Neonatal Abstinence Syndrome (NAS; Neonatal Withdrawal) — Pathophysiology and Treatment

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Neonatal abstinence syndrome is characterized by the onset of withdrawal symptoms in a neonate due to prenatal or postnatal exposure to illegal drugs or prescription drugs. The clinical presentation is usually dependent on the duration and time of exposure to the drug and not the drug itself. Meconium analysis or umbilical cord testing are the gold standard for the diagnosis of neonatal abstinence syndrome and for the confirmation of the offending drug. Pharmacologic treatment with opioids is indicated in any case of symptomatic neonatal abstinence syndrome that is caused by in-utero exposure to opiates.

Overview

Neonatal abstinence syndrome (NAS), also known as neonatal withdrawal syndrome, is a condition that is characterized by a collective of complex behavioral, psychological and physical symptoms that occur early after birth in a neonate who was exposed to illegal or prescription drugs during fetal life. Certain illegal drugs, such as cocaine and heroin, are known to cross the placenta and accumulate in the fetal tissues prenatally.

Withdrawal symptoms can happen within the first hours of life after birth in neonates who were exposed prenatally to illegal or prescription drugs. Another group of NAS neonates develop withdrawal symptoms due to intrapartum and postnatal exposure to fentanyl or morphine which are commonly used for pain control during labor.

Epidemiology of Neonatal Abstinence Syndrome

Approximately, one third of pregnant women in the United States are prescribed an opioid for several health indications during pregnancy. Additionally, many pregnant women can use illegal drugs during the pregnancy but the exact prevalence of this problem is unknown.

The use of illegal or prescription medications during pregnancy is associated with significant neonatal morbidity as the length of the hospital stay after delivery increased by about 7 times. The use of illegal drugs according to one recent epidemiological study of pregnant women of different age groups revealed very alarming statistics.

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<th>Percent</th>
<th>Age</th>
<th>Drug use</th>
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NAS has been estimated to occur in about **3.39** cases per 1000 hospital births per year.

NAS is more common after prenatal exposure to **opioids** and **heroin**, compared to exposure to other prescription medication or alcohol.

In-utero exposure to illicit drugs or maternal smoking habits is also different between different ethnicities and races. Pregnant white women are less likely to take illicit drugs while pregnant compared to black pregnant women. On the other hand, pregnant white women were found to have a higher incidence of smoking compared to other ethnicities.

### The prognosis of NAS

The prognosis of NAS **depends on whether the illicit drug has caused significant damage** to the brain or central nervous system of the child and on whether the pregnant woman has participated in some form of an addiction treatment plan during pregnancy.

Usually, addicted pregnant women who participate in addiction treatment programs during pregnancy have healthier offspring with a decreased likelihood of developing severe neurodevelopmental delays. Regardless, **behavioral problems in the offspring** of addicted or formerly addicted mothers are more common compared to the offspring of healthy mothers who are not taking any illegal or prescription medication.

Mortality is rarely affected in infants who are diagnosed with NAS unless the prenatal drug in question was an opioid. In that case, the risk of sudden infant death syndrome is usually increased, especially if the infant was exposed to methadone.

### Etiology of Neonatal Abstinence Syndrome

The most commonly implicated substances in prenatal exposure include **heroin** and **cocaine**. Additionally, women who are diagnosed with the major depressive disorder are more likely to be prescribed potent antidepressant medications that can cause NAS.

**Alcohol** use during pregnancy and **cigarette** smoking has also been associated with NAS. Alcohol use during pregnancy can also cause a distinctive disorder known as **fetal alcohol syndrome** that is associated with mental retardation.

Discontinuation of opioids after their acute use during delivery can also cause significant withdrawal symptoms in a newborn that can resemble NAS.

### Pathophysiology of Neonatal Abstinence Syndrome

Illegal drugs that influence the central nervous system are usually **lipophilic** and have a low molecular weight. These properties make it easy for such drugs to cross the placental barrier and to enter the fetal circulation. Due to the immaturity of the kidneys’ secretory function and the enzymatic pathways for drug metabolism in the fetus, the drug will **accumulate within the fetal tissues**. Once the fetus is delivered, the acute discontinuation of the trans-placental passage of the drugs that were accumulating during the prenatal period will **result in a withdrawal syndrome** or NAS.
Several body systems are affected by NAS including the central nervous system, the gastrointestinal system, and the respiratory system. The exact effects and symptoms of NAS are largely dependent on the type of drug involved, the dose, and the timing of exposure.

Opiates are very commonly associated with NAS in addition to low birth weight, prematurity and intrauterine growth restriction. The symptoms of NAS after opiate use, especially heroin, usually start after 24 hours after birth and peak within 48-72 hours.

Benzodiazepines that have long half-lives usually cause NAS in neonates aged between one and two weeks. Pregnant women who are addicted to heroin or other opiates are usually started on methadone due to its lower effects on the fetus. Methadone, however, still causes NAS but the presentation is usually delayed by one day compared to heroin. The symptoms and long-term consequences of methadone on the offspring are less severe compared to heroin, but the risk of sudden infant death syndrome is significantly increased.

Whenever available, buprenorphine should be used instead of methadone for the treatment of heroin addiction in a pregnant lady. Buprenorphine is associated with a shorter and less severe NAS compared to methadone.

