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Opioids in Pregnancy and Neonatal Abstinence Syndrome

Megan W. Stover, MD and **Jonathan M. Davis, MD**

The Department of Obstetrics and Gynecology, Tufts Medical Center, Boston, MA 02111, USA

The Department of Pediatrics and the Tufts Clinical and Translational Science Institute, the Floating Hospital for Children at Tufts Medical Center, Boston, MA 02111, USA

Abstract

Opiate use in pregnancy has increased dramatically over the past decade and now represents a major public health problem. More women are using prescription opioids, illegal opioids, and opioid substitution therapy. These drugs are associated with numerous obstetrical complications including intrauterine growth restriction, placental abruption, preterm delivery, oligohydramnios, stillbirth, and maternal death. Neonatal complications are also significant, such as an increased risk of mortality as well as neonatal abstinence syndrome (NAS). NAS is a serious and highly variable condition characterized by central nervous system hyperirritability and autonomic nervous system dysfunction. The present review seeks to define current practices regarding the management of opiate dependence in pregnancy and care of the neonate with prenatal opiate exposure. Since genetic factors appear to be associated with the incidence and severity of NAS, opportunities for “personalized genomic medicine” and unique therapeutic interventions could be developed in the future.

Keywords

Newborn; opioids; pregnancy; neonatal abstinence syndrome

Prevalence of opiate use in pregnancy

Opiate use in the US has risen dramatically in recent years. In 2012, prescribers wrote 82.5 opioid prescriptions and 37.6 benzodiazepine prescriptions per 100 persons, with significant variation observed between states and regions.[1] Reproductive-aged women have been significantly impacted, with approximately 28% of privately-insured and 39% of Medicaid enrolled women age 15–44 years filling a prescription for an opioid medication each year between the years of 2008–2012.[2] Maternal opiate use in pregnancy has also increased from 1.19 per 1000 births in 2000 to 5.63 in 2009, with 60% of these mothers covered by Medicaid.[3] The growth of maternal opiate use is significantly higher than the incidence of

Correspondence: Jonathan M. Davis, MD, Department of Pediatrics, The Floating Hospital for Children at Tufts Medical Center, TMC 44, 800 Washington Street, Boston, MA, 02111 USA, jdavis@tuftsmedicalcenter.org.

NAS, reinforcing the concept that that not all opiate-exposed newborns exhibit signs of withdrawal.

Maternal agonist treatment for opiate-dependent pregnant women

Maternal opioid-substitution programs have been shown to improve pregnancy outcomes by reducing withdrawal episodes and high-risk drug-seeking behaviors as well as improving compliance with prenatal care. Most of these programs use methadone, which is a full mu-opioid agonist in use since the 1970s.[4] The pharmacokinetics of methadone in pregnant women differs from the non-pregnant population and changes significantly throughout pregnancy. For example, the half-life of methadone falls from an average of 22–24 hours in non-pregnant women to 8.1 hours in pregnant women.[5] Although methadone is often administered via daily dosing, split-dosing (every 12 hours) can also be used to account for increased clearance throughout pregnancy. Established drug-drug interactions exist between methadone and some anti-epileptics, rifampin, as well as several anti-retrovirals.

A newer alternative for opiate maintenance therapy in pregnancy is buprenorphine, a partial mu-opioid agonist approved in 2002 for medication-assisted treatment of opiate dependence.[6] Demonstrated advantages of buprenorphine over methadone include a diminished risk of overdose (due to low intrinsic receptor efficacy), less abrupt withdrawal, fewer drug interactions, and prescriptions that are more readily available.[7, 8] In addition, emerging data suggests that buprenorphine may result in a reduction in the incidence and severity of NAS compared to methadone.[9, 10] Disadvantages of buprenorphine include significant dropout rates, more difficult initiation of treatment, increased risk of drug diversion, possible hepatic side effects, and lack of long-term pregnancy and childhood safety data.[11, 12]

Medically supervised withdrawal from opioids is a third alternative to treatment of opioid dependence in pregnancy. However, this practice is discouraged by the American College of Obstetrics and Gynecology (ACOG) if opioid maintenance treatment is available.[12] While opiate maintenance treatment reduces many negative outcomes in pregnancy, it does not prevent the development of NAS. In utero exposure to opioids in pregnancy is associated with a 60–80% risk of NAS, therefore close monitoring for this complex condition is recommended in all neonates with exposure to opiates in utero.[10, 13–15]

