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Neonatal abstinence syndrome: Pharmacologic strategies for the mother and infant

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ARTICLE INFO

Keywords:
Newborn
Opioids
Pregnancy
Neonatal abstinence syndrome

ABSTRACT

Opioid use in pregnancy has increased dramatically over the past decade. Since prenatal opioid use is associated with numerous obstetrical and neonatal complications, this now has become a major public health problem. In particular, *in utero* opioid exposure can result in neonatal abstinence syndrome (NAS) which is a serious condition characterized by central nervous system hyperirritability and autonomic nervous system dysfunction. The present review seeks to define current practices regarding the approach to the pregnant mother and neonate with prenatal opiate exposure. Although the cornerstone of prenatal management of opioid dependence is opioid maintenance therapy, the ideal agent has yet to be definitively established. Pharmacologic management of NAS is also highly variable and may include an opioid, barbiturate, and/or α-agonist. Genetic factors appear to be associated with the incidence and severity of NAS. Establishing pharmacogenetic risk factors for the development of NAS has the potential for creating opportunities for "personalized genomic medicine" and novel, individualized therapeutic interventions.

Prevalence of opiate use in pregnancy

Opiate use in the United States has risen dramatically in recent years. In 2012, health care professionals dispensed an average of 82.5 opioid prescriptions per 100 persons, with significant variation observed between states (up to 143 prescriptions per 100 persons in some southern states).[1] Women of reproductive age have been particularly impacted, with approximately 28% of privately insured and 39% of Medicaid-enrolled women aged 15–44 years filling a prescription for an opioid medication each year for 5 consecutive years.[2] Illicit use of opioids (especially heroin) has also increased significantly over this same time period. Consistent with these national trends, 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 insured through Medicaid.[3] In parallel, the burden of NAS has increased from 7 to 27 per 1000 NICU admissions between 2004 and 2013.[4] Factors

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http://dx.doi.org/10.1053/j.semperi.2015.12.007
0146-0005/

associated with worse NAS outcomes include maternal use of cigarettes and other psychotropic medications such as benzodiazepines and selective serotonin reuptake inhibitors (SSRIs).[5–8] The impact of these drug–drug interactions on the fetus and how they might influence NAS have not been fully characterized.

Maternal agonist treatment for opiate-dependent pregnant women

Substance abuse use during pregnancy is associated with fetal death, intrauterine growth retardation, placental insufficiency, postpartum hemorrhage, preeclampsia, and premature rupture of membranes.[9] Maternal opioid-substitution programs have been shown to improve pregnancy outcomes by minimizing the use of illicit drugs, reducing withdrawal and high-risk behaviors, and improving compliance with prenatal care.[10] The most common FDA-approved agents are methadone and buprenorphine. The pharmacokinetics of methadone in pregnant women differ from the nonpregnant population and change significantly throughout pregnancy. For example, the half-life of methadone falls from an average of 23 h in nonpregnant women to approximately 8 h in pregnant women.[11] The reduced half-life and increased volume of distribution in the pregnant woman often necessitates increased dosing as pregnancy progresses. Established drug–drug interactions exist between methadone and some antiepileptics, rifampin, and several antiretrovirals often used in the treatment of human immunodeficiency virus infection.

An alternative to methadone for maintenance therapy in pregnancy is buprenorphine, a partial mu-opioid agonist.[12] Demonstrated advantages of buprenorphine over methadone include a diminished risk of overdose (due to low intrinsic receptor efficacy), less abrupt withdrawal, fewer drug–drug interactions, and prescriptions that are easier to obtain.[13,14] In addition, buprenorphine has been associated with an overall reduction in the incidence and severity of NAS compared to methadone.[15,16] Disadvantages of buprenorphine include increased dropout rates, more difficult initiation of treatment, potential risk of drug diversion, less social support and counseling compared to conventional methadone maintenance programs, and lack of long-term pregnancy and childhood safety data.[17,18]

Neonatal abstinence syndrome

While opioid maintenance treatment during pregnancy improves maternal and infant outcomes, it does not prevent the development of NAS. *In utero* exposure to opioids in pregnancy is associated with a 60–80% risk of NAS requiring pharmacologic treatment.[4] NAS is a highly variable condition characterized by central nervous system hyperirritability, autonomic nervous system dysfunction, and gastrointestinal disturbances. Defining 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.[19,20] The specific pathophysiology of neonatal opioid withdrawal and the factors that influence severity remain incompletely understood. However, altered levels of neurotransmitters such as norepinephrine, dopamine, and serotonin are believed to play a significant role.[19,21–23] Conceptually, every infant with *in utero* opioid exposure resides along the continuum of signs of withdrawal. While some have mild, clinically insignificant signs, others have more severe disease that significantly impacts growth and development without treatment. Thus, the diagnosis of NAS is not made by the need for pharmacologic treatment, but instead by the cardinal signs of neonatal withdrawal.

The most common approach to monitoring infants for NAS is the Finnegan scoring instrument. The scoring is performed in a serial manner to help determine the following: (1) which neonates require pharmacologic therapy, (2) how dosing should be escalated, and (3) when weaning should occur. 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 h.[19] Each evaluation should take into account behavior observed over the entire 3–4 h period leading up to the assessment. A score of 7 on day 2 of life corresponds with the 95th percentile for nonexposed infants. A score of ≥ 8 is highly suggestive of NAS even in those denying opioid use during pregnancy.[24] The Finnegan scoring system is primarily designed for term infants, making use in both preterm and older (>30 days) infants nonstandardized. A significant limitation of the scoring system is the significant intraobserver variability that has been documented.[16] Thus, continuous staff education and gold standard evaluations are a critical piece of optimal NAS care.

Maternal history taken in a neutral and nonjudgmental fashion will identify the large majority of infants with *in utero* exposure. An adjunct to verbal history is typically provided via urine or meconium screening of the newborn. Hair and umbilical cord analyses have also been proposed, but their utility in medical management is limited.[25] Urine screening has the advantage of being easily performed but is limited by the identification of only recent exposures. Meconium testing has the advantage of screening for substance exposure extending back as far as 20 weeks gestation.

Treatment

The primary clinical concern for withdrawal is the impact upon growth and development. Secondary effects include impaired maternal bonding, infant discomfort, and seizures. The most effective treatment approaches are those that employ a systematic, multidisciplinary, and multimodal approach. Given the complexity of the disease and setting of treatment, a continuous process of quality improvement will lead to improved patient outcomes. Treatment is optimized when staff engage mothers with respect and acknowledge the struggles with substance abuse. Such mothers, who often experience other psychiatric and psychosocial comorbidities, are often sensitive to the perceived judgment of staff.