,[17] building the case for the epigenetic role in NAS. Their results help explain the often-cited wide range (75–90 percent) of infants who develop NAS after prenatal exposure.[2] Perhaps the reason why the remaining 10–25 percent do not develop signs of NAS is because of epigenetic change. Hudak and Tan[2] continue to pursue epigenetic changes.

Vision Problems

There is growing evidence that infant vision is affected by prolonged opioid exposure.[22–25] Strabismus[23,26] as well as reduced visual acuity, nystagmus, refractive errors, and cerebral visual impairment[23] have been described. Others have reported that visual evoked potential peak times were significantly slower ($p = .02$) with smaller amplitudes in a comparison study.[24] In a study of 28 children exposed to buprenorphine prenatally, Sundelin Wahlsten and Sarman[27] reported serious visual motor problems as measured by eye-hand coordination and visual-spatial ability of organization. The prevalence of strabismus and nystagmus was found to be significantly higher at age 5 years in a group of 301 children born after prenatal exposure to opiates, in comparison to 7,887 age-matched controls in Scotland.[25] A recent case-control study conducted in Norway with 13 cases and 14 controls reported no differences in neurocognitive functioning and lower left eye visual acuity at 4.5 years of age.[28] In addition to the few subjects, mothers were "detoxified" during their pregnancy, but the authors provided no information about that process or timing. Detoxification during pregnancy is not the standard in the United States, so these results may not be generalizable to the U.S. population.

Motor Problems

Multiple prospective longitudinal studies with comparison groups have reported inconsistent findings related to the consequences of methadone exposure on the long-term motor developmental outcomes of newborn infants.[29] Strauss and colleagues[30] reported that 60 methadone-exposed infants compared with 53 socioeconomically and medically similar infants born to non–drug-dependent mothers scored within the normal range for development on the Bayley Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) at 3, 6, and 12 months of age. These results are consistent with the findings reported by Kaltenbach and Finnegan[29] who found no differences in MDI scores and neurologic exams (performed by a pediatric neurologist) in 105 methadone-exposed newborns at 6 months. Data from Strauss and colleagues[30] also suggest that the PDI scores for the 60 methadone-exposed infants declined with age and were significantly different from 53 comparison infants at 12 months of age. A lack of significant difference in MDI scores and lower PDI scores between 69 methadone-exposed and 58 comparison infants at nine months was also reported.[31] Rosen and Johnson[32] found no differences between groups (n = 38/23) on MDI and PDI scores at six months of age; however, they reported methadone-exposed infants to have both lower MDI and PDI at 12 and 18 months. Johnson and colleagues[33] also reported lower MDI and PDI scores that continued at 18 and 24 months for 61 exposed and 32 control infants. More recently, Hunt and colleagues[34] reported the results of a case-control study conducted in Australia comparing 133 opiate-exposed infants to 103 drug-free healthy infant controls followed at an antenatal clinic during the same time period. They reported that the opiate-exposed infants were significantly more likely to have neurodevelopmental impairment compared with the healthy infant controls at 18 months and 3 years of age.[34] Beckwith and Burke[35] reported statistically significant lower mean level Bayley-III composite scores for language, cognition, and motor function in a sample of 28 infants with NAS exposed to methadone compared with historical normed data at three years of age.

The long-term effects of buprenorphine exposure on the motor development of infants has been less well studied. Sundelin Wahlsten and Sarman[27] reported neurodevelopmental outcomes of 28 preschool children born to opioid-dependent mothers in Sweden treated with buprenorphine during pregnancy. The children were given a battery of neurobehavioral tests including the *Wechsler Preschool and Primary Scale of Intelligence-Revised*, *McCarthy Scales of Children's Abilities* (MSCA), *Brown ADD Scales*, and *Strengths and Difficulties Questionnaire* (SDQ) at five to six years of age.[27] The children were found to have significant problems with motor skills and memory (as measured by the MSCA), hyperactivity, impulsivity, and attention (as measured by the teachers on the Brown and SDQ). Interestingly, the parents did not report any problems in the children.[27] The results of this study are limited because of the small sample size and lack of a matched control group.

As a whole, these studies reveal that motor problems were not found in infants <12 months but were found in studies that followed infants from at least one to six years of age. Three older studies found little or no differences in infants exposed to methadone,[29,30,33] whereas those in the last ten years were more consistent and included "opiates" and buprenorphine.[27,34,35] Early investigators may have been interested in providing negative results from the use of methadone to support its continued use. Furthermore, the authors provided no discussion of how bias was controlled in the case control designs.

