



Neonatal abstinence syndrome

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Purpose of review

This review will discuss the complex nature of maternal and other factors that can affect the infant's display of neonatal abstinence syndrome (NAS), clinical presentation and treatment of NAS, and the impact of recent findings on future directions for research.

Recent findings

NAS has traditionally been described as a constellation of signs/symptoms displayed by the neonate upon withdrawal of gestational opioid exposure; however, recent research has advanced our understanding of this disorder. Other psychoactive substances, such as increasingly prescribed serotonin reuptake inhibitors, may produce an independent or synergistic discontinuation syndrome. The wide variability in NAS presentation has generated interest in the interplay of prenatal and postnatal environmental and genetic factors that may moderate or mediate its expression. Finally, recent advances in the treatment of opioid-dependent pregnant women have suggested buprenorphine as an alternative treatment to methadone during pregnancy, largely due to reduced NAS severity in exposed neonates.

Summary

Physicians should be aware of the complexity of the maternal, fetal, and infant factors that combine to create the infant's display of NAS, and incorporate these aspects into comprehensive assessment and care of the dyad. Further research regarding the pathophysiology and treatment of NAS is warranted.

Keywords

buprenorphine, drug-exposed neonate, maternal drug use, methadone, neonatal abstinence syndrome, serotonin reuptake inhibitor

INTRODUCTION

Prenatal exposure to licit and illicit psychoactive substances can produce physiological and/or neurobehavioral problems in the newborn that can originate problems with feeding, sleeping, movement, interactional capacity, and in general a poor neonatal adaptation process. The mechanisms that underlie these symptoms are likely to be multifactorial, unique to each pregnancy, and in general are poorly understood and, therefore, difficult to define, assess, and treat. This review will offer information regarding the difficulties in defining the pathophysiology of neonatal abstinence syndrome (NAS) and in explaining the variability in NAS expression among infants, a review of recent findings regarding NAS, and directions for future research.

Recent trends in the use/abuse of gestational substances that can cause a NAS in exposed infants have highlighted the need to advance our understanding of this disorder. The use and/or abuse of prescription opioid analgesics among pregnant women has increased [1], as has the availability of methadone through opioid treatment programs. Buprenorphine, a medication usually delivered by

community practitioners and primary care physicians, has been suggested as an alternative to methadone treatment during pregnancy [2^{••}], and has also been associated with increased diversion among opioid-dependent individuals [3,4]. Finally, there has been an increased use of serotonin reuptake inhibitors (SRIs) for the treatment of maternal depressive or anxiety disorders during pregnancy [5,6] that may produce neonatal neurobehavioral disturbances among exposed infants.

What is neonatal abstinence syndrome?

Neonatal withdrawal, or NAS, is an array of signs and neurobehaviors experienced by the newborn that

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KEY POINTS

- The infant's display of neonatal abstinence syndrome (NAS) is widely variable and likely to be affected by many factors that may include licit and illicit exposures, maternal physiology, epigenetic modifications, and genetic predisposition.
- There exists today a dearth of empirically derived evidence to support the use of any one specific evaluation or treatment strategy over another for the infant with NAS.
- Buprenorphine treatment for pregnant opioid-dependent women has been suggested as an alternative to methadone therapy for some women, necessitating further research on the effects of in-utero exposure on the fetus and infant.
- The risks/benefits of maintaining or discontinuing a psychoactive substance during pregnancy must be carefully weighed, on an individual basis, for each pregnant woman.
- Coordinated and comprehensive care of the dyad in the neonatal period is important for optimal infant and child development.

occur after abrupt discontinuation of gestational exposure to substances taken by the mother. The term NAS has been principally used to describe neonatal symptoms occurring after in-utero exposure to opioids such as heroin, methadone, and buprenorphine, and use or misuse of prescription opioid-containing medications such as hydrocodone (e.g., vicodin) or oxycodone (e.g., oxycontin). However, other substances may produce neurobehavioral dysregulation in the neonatal period consistent with an abstinence syndrome, including alcohol [7,8], benzodiazepines [9,10], nicotine [11], and psychiatric medications such as antidepressants [12] or antipsychotics [13]. Exposures such as cocaine [14], nicotine [15], SRIs [16], and polydrugs [17] can potentiate the infant's expression of opioid-induced NAS.

