Opioid Use in Pregnant Women and the Increase in Neonatal Abstinence Syndrome: What Is the Cost?

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OBJECTIVES: To investigate the length of stay for observation and treatment of neonatal abstinence syndrome (NAS), as well as the costs associated with the medical care of affected newborns.

METHODS: A retrospective chart review was conducted at Shands Hospital at the University of Florida, Gainesville, Florida. Data were collected for newborns diagnosed with NAS, including their hospital length of stay and the associated hospital charges, from December 1, 2008, to November 30, 2011.

RESULTS: One hundred sixty eligible newborns were included in the study. During the 3-year study period, hospital charges related to the diagnosis and treatment of NAS increased from $1.1 million per year to $1.8 million per year. Compared with the cost of caring for newborns without the risk of NAS, an additional $4.1 million was spent in the medical care of these newborns.

CONCLUSIONS: The costs associated with treating newborns with NAS are exponentially higher than the costs associated with newborns not affected with NAS. The societal costs associated with treatment of newborns with NAS, as well as infant symptomatology experienced with NAS, can be reduced by encouraging physicians to be proactive in screening for drug use, urging women who use chronic opioids to actively engage in family planning and contraception, and encouraging pregnant women who use opioids to seek substance treatment.

KEY WORDS: buprenorphine, methadone, NAS, opiate dependence, pregnancy

(J Addict Med 2015;9: 222–225)

The prevalence of opioid analgesics has increased dramatically since the 1990s. A study by Kellogg et al. (2011) reported a 5-fold increase in the use of chronic opioid therapy (mostly for chronic pain) during pregnancy between 1998 and 2009. Of infants born to these opioid-using mothers, 5.6% met the criteria for neonatal abstinence syndrome (NAS). Other studies reported incidence rates ranging from 55% to 94% (Harper et al., 1974; Ostrea et al., 1976; Madden et al., 1977; Fricker & Segal, 1978; Hudak & Tan, 2012). A nation-wide study by Patrick et al. (2012), conducted from 2000 to 2009, reports that the incidence of NAS among newborns increased from 1.20 (95% confidence interval, 1.04-1.37) to 3.39 (95% confidence interval, 3.12-3.67) per 1000 hospital births per year.

There are significant adverse effects associated with opioid use and/or withdrawal during pregnancy, including NAS, sudden infant death syndrome, impaired fetal growth, abruptio placentae, preterm labor, fetal distress, intrapartum passage of meconium, and fetal demise (Wagner et al., 1998; ACOG Committee Opinion No. 524, 2012). Neonatal abstinence syndrome comprises a complex of signs that manifest upon withdrawal of any chronically administered opioid and include tremors/jitteriness, sneezing, high-pitched cry, feeding/sucking problems, poor weight gain, irritability, disturbed sleep, hypertonia, hyperactive deep tendon reflexes, temperature instability, seizures, and skin irritation. Although NAS is not exclusively caused by opioid use during pregnancy, and can manifest with in utero exposure to alternative substances, opioids remain the most common cause of NAS. The standard treatment for opioid dependence during pregnancy is opioid agonist treatment (OAT) with methadone or buprenorphine (Butrans, Purdue Pharma L.P., Stamford, Connecticut), both of which can lead to NAS (Jones et al., 2010).

To date, there is little published literature documenting the financial costs incurred by the evaluation and treatment of neonates with NAS. A nation-wide study by Patrick et al. (2012) found that mean hospital charges for infants discharged with NAS increased from $39,400 to $53,400 for the years 2000 to 2009. State Medicaid programs were found to be the predominant payer for 78% of newborns born with NAS (Patrick et al., 2012). The higher cost of treating a newborn infant with NAS may be attributed to an increased length of stay in the hospital, especially when the infant requires pharmacologic treatment for NAS symptoms (Kelly et al., 2000). The goal of this study was to investigate the length of stay for observation and treatment of NAS, and to determine the hospital charges associated with the medical care of these neonates.

METHODS
A research study was conducted into the current epidemic of prescription drug abuse in the United States and,
specifically, the complications of maternal drug use during pregnancy. Approval for this research was granted by the University of Florida Institutional Review Board. This study was conducted at Shands Hospital at the University of Florida, Gainesville, Florida. Shands Hospital is a tertiary care center, and houses a level III neonatal intensive care unit.

A retrospective chart review examined hospital data from December 1, 2008, through November 30, 2011. The hospital database was used to identify newborn infants who had the following International Classification of Diseases, ninth edition, codes: NAS, opioid addiction, opioid dependence, narcotic addiction, narcotic abuse, narcotic dependence, and methadone dependence. The database was analyzed for newborn infant hospital length of stay and hospital charges during admission. A total of 327 charts were identified that met the search criteria.

