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The opioid epidemic and neonatal abstinence syndrome in the USA: a review of the continuum of care

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Abstract

As the prescription opioid epidemic grew in the USA, its impact extended to pregnant women and their infants. This review summarises how increasing rates of neonatal abstinence syndrome resulted in a need to improve care to pregnant women and opioid-exposed infants. We discuss the variations in care delivery with particular emphasis on screening at-risk mothers, scoring systems for neonatal drug withdrawal, type and duration of pharmacotherapy, and discharge safety.

INTRODUCTION

Prescription opioid use among pregnant mothers and its sequelae among their infants have emerged as a major public health concern. Prescription opioids, such as hydrocodone, were historically used to treat acute and cancer pain.¹ However, these analgesics are now being used to treat non-cancer-related pain,² and the increase in prescribing has extended to pregnant women.³ As use of opioids grew among pregnant women, so did the rates of neonatal opioid withdrawal known as neonatal abstinence syndrome (NAS) with reported increases in several countries including the USA, Canada, England and Australia.⁴ NAS most commonly occurs after opioid exposure (eg, opioid pain relievers, heroin, methadone);

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however, other drugs (eg, benzodiazepines, barbiturates, selective serotonin reuptake inhibitors (SSRIs)) have also been associated with the syndrome.⁵ This review focuses on evidence-based practices along the continuum of care for mothers and infants in the USA impacted by the opioid epidemic, beginning with screening in pregnancy and concluding with strategies to optimise postdischarge outcomes for infants with NAS.

EPIDEMIOLOGY

In the USA, opioid prescription rates quadrupled over the last decade.⁶ In 2012, an estimated 259 million prescriptions were written for an opioid in the USA which is equivalent to more than one prescription per adult each year.⁷ A recent study found that 29% of women enrolled in Tennessee Medicaid filled at least one prescription for an opioid analgesic during pregnancy and demonstrated a twofold increase in opioid use among pregnant women between 1995 and 2009.⁸ Among privately insured women across the USA, 14% filled at least one opioid prescription during pregnancy.³

Chronic use of prescription opioids in pregnancy is associated with NAS.^{9,10} NAS refers to a constellation of clinical signs from opioid withdrawal in the neonate ranging from jitteriness, weight loss and poor feeding to seizures.⁹ In the USA, the incidence of NAS increased nearly fivefold from 2000 to 2012 (figure 1), with an associated increase in healthcare expenditures from \$200 million to \$1.5 billion in 2012.^{11,12} By 2012, the US incidence of NAS reached 5.8 per 1000 hospital births, or an average of one infant born every 25 min with NAS in the country.¹² Several US states reported much higher increase than the national average, including Florida, which reported a 10-fold increase during that time.⁵

Several other countries have also reported increases in NAS. A retrospective analysis by Davies *et al* examined the prevalence of NAS in England, the USA, western Australia and Canada from 1997 to 2011. Although stable in England and Australia, NAS rates continue to rise in the USA and Canada to a rate of 3.6 and 5.1 per 1000 live births, respectively.⁴ This global increase in NAS coincides with opioid prescribing practices in pregnancy and demonstrates that NAS is an epidemic that affects infants across the world. Due to a significant demand on healthcare resources, improvements to current healthcare delivery systems are necessary to reduce the burden of NAS and improve the health-care delivery process for mothers and their babies.

MATERNAL AND PRENATAL CARE

Improving healthcare delivery to the maternal-infant dyad impacted by opioid use begins with improvements in screening and access to treatment for opioid use disorder (OUD). Pregnant women should be screened for drug and alcohol use during the first prenatal visit and throughout pregnancy if signs or symptoms suggestive of a substance use disorder (eg, sedation, intoxication, withdrawal) occur.¹³ Screening should consist of a non-judgemental conversation about past and current alcohol, illicit drug use and the non-medical use of prescription drugs with the assistance of a validated screening tool such as the '4P's'.^{13–16} Clinicians should emphasise to patients that disclosure of substance use is critical to

optimising outcomes for both mom and baby and that results will be kept confidential to the degree permissible by state law.¹³¹⁷

Drug testing with biological specimens such as urine, blood and saliva should only be used in conjunction with verbal or written screening and should not replace patient-provider discussions.¹³¹⁴ While universal drug testing may appear to compensate for a lack of patient disclosure, limitations associated with laboratory immunoassays may fail to capture the true prevalence of maternal drug use.¹⁸ Universal drug testing also has legal and ethical implications¹⁹ as many states have passed mandatory reporting laws and punitive legislation designed to criminalise women with positive drug tests during pregnancy.²⁰ Therefore, prior to performing any drug test during pregnancy, reasons for testing should be discussed in detail and informed consent should be obtained and any mandatory reporting requirements should be explained.¹⁷