The distinctions between the postnatal effects of exposure to these various substances and their mechanisms, synergistic or independent, in affecting infants with signs of neurobehavioral dysregulation after birth are not clear. Traditionally, the symptoms of NAS were attributed only to the abrupt discontinuation of a substance, typically opioids, and the scales used today to measure NAS to any substance are, in general, those originally defined for the opioid-only exposed infant. Recently, more attention has been generated regarding the interplay of other genetic, epigenetic, and environmental factors that may serve to explain the variability in NAS presentation or the possibility of different

overlapping syndromes. For substance-dependent women, polysubstance use/abuse is the norm rather than the exception, and this population is additionally at higher risk for psychiatric comorbidities [18] that require medication therapy and coexist with other life factors, such as violence exposure, lack of prenatal care, poor nutrition, and so on, that can negatively impact the pregnancy, fetus, and neonate. So the substance-exposed infant with dysregulated neurobehaviors after birth may be having symptoms of withdrawal after chronic in-utero substance exposure(s), expressing effects of recent drug exposure(s), or effects of other factors, which may include epigenetic changes [19] or genetic factors [20] related to drug use/abuse. It is most likely that the substance-exposed infant's neonatal display is a unique combination of all of these, and therefore ascribing a NAS to one teratologic exposure may be inaccurate. It is, therefore, easy to comprehend the difficulties in defining the pathophysiology, symptomatology and optimal intervention strategies for infants that present with any NAS symptoms, the notable variability in expression of NAS in affected infants, and the potential for NAS to affect child development. Consider the case of SRI-only exposure, for example. A variety of symptoms have been reported after late pregnancy SRI exposure in approximately 30% of exposed infants [21–23]. These symptoms are similar to the signs seen in adult SRI discontinuation syndrome, and resemble the NAS seen in opioid-exposed infants. However, the clinical presentation is similar to an SRI toxicity syndrome resulting from overstimulation of the serotonergic system, with symptoms of the two being similar and perhaps overlapping [6,24]. There is also the issue of maternal depression effects on neonatal behaviors to consider [24]. Prenatal and early postnatal exposure to depressed mood has been associated with epigenetic changes in pregnant women and infants that may program behavior [25]. Finally, new evidence points to adverse child developmental outcomes in infants with as opposed to without, SRI-induced NAS at birth [5].

Research has pointed to a role of intrauterine programming of the infant's postnatal display stemming from prenatal exposure to intrauterine stressors such as drugs, stress, and poor nutrition, and has suggested that these intrauterine changes may affect neurobehavioral and possibly developmental outcomes [19]. This theory suggests that the fetus adapts to an unfavorable intrauterine environment by altering set points or physiologic systems as a response. The adaptations, which might be beneficial to the fetus *in utero*, may be maladaptive *ex utero*. Lester and Padbury [26] have described a model in which psychoactive drugs may act as

intrauterine stressors disrupting fetal–placental environment that initiate alterations in fetal programming and development that might produce alterations in the child’s behavior at any age [26[¶]]. Fetal developmental trajectories may be disrupted by different mechanisms, including epigenetic processes that alter gene expression, hypothalamic–pituitary–adrenal axis functioning, and genetic programming of fetal–placental development [27[¶]]. A similar mechanism has been suggested for NAS expression among opioid-exposed infants [28]. Variations in maternal vagal tone (activation or suppression) in response to methadone administration were correlated with more severe NAS expression in offspring. One explanatory theory is that the fetus’s physiologic responses to changes in maternal autonomic functioning caused by daily methadone may alter physiologic set points, which can moderate the severity of the maladaptive neurobehaviors generated by the discontinuation of opioids after delivery, which we interpret as more severe NAS expression. Epigenetic modifications, such as those that have been found to occur in children of women with depressed mood [25] or exposed to interpersonal violence during pregnancy [29], are further likely to have a role in the outcomes of substance-exposed children, as it is well accepted that substance-dependent women have a higher incidence of psychiatric comorbidity [18] and/or are frequently involved in abusive relationships during pregnancy [30].