Behavioral and Cognitive Problems

Children between three and six years of age who were exposed prenatally to heroin (n = 22) had significantly lower height, weight, and head circumference and performed significantly poorer on the Columbia Mental Maturity Scale than 20 matched controls.[36] These same researchers reported that three- to six-year-old children exposed to heroin prenatally performed more poorly than a comparison group on the general cognitive index, perceptual, quantitative, and memory subscales of the McCarthy Scales.[36] Follow-up of those children indicated that 65 percent had repeated one or more grades or needed special education services. Ornoy and colleagues[37] compared Israeli children born to mothers addicted to heroin who were either raised by their parents or adopted at an early age. The adopted children had normal verbal IQ scores and learning abilities in math and reading, whereas the children raised by their parents who are addicted functioned lower in those domains. Both groups had reduced function on performance IQ scores.[37] Although these results may not be generalizable to U.S. children, the findings speak to the importance of the caregiving environment to children born to mothers with an addiction to heroin. Prenatal methadone exposure has been linked to short attention span and hyperactivity among toddlers.[32] Investigators have reported impaired verbal and performance skills[38] as well as visual-motor weakness and perceptual abilities.[39] Memory and perceptual problems have also been found among school-aged children with prenatal opioid exposure.[40] Buprenorphine exposure during gestation is also associated with poor outcomes in children ages five to six years, including significant hyperactivity, impulsivity, and attention problems.[27]

Research on prenatal opiate exposure is difficult to conduct with this population because of confounding factors including poverty, high-risk environments, and maternal polydrug use which also contribute to poor outcomes. As an example, a study with children from poverty and high-risk backgrounds found that children's scores fell below national norms and continued to decline over time.[41] Many researchers agree that environmental risk will magnify any weaknesses caused by the opiate exposure. These studies all had small numbers of subjects except the one that reported on exposed children of adopted families.[37] Only two reported on methadone,[30,32] and the other two were heroin[36] and buprenorphine[27]

exposures. In addition, they all used different measures of behavior and cognition.

Otitis Media

Only one study was found that mentioned otitis media as an outcome of infants with NAS.[32] These investigators collected 18-month data on 38 exposed and 23 control infants and reported that infants exposed to methadone prenatally had a significantly higher incidence of otitis media ($p < .0001$). Severe or chronic otitis media is associated with hearing and developmental and learning disabilities. Recurrent otitis media is often associated with persistent hearing loss, which can lead to impairments in the development of language skills.[42] In general, children with recurrent otitis media have impaired development in articulating, producing speech, and understanding language[43] with no impairment of visual development.[42] This is most likely because of the fact that the hearing impairment occurs during a time where auditory stimuli are essential for the development of language.[44] Children with earlier onset and greater severity of otitis media show higher rates of learning disabilities and decreased school achievement.[42] Although otitis media may be a concern in methadone-exposed infants, not enough investigators have collected that information, despite the risk for long-term hearing deficits and learning disabilities.[42]

Child Abuse and Neglect

The landmark adverse childhood experience (ACE) study drew a direct relationship between childhood exposure to household dysfunction, emotional, physical, and/or sexual abuse, including substance use by persons in the home, and later health outcomes.[45] Ranging from obesity and cardiovascular disease to psychiatric illnesses, ACEs are considered strongly associated with alcohol and drug abuse in exposed children.[46] Research on the epidemiology of disorders of drug use and abuse repeatedly reports on the complex interplay between genetic, social, and environmental factors in their etiology.[47–49] Salient to concerns of child abuse and neglect is research suggesting connections between direct (specific) and indirect (general) intergenerational trauma transmission of distorted thought and behavior, leading to cycles of problematic parenting interactions, beliefs of low self-efficacy, and heightened sensitivity to stimuli on the part of mothers with trauma history.[50] Furthermore, substance abuse is associated with both decreased social affiliation and relationship to social roles such as parent and worker, leading to unemployment and loss of parental rights.[51]

The human complexities of physical and mental health, as well as social, financial, relational, legal, cultural, educational, vocational, and housing inherent with substance abuse multiply with pregnancy and parenting. Neurologic changes in addiction from inhibitory control and emotional regulation to self-awareness, from motivation and reward to memory and attention, impact the capacity of substance-dependent mothers to safely perform significant developmental tasks with their infants.[52] Highly taxed stress systems in the brain, altered by addiction, lead to both a lack of responsiveness to children's needs and heightened punitive parental reactivity.[53] One small study of pregnant women dependent on prescription opioids demonstrated their lack of parenting skills (i.e., lack of empathy, inappropriate expectations of the child, and belief in use of corporal punishment).[54]

