Neonatal Drug Withdrawal

Katherine Wang, MD, FAAP
Avera McKennan Children’s Hospital NICU

History

• Morphine has been used for pain for many years
• “Congenital morphinism” was not recognized as an entity until ~1950
• First reported case of successful treatment of seizures in an infant with congenital morphinism
• At that time it was renamed neonatal abstinence syndrome
• Methadone was introduced in 1964
• Initial misconception that use was not associated with withdrawal in neonates

Recent trends in Drug Use in Pregnancy

• The dramatic increase in rates of drug use in the last 10 years has brought neonatal drug withdrawal to its current prominence
• 2009 National Survey on Drug Use and Health
  • Showed dramatic increases in illicit drug use as well as nonmedical use of prescription medications (including pain relievers, tranquilizers, stimulants, and sedatives)
  • In pregnant women aged 15-44 yrs:
    • 4.5% reported recent use of illicit drugs
    • 11.9% reported binge or heavy drinking in first trimester
    • 15.3% report recent tobacco use

• In general, rates of drug use and smoking were lower among pregnant women compared with non-pregnant women
• EXCEPT for the age group 15-17 years
• Rates were higher in pregnant women
• Illicit drug use in pregnant women = 15.8% vs 13% in non-pregnancy women
• Smoking in pregnant women = 20.6% vs 13.9% in non-pregnant women

Drugs of Abuse

Cocaine and Stimulants

• Primarily looking at the effects of intrauterine use of cocaine and amphetamines
• In moms there is an increased risk of preterm birth, placental abruption, fetal distress, and intrauterine growth restriction (IUGR)
• No well defined “syndrome” in the neonate
• Some studies suggest may see irritability, hyperactivity, tremors, high-pitched cry, excessive sucking
• Theses are typically seen 2nd-3rd postnatal day
• There are reports of long-term effects on behavior, cognitive skills, and physical dexterity
Methamphetamines

- Given the recent epidemic of methamphetamine use, there has been a push for increased research.
- However, reliable results are often difficult to obtain due to poly-drug abuse.
  - The drug use can be at any time during the pregnancy so it is difficult to assess exposure at time of delivery.
- Withdrawal symptoms, if present, usually clear in 3-10 days.
  - Again, this picture is clouded by high likelihood of poly-drug abuse.
  - So may need pharmacologic treatment but may not be for the cocaine/methamphetamine.

Depressants and Sedatives

- Alcohol – one of the few substances that are known to have teratogenic effects in utero.
  - Can lead to Fetal Alcohol Syndrome.
    - Characteristic facies, growth retardation, mental retardation, hyperventilation, gross/fine motor delay, memory problems, learning problems, seizures.
  - Signs of withdrawal can begin 3-12 hours after birth.
- Concomitant use with narcotics can sometimes exacerbate symptoms of NAS.

Selective Serotonin Reuptake Inhibitors (SSRIs)

- Class of antidepressant medications.
  - Fluoxetine/Prozac, paroxetine/Paxil, sertraline/Zoloft, citalopram/Celexa, escitalopram/Lexapro.
  - Most commonly used antidepressants.
  - 1.8% of pregnant mothers use antidepressants.
  - Some studies link third trimester use to neonatal signs of withdrawal.
    - Can be seen in up to 30% of exposed neonates.
    - Symptoms typically seen in first 48 hours of life.
    - Some studies have linked maternal use in the last half of pregnancy with development of persistent pulmonary hypertension (PPHN) in the newborn.

Opiates and Narcotics

- This is the class of drugs which has been studied most.
  - Includes morphine, oxycodone, codeine, heroin, methadone, buprenorphine.
  - There has been significant increase in use of opiates over the last 20 years.
  - There has been large increase in prescriptions written by physicians.
  - Subsequently also an increase in the non-prescription use of narcotics.

- In utero opioid use is associated with 60-80% risk of NAS requiring pharmacologic treatment.
- Thus far, there is no correlation between maternal dose and risk of NAS in the infant.
- Symptoms can peak at 3-4 days or may not appear until 10-14 days of age.
  - Subacute withdrawal may persist for as long as 4-6 months.

Neonatal Abstinence Syndrome

Epidemiology
• The term NAS originally was coined to refer specifically to neonatal withdrawal from narcotics
• As research has expanded, it has also expanded
• Includes almost any substance of abuse which could result in withdrawal symptoms in a neonate
• Admissions for NAS have increased from 7 per 1000 NICU admission to 27 per 1000 admissions from 2004 to 2013

NAS Symptoms
• Can be varied based on type of opioid, and most recent use of drug before delivery
  • Synthetic opiates cross the placenta more easily than semisynthetic opiates
  • Presentation is also varied due to maternal metabolism, transfer of drug across the placenta, and placental metabolism
  • Again, also influenced by other potential concomitant drug use
  • If withdrawal is from heroin, typically will see symptoms within 24hrs of birth
  • If methadone, there is a delay, typically 24-72hrs of birth
  • Could be as late as 7 days
  • Opioid receptors are concentrated in the CNS and GI systems, thus the symptoms follow