Finally, there is evidence that postnatal experiences also shape physiological and behavioral protective/susceptibility factors [31]. In a recent study, infants with opioid-induced NAS required less pharmacotherapy for NAS and had shorter durations of hospital stay when placed with their mothers in the postnatal unit as compared with infants admitted to the neonatal unit. The authors suggest that the quieter environment and individualized maternal care may explain the results [32]. Thus, the presentation, severity, and/or quality of NAS symptoms are also affected by the care, pharmacologic and/or supportive, of the newborn during and after hospitalization, suggesting that prenatal experiences interact with early postnatal experiences in shaping developmental outcome. So, although symptoms of NAS among newborns prenatally exposed to opiates have been traditionally attributed to the discontinuation of opiates, on the basis of findings from the last decade, it is appropriate to consider that the symptoms of NAS are initiated by multiple factors, that each instance of NAS is likely to be a unique combination of factors that affect the infant’s display, and that interventions for the mother and the infant must be comprehensive and dyadic,

and extend well beyond pharmacologic treatment of cumulative symptoms.

Buprenorphine and neonatal abstinence syndrome

Methadone is a full mu-opioid agonist, and methadone maintenance has been the standard of care for the treatment of opioid dependency during pregnancy for the past 40 years in the United States. Buprenorphine is a partial mu-opioid agonist and kappa-opioid antagonist, which has been used previously in European treatment facilities [33–35]. Recently, a large, international, randomized clinical trial (the Maternal Opioid Treatment: Human Experimental Research, or MOTHER project) evaluating the safety/efficacy of buprenorphine treatment during pregnancy has suggested buprenorphine as an alternative therapy for this population of women [2[¶]]. Neonates exposed *in utero* to buprenorphine required less medication for the treatment of NAS, and had shorter duration of NAS treatment and fewer hospital days. Preliminary data also indicate that, at times of peak maternal levels of medication, buprenorphine-exposed fetuses appeared to have more optimal functioning in early [36] and late [36,37] gestation than methadone-exposed fetuses.

Although buprenorphine appears to provide some advantage for this population, principally due to improved neonatal outcomes, there are aspects of the use of this medication during pregnancy that warrant further exploration. Due to the partial agonist features of buprenorphine, methadone-treated women cannot transition to buprenorphine without undergoing some withdrawal, theoretically providing some risk to fetal or child development, particularly when viewed in light of the fetal origin theories of development that posit that unfavorable intrauterine environments can predispose individuals to poorer health outcomes. Current recommendations are that stable, methadone-maintained women who become pregnant should remain on methadone therapy; however, methadone itself may provide some risk to the fetus [38]. Additionally, buprenorphine is a medication that is more likely to be delivered by community health resources rather than center-based treatment programs. This may portend that pregnant drug-dependent women, who are a population with significant requirements for comprehensive care that includes obstetrics, mental health/psychiatry, drug treatment, and pediatrics, might be treated in outpatient settings in absence of these necessary interventions of comprehensive healthcare. In these cases, the risks associated with the medication *per se* may be borne by the fetus in absence of the

benefits provided by maternal access to obstetric and other care, as would be the case for methadone-treated women receiving medication only. Future research should focus on factors that might predict maternal response to methadone or buprenorphine to allow providers to tailor medical regimens to patients.