ODU is defined in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as a 'problematic pattern of opioid use leading to clinically significant impairment or distress' exhibited by a series of clinical manifestations such as tolerance, withdrawal, recurrent opioid use resulting in a failure to fulfil obligations or an inability to reduce opioid use.²¹ Once OUD is identified, a thorough substance use history should be elicited including the type, route, frequency and length of opioid use as well as the use of other illicit drugs.²² Clinicians should discuss the implications of chronic opioid use on maternal and neonatal outcomes including an increased risk of preterm birth, intrauterine growth restriction and NAS.^{23–26} Prenatal care clinicians should also refer patients to addiction medicine, psychiatry and social services providers to begin counselling or behavioural therapy, identify resource needs and initiate medication-assisted treatment (MAT).²² The creation of a coordinated and interdisciplinary team of healthcare providers familiar with the treatment of substance use disorders and pregnancy is essential to maximise maternal and neonatal outcomes.²⁷

Patients not enrolled in drug treatment for OUD should be initiated on MAT with either methadone or buprenorphine.¹³ Stabilisation on MAT during pregnancy decreases maternal and neonatal morbidity by providing a steady opioid dose, minimising withdrawal and reducing high-risk behaviour such as intravenous drug use.²⁸ Group and/or individual counselling with clinicians trained in drug and alcohol behavioural therapy should accompany MAT initiation and is essential for successful drug treatment.^{29–31} Opioid withdrawal is associated with illicit drug use relapse in pregnancy.³²³³

Methadone, a full opioid receptor agonist, is the standard MAT for pregnant women.³⁴ However, in 2002, buprenorphine was approved for the treatment of OUD, and evaluations in pregnancy have established an equivalent safety profile compared with methadone.^{35–38} A partial opioid agonist, buprenorphine has important maternal and neonatal advantages compared with methadone.³⁹ With decreased risk of respiratory depression and overdose, buprenorphine inductions can occur in office-based settings with medication filled by an outpatient pharmacy. Buprenorphine has also been associated with improved neonatal outcomes. In a randomised clinical trial, infants exposed to buprenorphine had a shorter duration of treatment for NAS, required less morphine treatment and had a shorter hospital

length of stay compared with infants exposed methadone during pregnancy.³⁹⁴⁰ Despite these advantages, buprenorphine may not adequately alleviate cravings for women with severe addiction and is associated with an increased risk of diversion and treatment dropout.⁴¹⁴² As a result, the initiation of methadone versus buprenorphine during pregnancy should be individualised and involve a thorough discussion of the risks and benefits of each medication.¹³

High-risk behaviours are prevalent among pregnant women with OUD with over 60% of women reporting a history of intravenous drug use, and approximately 5% of women reporting a history of prostitution or exchange of sex for drugs.⁴³ As a result, all patients with a history of opioid abuse should receive screening for HIV, hepatitis C virus, gonorrhoea and chlamydia during the first prenatal visit and in the third trimester.²² Up to 95% of women with OUD also smoke tobacco during pregnancy and should receive smoking cessation counselling at each prenatal visit.^{44–48} Screening for co-occurring psychiatric disorders is essential as rates of anxiety and depression range from 65% to 73%.⁴⁹⁵⁰ Failure to identify and treat psychiatric disorders in pregnancy results in an increased risk of treatment discontinuation and postpartum depression.⁴⁹⁵¹⁵² Finally, all pregnant women with OUD should be screened for physical and sexual violence and referred to social work and/or social service organisations due to high rates of unstable housing, incarceration and inadequate resources.²⁷⁵³

NEONATAL DIAGNOSIS AND PRESENTATION

Communication between obstetric and paediatric clinicians is critical to ensure appropriate identification of infants at risk for NAS. When opioid exposure is unclear, toxicology samples should be collected at birth, if possible (cord), and shortly after arrival (urine/meconium) to aid in diagnosis and management. Timing of symptom presentation for NAS may vary depending on exposure type and timing; therefore, the American Academy of Pediatrics recommends monitoring opioid-exposed infants inpatient for 4–7 days after birth.⁵

Established scoring systems quantify clinical signs of NAS, jitteriness/tremors, poor feeding/weight loss, loose stools, diaphoresis, tachycardia, excoriations, excessive crying/irritability and seizures.⁵⁴ The most commonly used scoring tool for NAS is a modified Finnegan Scoring System. This 19-item scale, a modified version of the original created in 1975,⁵⁵ evaluates multiple signs related to NAS and helps guide treatment initiation and dosing.⁵⁴ These scoring tools are semiobjective systems that suffer from poor interoperator reliability, particularly in regard to neurological symptoms.⁵⁶ Quality improvement initiatives have shown an increase in validity and reliability of NAS scoring through enhanced staff education and scoring by two providers when scores indicate a possible need for pharmacotherapy.⁵⁷ Though these methods may be subject to error, literature shows that a standardised NAS scoring system is associated with shorter length of stay. A recent multicentre quality improvement initiative showed a reduction in length of stay and length of treatment when practices were standardised.⁵⁸⁵⁹

Risk and severity of NAS appears to be modified by opioid type and exposure to additional substances. A recent study found cumulative maternal opioid exposure for short-acting opioids (eg, hydrocodone), opioid type, maternal smoking and concomitant use of SSRIs increase an infant's risk for NAS.¹⁰ Once diagnosed with NAS, decisions must be made in terms of when to initiate treatment, non-pharmacological treatment versus medication, type of medication, weaning of given medication and plan for discharge.