In addition, complex interpersonal trauma is associated with increased maternal aggression and physical punishment, along with dissatisfaction and difficulty with parenting.[52] Repeated studies found a majority of pregnant or parenting women entering drug treatment endorsed a history of physical and emotional abuse often witnessed by children.[55,56] Such abusive and neglectful behaviors have been shown to be transmitted intergenerationally.[53]

Controlling for social isolation, socioeconomic status, and other psychiatric diagnoses, substance-abusing parents report significantly more physically abusing and neglectful behaviors toward their children than study subjects not abusing drugs or alcohol.[57] With 40 to 56 percent of abusive or neglectful parents diagnosed with a substance abuse disorder, the substantive association between substance abuse and the risk of child maltreatment (abuse and neglect) tripled when controlled for other environmental and psychiatric factors.[57,58] Fifteen years later, the significance of maternal drug abuse in the involvement of child protection agencies for both physical abuse and neglect of children remains high, yet some reduction of risk is shown when there is compliance with methadone maintenance programs.[59] In a 2003 study, the increase in the risk of childhood abuse doubled when associated with parental substance abuse.[60]

Child protective service systems consider parental drug abuse to be a primary factor in abuse and neglect cases, with rates ranging from 50 to 80 percent of all cases.[60,61] Differences, for example, between rural and metropolitan populations have been shown to be significant for involvement with local social service systems for child abuse and neglect.[62] These associations remain complicated to tease out since reporting to and involvement with child protection and social service systems are subjectively made, and criteria vary from location to location (baseline triggers for reporting: length of hospital stays for babies with NAS; reporting of suspicions of child abuse and neglect; referrals of families into the social service systems because of the perceived risk of parenting by mothers who are known to have substance abuse diagnoses; families separated by the foster care system; children adopted; children reunited with birth families). Although black children and families are disproportionally represented in reports to and involvement with child protection and social service systems, data comparison shows that both systemic racial bias and increased risk appear to be interwoven factors in seeking explanation of this phenomenon.[63] The tangled interconnectedness and bidirectionality of vulnerable environmental settings, exposure to home

and community violence, and parental opioid abuse appear to point to a heightened risk of child abuse and neglect in the parenting of children with NAS.

Risk of Future Substance Abuse and Sudden Infant Death Syndrome

To date, there are no published data to determine the effect of prenatal opioid exposure on subsequent drug abuse. Some studies have demonstrated higher rates of substance use among individuals prenatally exposed to other drugs such as tobacco and marijuana[64,65]; however, conclusions cannot be drawn regarding cause and effect because of the numerous environmental variables that may influence this correlation. Longitudinal research following large cohorts of NAS infants into adulthood is needed to determine the potential impact of prenatal exposure to opioids on drug addiction later in life.

Two studies were found that reported SIDS as an outcome,[66,67] and because one was available only in Norwegian,[67] only the abstract was able to be reviewed. Kahila and colleagues[66] reported short-term outcomes of 67 infants born to women taking buprenorphine in Finland, such as rate of NAS and length of stay. The three SIDS deaths they reported represented a rate 150 times greater than their national average. Nearly all women in their study smoked tobacco, and the mothers of the infants who died were all in the "noncompliant" group of their study. The report does not include information on how women were followed long term, so the results of this study must be interpreted with caution. Similarly, Sandtorv and colleagues[67] reported two SIDS outcomes in a small group of 15 infants who were exposed to methadone, buprenorphine, heroin, benzodiazepines, or cannabis. It is unknown if those deaths were from the group of ten infants who were treated for NAS or even which drugs the infants were exposed to prenatally. SIDS is certainly an outcome that should be studied on a larger scale in this population.

Research on the long-term outcomes for infants with NAS is very complicated because of several confounding factors which may also have adverse effects on children's health, development, and learning. For example, many infants with NAS have been exposed to more than one substance prenatally, at different times during the pregnancy, and the health and well-being of their mothers during their pregnancy may not have been well documented. The caregiving environment after birth and early experiences are of critical importance to development yet may not have been accounted for in the reviewed studies. Circumstances including poverty, parental mental health problems, exposure to family violence, chronic stress, trauma, and out-of-home placements are often interrelated and may affect infants with NAS disproportionately. Lastly, because of the uniqueness of this population, sample sizes may be too small to generalize results.