In-utero exposure to cocaine usually results in behavior problems in the neonate once they develop NAS. Nicotine from cigarette smoking is associated with impaired neonatal habitation, orientation, and neonatal tremors. Exposure to antidepressants can cause seizures, tremors, hypertonia, and fever in the neonate.

Marijuana use during pregnancy is rarely associated with a severe NAS but few cases of severe NAS that are also associated with hypoglycemia have been reported in the offspring of heavy smokers of Marijuana.

Clinical Presentation of Neonatal Abstinence Syndrome

The clinical presentation of NAS has many common features regardless of the drug involved. The most important part in establishing the diagnosis of NAS is to confirm the maternal use of illegal drugs during pregnancy or the use of prescription drugs during pregnancy or intrapartum.

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<tr>
<th>GI</th>
<th>Neuro</th>
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<tbody>
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<td>Vomiting</td>
<td>Irritability</td>
<td>Fever</td>
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<td>Diarrhea</td>
<td>Jitteriness</td>
<td>Sweating</td>
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<td>Uncoordinated and constant suck</td>
<td>Shril cry</td>
<td>Tachycardia</td>
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<td>Poor weight gain</td>
<td>Hypertonia</td>
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The physical examination of the newborn should include the measurement of the baby’s weight, length, and head circumference to diagnose small for gestational age or microcephaly. The presence of major or minor congenital malformations should be documented and it should be noted whether the newborn is premature or full-term. Certain illicit drugs such as cocaine have been linked to premature delivery.

Central nervous system signs of NAS are usually shared between the different drugs and include a high-pitched cry, restlessness, hyperactive reflexes, tremors, hypertonia and
convulsions. Fever, sweating, and skin mottling can also be seen in NAS. Apnea or respiratory depression might be seen during the acute stage of opioid exposure. Poor feeding, hyperphagia, projectile vomiting and diarrhea are also commonly seen in newborns with NAS.

Special attention should be made towards NAS that might be caused by in-utero exposure to **alcohol**. These infants usually have dysmorphic features suggestive of fetal alcohol syndrome, seizures, tremors, and abdominal distention.

Maternal history of **lysergic acid** use during pregnancy is alarming as the risk of polydrug abuse is usually high. Excessive use of **caffeinated** products during pregnancy has also been associated with NAS. Such newborns usually develop symptoms after five days of birth. They complain of excessive crying, irritability and poor sleeping habits. Symptoms of caffeine withdrawal can last for months.

A scale system such as the **Finnegan scale** should be used to assess the likelihood of drug abuse during pregnancy and NAS. Such scale systems can also point towards the severity of NAS and whether pharmacological intervention is required or not.

### Diagnostic Workup for Neonatal Abstinence Syndrome

#### Blood and urine immunoassays

While blood and urine immunoassays can be used to identify the offending drug in NAS, meconium analysis is currently considered as the gold standard. Urine analysis is reliable in the identification of cocaine or opioid in-utero exposure but has several limitations. First, the test requires the use of adhesive collection bags for the collection of urine which can be troublesome and even allergic to the neonate. Second, urine tests usually have a limited time window for the detection of recent exposure compared to meconium analysis.

**Meconium analysis**

Meconium analysis has the advantage of detecting illicit drug exposure as early as within the first trimester. Additionally, the currently available immunoassays also allow for the identification of prescribed medications from meconium analysis.

**Umbilical cord testing**

The meconium is usually passed after several days of birth. In some cases, the diagnosis of NAS must be made before meconium becomes available. In such cases, umbilical cord testing should be used. Umbilical cord testing is at least as reliable as meconium analysis but has the advantage of being available immediately after birth.

**Hair analysis**

Infants who present later who might have been exposed to illicit drugs in-utero might benefit from hair analysis. A hair analysis test can be positive for narcotics, marijuana, or cocaine in-utero exposure up to 3 months after birth. Because fetal hair starts growing within the last trimester, in-utero exposure to drugs during the first and second trimester cannot be confirmed by neonatal hair testing.
Treatment of Neonatal Abstinence Syndrome

The treatment of NAS is **dependent on the severity of the symptoms and the drug involved**. Current literature has focused on in-utero opioid exposure, but similar conclusions can be made on any prenatal illicit drug exposure.

**Hospitalization**

Newborns should be admitted for close monitoring for the early detection of NAS whenever there is a risk of prenatal drug exposure. The duration of hospital admission should be based on the current literature about the typical onset time of NAS symptoms for the most likely involved drug. For example, if methadone exposure is suspected or confirmed, the neonate should stay at the hospital for up to one week to diagnose NAS.

**Pharmacologic treatment**

Neonates who develop vomiting and diarrhea without any significant other symptoms of NAS and who do not have any other possible cause of their gastrointestinal symptoms should be diagnosed with NAS and pharmacologic treatment should be started. Additionally, any newborn who develops more specific symptoms of drug withdrawal during the monitoring period should receive pharmacologic treatment.

Neonates who are exposed to opioids acutely, i.e., due to maternal use for pain control during labor, should receive naloxone if they have respiratory depression despite positive pressure ventilation. On the other hand, babies of women who are addicted to opioids or who have used opioids for a prolonged period for a clinical indication during pregnancy should not receive naloxone due to the increased risk of induced seizures.

If pharmacologic treatment is indicated in an opioid-caused NAS, the treatment of choice is either oral methadone or oral morphine sulfate. Both oral medications have been shown to be successful in weaning the neonate from the drug that caused his or her dependence and to shorten the hospital stay.

**References**


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