Clinical presentation

Neonatal symptoms of intrauterine exposures indicate dysfunction in autonomic regulation, state control capabilities, and sensory/motor functioning. Symptoms of NAS and severity of display are widely variable, both between infants and in the same infant over time. The specific symptoms associated with NAS include excessive high-pitched cry/irritability, sleep-wake disturbances, alterations in infant tone and movement (hyperactive primitive reflexes, hypertonicity, and tremors with resultant skin excoriations), feeding difficulties, gastrointestinal disturbances (vomiting and loose stools), autonomic dysfunction (sweating, sneezing, fever, nasal stuffiness, and yawning), and failure to thrive. The infant may have each as a feature of his NAS display, or have significant expression of one or several signs, and little to no expression of other signs during his course. Infants presenting with more pronounced symptoms of autonomic dysregulation (i.e., mottling, tachypnea, and fever) may have less clear signs and behaviors and hence may be more difficult to diagnose and to treat for several reasons, including the overlap with symptoms related to other neonatal differential diagnoses and a sometimes less pronounced response to pharmacotherapeutic treatments. Hypersensitivity to the internal (being tired, needing to burp or pass stool) or external (tactile or auditory stimuli) environment, or general hyposensitivity (poor response to stimuli, as demonstrated by the need to undress the infant to increase arousal before feeding) often contributes to the infant's NAS display, is not easily recognized, and is not directly responsive to medication therapy, but needs to be considered in each infant as part of NAS assessment and treatment.

Neonatal abstinence syndrome evaluation and pharmacologic treatment

NAS symptoms due to methadone usually start within the first 72 h of life. Although there are sparse data regarding the onset of NAS in buprenorphine-exposed neonates, new data point to a later onset of medically treatable NAS symptoms when compared with methadone-exposed infants [39]. Symptoms after prenatal exposure to SRIs generally occur within 2 days after birth [22] and are usually self-limiting and

can be managed with supportive care [40,41]. Infant withdrawal after benzodiazepine exposure can appear within a few days to 3 weeks after birth and last for several months [10]. There are several scoring mechanisms for NAS evaluation [42,43]; the most commonly used tool is the Finnegan Scoring System [44] or a variant thereof [45], developed to assess opioid-induced withdrawal. The general goal of NAS scoring is to quantify the severity of symptoms to determine the need for pharmacotherapeutic intervention. In general, these tools require a qualified, thorough, and ongoing evaluation of the infant, with scores applied at intervals of not more than every 4 h [46]. When the infant reaches a cutoff value, medication is begun. Opioid-containing medications (i.e., morphine, tincture of opium, or methadone) are indicated for opioid withdrawal in the infant [47], with newer agents under consideration, such as buprenorphine [48^a] and clonidine [49]. If the infant fails to adequately respond with de-escalation in behaviors with one medication at a maximal dose, a second is generally added. There is some variation in the use of second medication, and some commonly used medications are clonidine [50] and phenobarbital [51]. The goal of medication therapy is to reduce the NAS display in the infant to one that is manageable for the infant and his caretakers, allowing him to sleep, feed, and interact. This is generally recognized by a reduction in NAS scores to a defined value. When this goal is achieved and the infant is stabilized, the medication is gradually withdrawn, keeping the infant's symptomatology manageable.

Currently, there is a near-complete dearth of empiric evidence to support the use of one evaluation (i.e., weight-based medication scales, wherein medication is delivered on a mg/kg basis, vs. symptom-based medication scales, wherein medication dosing is driven by infant NAS expression) or treatment (i.e., morphine vs. methadone for opioid-induced NAS) strategy for NAS. Randomized trials that evaluate the efficacy of differing strategies for evaluating and treating NAS are needed, as there is considerable variability in the treatment of this disorder. Although opioid-containing medications are the mainstay of treatment for opioid-exposed infants, the safety and efficacy of other medications, such as clonidine and buprenorphine, for the first-line treatment of NAS should be explored. The role of other exposures, including licit exposures such as psychiatric medications, in the infant's display of NAS warrants further exploration, as multiple medication strategies employed for specific exposures or various combinations of exposures may be beneficial, but have not been explored. Infants with severe symptoms related to SRI-only exposure, for example, may require pharmacotherapy with

medications such as phenobarbital, but this has not been well defined [6].