Many of the studies included in this review reported inconsistent findings. Although some controlled for a specific substance, in many cases, different measures were used to quantify outcomes. Only one author made any attempt to limit bias in these descriptive studies; McGlone and colleagues[24] indicated that the evaluators were blinded to the group. The problem of long-term outcomes in infants with NAS has not been well studied, and much still remains unknown. The results of these studies should be considered possible and perhaps probable but should be used with caution.

IMPORTANCE OF INTERVENTION PROGRAMS

Although the care of the neonate with NAS has largely focused specifically on identification and treatment, the global aims should focus on addressing the needs of the mother/infant dyad, including improving access to treatment programs for the mother and improved care of the newborn with NAS, while reducing per capita costs for NAS hospitalizations.[68] Opportunities to impact the outcomes of NAS patients and their families occur at many points in the continuum of care, ranging from preconception counseling to support of patients and their families during hospitalization of the drug-affected infant and long-term support of healthy lifestyles. Clinicians should screen for and be educated about recognizing drug abuse in pregnancy and provide preventive counseling.[69] Pregnant women with a history of opioid use may not otherwise seek medical attention, and seeking prenatal care may provide a limited opportunity to evaluate overall health status and intervene to decrease the incidence of illicit drug abuse and its associated complications, such as sexually transmitted diseases, as well as to enhance the parents' child-caring capabilities.[70,71] Coordination of care and prenatal intervention programs may provide comprehensive services through home visits and multiagency collaboration, thus preventing prenatal and birth complications and improving outcomes for the neonate.[69]

Between 2008 and 2014, the Government Accountability Office (GAO) reported a total of $21.6 million spent on researching prenatal opioid use and noted "a lack of guidance and coordination of efforts to address prenatal opioid use and NAS" in this population.[72] Recommendations for improvement include best practices for medication-assisted treatment and overcoming barriers to access as well as standardizing care of patients with NAS by establishing nationally accepted guidelines with medication regimens. National goals should align with those of the Healthy People 2020 Objective MICH-11.4, to increase abstinence from illicit drugs among pregnant women to 98.3 percent.[73] State programs may vary in fulfillment of this objective. In Florida, a Statewide Task Force on Prescription on Drug Abuse and Newborns was established to (1) provide individuals with information and skills to stop prescription drug abuse; (2) provide medical training, prenatal health care screenings, and methods to detect and respond to substance exposure as well

as provide services for the newborn and family after birth; (3) provide medical and/or psychotherapeutic care for substance dependencies; and (4) add NAS to the list of reportable diseases and events, which allows for government agencies to gather more data on the extent of NAS in Florida.[74]

Public health strategies in Florida, for example, include 32 Healthy Start Coalitions that assess the needs of newborns and their families and provide care coordination.[75] Additional funding is provided through the Targeted Outreach for Pregnant Women Act[14] to expand services to HIV-infected pregnant women in need of prenatal care. The goal of this program is to decrease both prenatal drug exposure and HIV infection to the newborn. Local and regional postpartum support programs should be in place to encourage compliance with treatment programs postdelivery. These programs present an opportunity to further develop parenting skills and encourage better care for the mother/infant dyad and are often supported public and/or government-funded programs.

Neonatal nurses are at the forefront in caring for infants with NAS and their mothers and play an important role in advocating for the patient and supporting the maternal–infant bonding process. The mother's postpartum period is characterized by vulnerability, guilt, and a deep-rooted wish to overcome drug addiction. Hence, the nurses' role is key in educating and empowering mothers in a nonjudgmental, family-centered environment and allowing for an optimal and smooth transition home.[76] Nurses are also in a position to guide policy and establish nursing protocols for more efficient care[77] and often serve as a liaison between health care providers, social services, and the family.

Because infants with NAS may be at high risk for behavioral problems, interventions at the societal level are paramount and should reinforce healthy parent–child attachment and interaction.[69] Several evidence-based in-home parenting intervention programs have been reported.[69,78] For instance, Suchman and colleagues[78] describe the importance of the emotional quality of the mother–child relationship to the child's psychological development and present an attachment-based parenting intervention for drug-dependent mothers. A recent realist systematic review of family-based intervention programs explored factors that impact a given program's effectiveness and found the following positive predictors: (1) opportunities for positive parent–child interactions, (2) supportive peer-to-peer relationships, (3) power of knowledge, and (4) engaging families using strategies that are responsive to their socioeconomic needs and offering services that match the client-lived experience.[79] Hence, local and regional early intervention efforts and long-term programs focused on the healthy and stable progression of the infant–caregiver relationship are essential in positively impacting the outcomes of NAS. The future of NAS care delivery needs to focus on better health for individuals and populations and a reduction in the cost of care.