NEONATAL MANAGEMENT

Initial non-pharmacological management of an infant experiencing acute opioid withdrawal often involves minimising stimulation, frequent small volume feeds and comforting when necessary.⁵ These techniques may be adequate treatment for some infants with NAS; however, pharmacological intervention is often necessary. Numerous medications have been used to treat NAS including tincture of opium and paregoric (neither of which are now recommended for treatment of NAS), morphine, methadone, barbituates and benzodiazepines.⁵ A large multisite quality improvement initiative by the Vermont Oxford Network found that morphine was the initial pharmacological choice in approximately 80% of infants with NAS.⁵⁸ Methadone and morphine are both recommended by the American Academy of Pediatrics for primary pharmacological treatment for NAS, though multiple studies have yet to prove one agent superior to the other.^{60,61} With the increase in pregnant women receiving replacement therapy with buprenorphine, several small studies investigated buprenorphine treatment in the infant. Kraft *et al*⁶² found a reduction in length of hospitalisation among infants receiving buprenorphine in comparison to opioid replacement therapy. Though this and other initial studies demonstrate promising results, larger studies are needed to assess the safety and efficacy of buprenorphine treatment for NAS before recommendations can be made. The two most commonly used adjunctive medications are phenobarbital and clonidine. Several studies yielded contradictory results in evaluating the efficacy of adjunctive treatment with phenobarbital and clonidine; however, a 2010 Cochrane Review of six studies concluded that addition of phenobarbital or clonidine may reduce duration of treatment for NAS.⁶³ These medications have also been compared directly to one another (in combination with morphine).⁶⁴ Surran *et al*⁶⁴ found that infants receiving adjunctive treatment with phenobarbital had a shorter duration of hospitalisation than those adjunctively treated with clonidine, notably, however, infants were discharged home on phenobarbital resulting in a much longer duration of treatment.

Location of treatment for infants with NAS appears to have an impact on outcomes for opioid-exposed infants. Recently, studies assessed the impact of 'rooming-in' with the mother on outcomes of opioid-exposed infants. This environment has potential advantages of maintaining the mother-infant dyad, less interruption of breast feeding and possibly less need for pharmacological treatment.^{65,66} Abrahams *et al*⁶⁵ found that opioid-exposed infants managed in the mother's room were less likely to need medical interventions and had a shorter duration of stay. A recent study from Dartmouth revealed that rooming-in with the mother can reduce use of morphine, length of stay and resultant expenditures among opioid-exposed infants.⁶⁷ Treatment of opioid-exposed infants in a postnatal ward or in the mother's room appears to have multiple advantages, but often, issues with resource allocation or hospital culture provide a barrier to this model. This may also impact

successful implementation of breast feeding, another important aspect of treatment in the opioid-exposed infant.

The literature suggests that breast feeding can be of therapeutic value in cases of NAS.⁶⁸ Breast feeding infants with opioid exposure can increase mother/infant bonding and can decrease symptoms and reduce duration of NAS.^{69,70} Prior to initiating breast feeding, a detailed maternal drug history must be obtained.

The Academy of Breastfeeding Medicine recommends breast feeding of these infants if the following criteria are met: participation in a substance abuse treatment programme, prenatal sobriety, abstinence from illicit drug use 90 days prior to delivery and maternal plans to continue involvement in the treatment programme in the postpartum period.⁷¹

While NAS treatment traditionally occurs in the inpatient setting, there is an emerging literature describing outpatient pharmacotherapy for infants with NAS. This literature suggests that combination inpatient and outpatient management is associated with a reduction in length of hospital stay;^{72–74} however, in some studies this led to an increase in overall length of treatment.⁷⁵ Ultimately, more literature is needed evaluating out-patient treatment for NAS, including the most effective support systems and comparing developmental outcomes of medication weans in both settings.

DISCHARGE PLANNING

Infants with NAS have an increased risk for adverse post-discharge outcomes, including hospital readmission, child abuse and neglect.^{76,77} The process for discharging an infant with NAS should begin before the infant is deemed suitable and involves interaction between parents, physicians, social workers and community services. Close follow-up with a primary care provider should be established prior to leaving the hospital. Safety of the infant is paramount, and this often includes coordination with child welfare systems.

Significant research gaps exist in understanding how best to improve postdischarge outcomes for infants with NAS. Future research should evaluate how treatment strategies, care coordination, home visitation and early intervention systems may positively impact outcomes for infants with NAS. Programmes advocating for continuation of maternal postpartum treatment as well the provision of case management services to the mother and infant could prove beneficial in improving outcomes outside of the hospital. Even as research emerges, it is clear that a standardised approach to discharge and early involvement from a multidisciplinary team can promote a safer transition, and communication between clinicians and community services remain at the centre of fostering a safe environment after discharge.

CONCLUSION

NAS has emerged as a serious public health issue across the globe in recent years. Standardising care through the continuum has been shown to improve outcomes. Still, large knowledge gaps exist throughout the care continuum highlighting the need for rigorous research to improve outcomes for women and infants impacted by opioid use.

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Figure 1.
US incidence of neonatal abstinence syndrome (NAS), 2000–2012.