Neonatal Abstinence Syndrome

NAS is a complex and highly variable condition characterized by central nervous system hyperirritability, autonomic nervous system dysfunction and gastrointestinal disturbances. Frequently observed features include excessive crying, irritability, poor sleep, increased muscle tone, tremors, excoriations of the skin from excessive movements, hyperthermia, loose stools, yawning, sweating, nasal stuffiness, and sneezing. In addition, seizures can occur in 2–11% of infants with NAS.[16,17] Significant variability in the timing and presentation of symptoms among opiate-exposed neonates has been observed. The reasons for such variability are poorly understood and likely multifactorial in nature. Possible etiologies include variability in maternal treatment, differences in placental opioid metabolism, pharmacogenomics, and neonatal comorbidities. In general, signs of NAS from

heroin occur at 24–48 hours of life (though dependent on last maternal dose), buprenorphine 36–60 hours of life, and methadone 48–72 hours of life (but up to 5 days due to the long half-life).[17] History of exposure to multiple substances (e.g. benzodiazepines, anti-depressants, cigarette smoking) may alter the onset of symptoms and increase the severity of NAS.[17–19] The specific pathophysiology of neonatal opioid withdrawal remains incompletely understood, although altered levels of neurotransmitters such as norepinephrine, dopamine, and serotonin are believed to play a significant role.[17, 20–22]

The AAP recommends 4 to 7 days of inpatient monitoring in neonates with known in utero exposure to opioids.[23] The most common mode of assessment is the Finnegan scoring system (often conducted with modifications). The scoring system is performed in a serial manner to help determine which neonates require pharmacologic therapy as well as dose escalation and weaning schedules. The traditional Finnegan scoring system consists of a 31-item scale used to assess the presence and severity of various NAS-associated symptoms and is performed every 3–4 hours.[16] Each evaluation should take into account behavior observed over the entire 3–4 hour period leading up to the assessment. Of note, the Finnegan scoring system is primarily designed for term infants and is associated with significant intra-observer variability.

Clarification of specific substance exposure is typically provided via urine or meconium screening of the newborn. Urine screening has the advantage of being easily performed, but is limited by the identification of only recent exposures. Meconium testing does have the advantage of screening for substance exposure extending back as far as 20 weeks gestation.

Treatment

The initial approach to NAS treatment is non-pharmacologic therapy which involves creating a gentle, soothing environment with minimal environmental stimulation for the neonate. Frequent hypercaloric feeds are typically administered to minimize hunger and promote growth. Maternal involvement in the infant's care is an important component of non-pharmacologic management.[16, 24]

Pharmacologic treatment is required in the majority of infants with NAS.[17] Several treatment approaches are used and no universal standard of care for NAS exists. In general, opioid compounds (morphine, methadone) are thought to be more efficacious than other drugs in the treatment of NAS. However, a Cochrane review published in 2005 concluded that there was insufficient evidence to support the use of one opioid over another.[25] Oral morphine is the most common first-line approach. An alternative to morphine is methadone, which has a longer (and more variable) half-life, requiring less frequent administration and titration. NAS treatment with sublingual buprenorphine is also being studied.[26] Doses of these medications are administered based on the weight of the infant, the maximum Finnegan score, or a combination of both. When symptoms remain inadequately controlled on the maximum dose of a first-line medication, second-line agents such as phenobarbital and clonidine are used. All of these pharmacologic agents can have significant concentrations of excipients such as alcohol and propylene glycol, which can also have

potential side effects. In general, weaning of pharmacologic treatment begins once symptoms are stable for 24–48 hours (10% of the maximum dose with each wean).

In the absence of maternal HIV, illicit drug use, or other contraindications, both the American Congress of Obstetrics and Gynecology (ACOG) and the AAP encourage breastfeeding in women in methadone or buprenorphine treatment programs.[12,23] Although the amounts of maternal drug in the breastmilk are quite low, breastfeeding has been associated with a decrease in the incidence and severity of NAS and should be encouraged if possible.[27]

Long-term follow-up

Adverse neurodevelopmental outcomes have been described in infants/children exposed in utero to opioids. However, there is a paucity of data regarding long-term neurodevelopmental function, as most studies are small and are unable to differentiate the effects of in utero exposures, postnatal treatments and environmental influences. In general, opioid exposed children more likely to have attention deficit disorders, disruptive behavior, and the need for comprehensive psychiatric referrals.[28, 29] Polydrug (including opiates) exposed children have smaller brains, thinner cortex, reduced cognitive ability and more behavioral problems.[30] Clearly more long-term follow-up is needed in regard to the effects of treatment (i.e. pharmacologic vs. non-pharmacologic) and the types of agents being utilized (i.e. opiates vs. benzodiazepines).

Predictive factors

Factors that influence the onset and severity of NAS remain incompletely understood. Potential variables include maternal opiate dose, the specific maintenance agent, concurrent use of other drugs (e.g. nicotine, benzodiazepines, selective serotonin reuptake inhibitors - SSRIs), gestational age, birth weight, and pharmacogenomics. Outcomes typically evaluated include treatment for NAS, peak NAS score, total dose required for treatment, duration of treatment, and length of hospitalization.