There may be reason for optimism, however, among families (especially women) who remain committed to methadone treatment. Skinner and colleages[80] followed 130 families who participated in a clinical trial treatment program for 12 years. Women were more likely to be in long-term recovery than men and cited that their children and grandchildren were the most important focus of their lives. Issues that these families struggled with included unemployment (52 percent), incarceration (54 percent), residential mobility (89 percent), and death of the parent with addiction (25 percent, men more likely). Women in recovery were more likely to be employed, have continued education, and have less homelessness and fewer marital transitions. Interviews with the children (young adults by that time) demonstrated a significant reduction in the likelihood of developing a substance abuse disorder among the boys compared with the control group. Girls appeared to be more resilient than boys.[81] Although the authors did not report whether the children had been exposed prenatally to opiates, their results have important implications for children being cared for by a parent with a history of substance abuse.

CONCLUSION

Simply conducting this search and reviewing the literature uncovered an enormous gap in current knowledge. This population is being largely ignored by the scientific community, despite its unprecedented growth and presence in the NICU, which may reflect the marginalization that their mothers already experience in society. We still know little about long-term outcomes of infants with NAS. Parents of infants with NAS in the NICU may have questions about the long-term consequences of prenatal exposure to methadone, both asked and unasked. Although the signs of withdrawal will abate relatively quickly, parents should be aware of potential vision, motor, and behavioral/cognitive problems, as well as sleeping disturbances and ear infections so the infants can be followed closely and monitored by their pediatrician with appropriate referrals made. Furthermore, this knowledge may inspire parents to enroll their infants in an early intervention program to help optimize their outcomes. There are still many unanswered questions about epigenetic consequences, risk for child abuse/neglect, and risk of future substance abuse in this population.

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About the Authors

Denise J. Maguire, PhD, RN, CNL, is an associate professor of nursing at the University of South Florida College of Nursing. She has 20 years of experience in neonatal nursing, with expertise in caring for infants with neonatal abstinence syndrome and their mothers.

Susan Taylor, MSW, LCSW-C, CMA, is a psychotherapist (Women's Growth Center) and clinical researcher (Kennedy Krieger Institute) in Baltimore, Maryland. Her areas of expertise include family therapy

and attachment-based parent–child interventions with families experiencing homelessness and trauma.

Kathleen Armstrong, PhD, is a professor of pediatrics at the University of South Florida College of Medicine. She is the director of pediatric psychology at USF College of Medicine, with expertise in the care for children with developmental disabilities and behavioral health disorders.

Emily Shaffer-Hudkins, PhD, is an assistant professor at the University of South Florida College of Medicine. She is the assistant clinical director of Bay Area Early Steps at the USF College of Medicine Department of Pediatrics. Her expertise is in the care of children with developmental disabilities and behavioral health disorders.

Aaron M. Germain, MD, is an attending neonatologist and director of clinical practice at All Children's Hospital John Hopkins Medicine in St. Petersburg, Florida; instructor in pediatrics at Johns Hopkins University School of Medicine; and affiliate associate professor of pediatrics at University of South Florida College of Medicine. His area of expertise is management of infants with neonatal abstinence syndrome.

Sandra S. Brooks, MD, MPH, is an attending neonatologist at All Children's Hospital John Hopkins Medicine in St. Petersburg, Florida; instructor in pediatrics at Johns Hopkins University School of Medicine; and affiliate associate professor of pediatrics at University of South Florida College of Medicine. She is director of research for neonatology at All Children's Hospital John Hopkins Medicine, and her area of expertise is neonatal critical care.

Genieveve J. Cline, DNP, ARNP, NNP-BC, CNE, RN-BC, is an advanced practice research education specialist at All Children's Hospital John Hopkins Medicine in St. Petersburg, Florida.

Leah Clark is a medical student at the University of South Florida Morsani College of Medicine.

For further information, please contact:
Denise J. Maguire, PhD, RN, CNL
College of Nursing
University of South Florida
12901 Bruce B. Downs Blvd, MDC 22
Tampa, FL 33612
E-mail: dmaguire@health.usf.edu

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