Nonpharmacologic treatment of the infant with neonatal abstinence syndrome and the importance of dyadic care

Regardless of the need for medication for the treatment of NAS, all drug-exposed infants should receive individualized nonpharmacologic supportive management, as NAS *per se* is not defined solely by the need for medication therapy. Nonpharmacologic treatment includes a thorough evaluation of the infant's behaviors and responses to interactions and the environment to determine the need for specific soothing techniques (i.e., nonnutritive sucking, positioning/swaddling, and/or gentle movement) and/or environmental and interactive modifications in response to the specific needs of the infant and his mother or caregiver [52]. The spectrum of NAS can produce many feelings of guilt and anxiety in women and their families, which can lead to relapse to substance abuse, maternal–infant communication failures, and subsequent maladaptive developmental trajectories in the infant. Therefore, parental preparation for the expectation of infant neurobehavioral dysregulation in the immediate postnatal period and beyond is critical. Additionally, it is important to prepare the mother to identify her feelings about an infant with NAS and to practice the emotional responses that will allow her to support the infant's recovery. Sometimes it is impossible to determine whether infant behaviors after hospital discharge (i.e., crying, feeding, or sleeping problems) are due to subacute or resolving NAS, normal adaptation processes, maternal misinterpretation of the infant's communication patterns and/or her feelings of guilt and anxiety regarding her role in the infant's discomfort, or some combination of all. Frequently, mothers externalize these feelings and suggest formula changes or medications for the infant to alleviate their own concerns. In these cases, frequent maternal–infant assessments, reassurance, and support are important. Emerging research in resilience supports the notion that early experiences, such as positive caregiving during critical periods, can induce programming or reprogramming of key adaptive systems, such as stress response, that promote positive adaptation in young children that can result in healthier developmental, behavioral, and social–emotional trajectories [53].

Optimal care for the dyad in the perinatal period involves the coordinated efforts of drug treatment counselors and programs providing gender-specific care, obstetricians who provide prenatal and

postnatal care including contraceptive services, neonatologists providing care for the high-risk newborns, and pediatricians who will provide ongoing assessment of the infant, his mother/caregivers, and his environment. Ongoing psychological or psychiatric care for the mother with psychiatric problems is of extreme importance. Women who are not emotionally stable or not receiving appropriate medication and/or therapy are at high risk for relapse to drug use, neglect, or abuse of the child. Each specialty must communicate with and provide honest feedback to other providers and to the mother/caregiver. Adequate and accessible drug treatment with appropriate psychiatric care for the mother in the postnatal period is often difficult to find, but must be comprehensive in scope and include accommodations for the infant. The population of substance-exposed infants and their caregivers is a complex and vulnerable group that requires the extension of traditional boundaries by specialty for adequate care. Only through coordinated, comprehensive, and compassionate care can the difficulties created by in-utero substance exposure for the mother and the infant be overcome.

CONCLUSION

Clearly, NAS is a poorly understood cause of significant infant morbidity, one for which insufficient empirical evidence exists for optimal evaluation or treatment. Further research is needed to understand optimal treatment for the pregnant woman with addiction and/or psychiatric concerns. Studies are needed that identify the right 'fit' between pharmacological agents and maternal and neonatal factors to contribute to successful management of maternal illnesses while decreasing adverse neonatal outcomes [54]. More research is also needed to discern the true pathophysiology of NAS and the maternal, fetal, and infant factors that affect its presentation and severity, and studies are needed to distinguish withdrawal from symptoms related to drug effects or due to toxicity. More research is required to develop standardized assessment and treatment protocols that can be tailored to the infant's specific NAS display and drug, other substance, and medication exposures. More research is also needed to understand the long-term development of affected infants and to delineate appropriate therapeutic interventions. Only by comprehensively understanding this group of infants, who are at the highest risk for altered developmental and behavioral outcomes, can we provide them with optimal care and lessen the impact of this population on the healthcare system and society.

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Conflicts of interest

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There are no conflicts of interest.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 284).

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