Maternal opiate dose

Several studies have examined the relationship between maternal methadone dose and the incidence and severity of NAS. However, a lack of consensus exists regarding whether higher doses are associated with more severe NAS.[18, 24, 31–37] A systematic literature review and meta-analysis performed by Cleary and colleagues suggested that maternal methadone dose does not correlate with the severity of NAS.[38]

Maternal maintenance agent

Although methadone remains the most studied treatment for opiate dependence in pregnancy, initial studies have suggested that neonates exposed to buprenorphine in utero may be less likely to develop NAS compared to methadone.[39] The Maternal Opioid Treatment: Human Experimental Research (MOTHER) project was a multicenter, randomized controlled trial designed to compare neonatal outcomes in pregnancies with exposure to buprenorphine versus methadone.[10] The authors found that buprenorphine was

associated with a significantly lower cumulative amount of morphine needed to treat NAS, shorter duration of treatment, and a 58% reduction in length of hospital stay. There were no differences between the buprenorphine and methadone groups with respect for the need for treatment, peak NAS score, or rate of serious maternal or neonatal adverse events. While the study suggested a less severe NAS course in neonates previously exposed to buprenorphine, a significantly higher dropout rate was observed in the buprenorphine group compared to the methadone group (33% vs 18%).

A Cochrane review published in 2013 concluded that existing data was insufficient to conclude whether methadone, buprenorphine, or slow-release morphine was superior for any relevant outcome.[40] Limited information is available regarding the combined formulation of buprenorphine and naloxone compared to buprenorphine or methadone alone with respect to important NAS outcomes. However, some studies suggest less need for treatment, lower peak NAS scores, and shorter length of hospitalization in neonates exposed to the combined formulation.[6, 41, 42]

Exposure to additional substances

Several studies have documented effects of combined exposure to opiates and other substances on the incidence and severity of NAS. In a secondary analysis of the MOTHER study, Kaltenbach and colleagues found that greater nicotine use at delivery (defined by number of cigarettes smoked in the preceding twenty-four hours prior to birth) was associated with higher rates of treatment for NAS as well as total dose of medication required for treatment.[18] However, maternal nicotine use did not correlate with higher peak NAS scores or duration of treatment. Although this study demonstrated that maternal SSRI use did not correlate with whether an infant received treatment for NAS, maternal SSRI use was associated with higher peak NAS scores and total dose of medication compared to those who did require treatment. This was in contrast with the work of Seligman and colleagues who did not find an association between general use of antidepressants and incidence or severity of NAS.[31] However, this study did find an association with concomitant exposure to benzodiazepines with longer length of treatment, which confirmed earlier work on the topic.[27, 31, 33, 43]

Gestational age

Preterm neonates have a lower rate of NAS than term infants.[13, 31, 35] Suggested mechanisms include immaturity of the fetal CNS, lower cumulative drug exposure, less placental transfer, delayed hepatic and placental metabolism, and less drug deposition secondary to lower fat content. Of note, assessment of NAS in preterm neonates is also limited by the lack of a validated scoring system specifically designed for this population.

Pharmacogenomics

Genetic factors are known to contribute to adults' risk of opiate addiction.[44] For example, single-nucleotide polymorphisms (SNPs) in the mu-opioid receptor (OPRM1), multidrug resistance (ABCB1), and catechol-O-methyltransferase (COMT) genes have been associated with variability in adult opioid dependence.[45–47] Initial studies of the OPRM1 and COMT genes indicated that neonates with in utero opiate exposure and the OPRM1 118A>G

AG/GG genotype were less likely to receive treatment for NAS than those with the AA genotype and had shortened length of hospitalization.[48] Neonates with the COMT 158A>G AG/GG genotype also had a shortened length of stay compared to neonates with the AA genotype and were less likely to be treated with 2 or more medications. Epigenetic changes (methylation of DNA which does not change the sequence, but does alter the function of the protein) of the OPRM1 promoter was also associated with a requirement of 2 or more medications for the treatment of NAS.[49] Ongoing work in the field is needed to confirm these initial findings.

Future Directions

As the number of pregnancies affected by maternal opiate dependence continues to rise, work is urgently needed to fill the significant knowledge gaps regarding optimal prenatal and postnatal care of opiate dependent mothers and neonates. Specific areas of focus should include:

1) Reducing opiate exposure in young women of child bearing age

2) Improving maternal treatment programs to reduce the incidence and severity of NAS,

3) Better identifying and treating high-risk neonates through personalized genomic medicine,

4) Developing evidence-based strategies for diagnosing, treating, and weaning neonates with NAS,

5) Increasing knowledge regarding the long-term effects of in utero opiate exposure and various neonatal treatment modalities

Clearly a multidisciplinary approach is needed with Obstetricians, Pediatricians, Nurses, Social Workers, Addiction Specialists, Law Enforcement, and Politicians all working together if we hope to significantly impact this important public health problem that is affecting our most vulnerable population.

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