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Opioids in pregnancy and neonatal abstinence syndrome

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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 have been 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.

Prevalence of opiate use in pregnancy

Opiate use in the United States 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] Women of reproductive age have been significantly 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 between the years 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 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

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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 h in non-pregnant women to 8.1 h in pregnant women (American Academy of Pediatrics (AAP)).[5] Although methadone is often administered via daily dosing, split-dosing (every 12 h) 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 the 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 h of life (though dependent on last maternal dose), buprenorphine 36–60 h of life, and methadone 48–72 h of life (but up to 5 days due to the long half-life).[17] History of exposure to multiple substances (e.g., benzodiazepines, antidepressants, and 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 4–7 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 h.[16] Each evaluation should take into account behavior observed over the entire 3–4-h 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 and 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, and 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,