• Neurologic Excitability Symptoms
  • Tremors
  • Irritability
  • Increased wakefulness
  • High-pitched crying
  • Increased muscle tone
  • Hyperactive deep tendon reflexes
  • Exaggerated Moro reflex
  • Seizures
  • Frequent yawning and sneezing

• Gastrointestinal Dysfunction Symptoms
  • Poor feeding
  • Uncoordinated and constant sucking
  • Vomiting
  • Diarrhea
  • Dehydration
  • Poor weight gain

• Metabolic/Vasomotor/Respiratory Symptoms
  • Sweating
  • Hyperthermia
  • Nasal flaring
  • Tachypnea
  • Nasal stuffiness, excessive secretions
  • Mottling
  • Temperature instability
Assessment

- Drug screening
  - Urine - helpful if maternal sample is obtained as well
    - only few days for window of detection, typically better yield if infant sample obtained from first void
  - Meconium - can detect substances from 20wks gestational age may get false negative results for marijuana
  - Combo of maternal urine and infant meconium usually yields best results
  - Natural opioids are easily detected but semisynthetic and synthetics are not
  - Can get false-positive results with amphetamines
  - Can also get false positives if soap or alcohol has been used for cleaning before collection

- There are (4-5) commonly available clinical assessment tools
  - Modified Finnegan
  - Lipsitz
  - Ostrea
  - Neonatal Withdrawal Inventory
  - Neonatal Narcotic Withdrawal Index
  - Modified Finnegan tool is the most widely used

The Neonatal Drug Withdrawal Scoring System (Lipsitz tool)

- This is a screening tool
- Shorter – only 11 items
- 77% sensitivity when using a value of >4 as indication of significant signs of withdrawal
- Infant should be monitored for first 72 hours of life
- Use a new scoring sheet for each date – make sure to include date and time of each score
- Infants are scored every 3 hours
- Do not wake a baby to score

Modified Finnegan's Neonatal Abstinence Scoring Tool

- Screening, monitoring, and management tool
- More complex – 31 items
- More resource intensive
- More potential for bias and subjectivity
- Initiate pharmacologic treatment if one score >12 or two scores ≥8

- Begin scoring 2-3hrs after birth
- Score q4hr after a feed; do not wake if infant sleeping
- If score ≥8, then increase scoring to q2hr
Special Population: Premature infants
- Neither has been validated in premature infants
- In general, premature infants do not typically manifest symptoms of NAS
- Overall less exposure to drug due to shorter gestation
- Possibly due to immaturity of brain receptors

Treatment

Monitoring
- Infants at high risk of NAS should be observed for at least 3 days prior to discharge
- Modified Finnegan tool is used to monitor progress
- May still manifest symptoms later, depending on presence/amount of other illicit substances
- Picture can be confused by breastfeeding
- If mom abruptly stops breastfeeding, can result in withdrawal symptoms

Non-pharmacologic therapy
- First line treatment is non-pharmacologic therapy – this is the cornerstone of treatment
- Ad lib feeds
  - make sure to monitor hydration and weight closely
  - May need increased caloric feeds
  - Breast milk if possible
  - AAP removed restrictions on breastfeeding for moms on any dose of methadone
  - While there is no research to support the association between abrupt cessation of breastfeeding
- Swaddling
- Low stimulation – dim lights, quiet (ear muffs if needed)
- Clothed cuddling
- Rocking/swaying
- Rooming in
- Cluster care to minimize handling
- Soft blankets/sheepskin if needed for skin excoriations
Pharmacologic Therapies

- Medical intervention is needed in 27-91% of infants with NAS
- Used when non-pharmacologic interventions fail to control symptoms, serious signs (ie, seizure) are observed, association with severe dehydration
- Delays in treatment are associated with higher morbidity and longer hospital stays
- Remember that opioid antagonists (Narcan) are contraindicated because they may precipitate seizures

- Morphine – most commonly used
  - Short half life so must be dosed every 3-4 hrs
  - Stable and easy to administer
  - Typically favored for inpatient treatment because of its short half life
  - Methadone
    - Most common alternative to morphine
    - Longer half life so sometimes titration can be a little more prolonged/difficult
  - Phenobarbital – drug of choice for non-opiate withdrawal
    - Also used as adjunct therapy in difficult opiate withdrawal cases
  - Clonidine – also typically used as adjunct therapy
    - Theoretical risk of hypotension and bradycardia

Treatment pearls

- If you are going to treat NAS, it is better to have an algorithm or protocol
- Studies have demonstrated decreased length of hospital stay and fewer treatment failures
- The more involved family is, the better the outcome
  - Moms who room in to help hold or cuddle provide soothing
  - Also more emotionally attached to infants

Follow-up

- Infant may or may not be discharged home on medication
  - Depends on reliability of follow-up
  - Community resources available
  - The level of comfort of primary care physician with NAS management
  - Social situation – ie, mom receiving treatment or not
- Follow-up is especially important in these patients as they may continue to display subacute symptoms for months
- For mom’s that are breastfeeding it is suggested that mom’s wean gradually from breast milk