Neonates were excluded from the study if (1) they were less than 36 weeks and 0 day of gestation; (2) they had any coexisting medical conditions that affected length of stay; (3) they developed sepsis during the index hospitalization; or (4) they were transferred to another hospital for continued treatment of NAS. These infants were excluded in an effort to determine the cost attributed solely to NAS. Of the 327 identified neonates, 160 were eligible and selected for the study. Data collected on these 160 newborn infants included need for treatment of NAS, length of hospital stay, and hospital charges. The data were stratified by year: year one (n = 40)—December 1, 2008, to November 30, 2009; year two (n = 57)—December 1, 2009, to November 30, 2010; and year three (n = 63)—December 1, 2010, to November 30, 2011.

Length of stay, incidence of pharmacologic treatment, cost of treatment, and hospital charges for infants with NAS were compared with average length of stay and hospital charges for infants born without risk for NAS during the same periods. The comparison group was selected randomly using the same inclusion criteria as the study group: greater than 36 weeks and 0 day of gestation with no coexisting medical conditions, and excluding any infant with a history of maternal drug use. All data collected were obtained from the same hospital database.

The typical length of stay for normal healthy newborn infants during the study period was 1 to 2 days, and average hospital charges for normal routine postpartum care of this group at Shands Hospital were $873 per day. The average length of stay for newborns diagnosed with NAS, but not requiring pharmacologic management, was approximately 5 days, an appropriate length of time required to determine the need for pharmacologic treatment on the basis of the half-life of the opioids used by the mother.

In year one, 40 infants were hospitalized for a total of 650 days (average 16.2 days per infant), at an average charge per infant of $1713 per day, $27,838 per hospital stay, and a cumulative charge of $1,113,519. Charges for 40 unexposed infants, on the basis of the most conservative estimates of 2 hospital days per infant at an average charge of $873 per infant-day, were estimated at $1746 per hospital stay, and a cumulative charge of $69,840; this represents a variance of $1,043,679.

In year two, 57 infants were hospitalized for a total of 861 days (average 15.1 days per infant), at a charge per infant of $1731 per day, $19,535 per hospital stay, and a cumulative charge of $1,490,447. Cumulative charges for 57 unexposed infants were estimated at $99,522; this represents a variance of $1,390,925.

In year three, 63 infants were hospitalized for a total of 965 days (average 15.3 days per infant), at a charge per infant of $1867 per day, $28,592 per hospital stay, and a cumulative charge of $1,801,323. The cumulative charges estimated for 63 unexposed infants would have been $109,998; this represents a variance of $1,691,325 (Fig. 1).

During the 3-year study period, the additional hospital stays required for monitoring of nonpharmacologically managed infants with NAS were associated with an average total expenditure of $4215 per infant, compared with a total expenditure of $1746 per infant without NAS, representing a variance of $2469 per infant. The average length of stay for pharmacologically managed infants with NAS was 23 days, at an average cost of $43,000 per infant; this corresponds to a variance of approximately $40,500 per pharmacologically managed infant compared with infants without NAS.

RESULTS

Of the 160 infants included in this study with in utero opioid exposure, 86 infants had documented methadone exposure, 9 infants had documented buprenorphine exposure, and 49 infants were exposed to short-acting opioids. We were unable to determine the type of opioid exposure (long- or short-acting) for the remaining 16 infants. In addition, 9 infants were exposed to other substances in utero (aside from the documented opioid used), as evidenced by chart documentation of positive maternal drug screening. These screens included 6 women positive for cocaine, 2 patients positive for marijuana, and 3 patients positive for alprazolam.

In year one, 25 of the 40 infants with NAS required treatment with morphine; in year two, 29 of the 57 infants with NAS required treatment with morphine; and in year three, 40 of the 63 infants with NAS required treatment with morphine. The remaining infants did not meet the criteria for pharmacologic intervention on the basis of Modified Finnegan Scale scoring.

The comparison group was selected randomly using the same criteria. The comparison group was selected randomly using the same criteria. The data collected and analyzed for newborn infants with NAS included the following:

- Need for pharmacologic treatment on the basis of the half-life of the opioids used by the mother.
- Average length of stay and hospital charges for newborns diagnosed with NAS versus other infants during the study period.

FIGURE 1. A comparison of hospital charges for newborns diagnosed with neonatal abstinence syndrome versus otherwise healthy newborns.
DISCUSSION

Neonatal abstinence syndrome is a predictable and treatable condition that follows chronic prenatal exposure to opioid agonists (Hudak & Tan, 2012). The standard of care for opioid dependence in pregnancy is OAT on the basis of data showing safety and improved birth outcomes (Ebner et al., 2007; Welle-Strand et al., 2013). Methadone and buprenorphine are the 2 most commonly used opioid agonists. Both are long-acting opioids that ameliorate opioid craving and diminish the compulsive and uncontrolled use of other opioids in pregnant women. Although the results of this study were not stratified to the type of opioids used during pregnancy, the majority of mothers were found to be using long-acting opioids, specifically methadone and buprenorphine. Maternal use of methadone, when compared with buprenorphine, is found to contribute to longer hospital stays, elevated recorded NAS scores, and higher doses of morphine for treating NAS (Jones et al., 2010). Nonpharmacologic treatment measures, such as maternal rooming-in and breastfeeding, have been shown to decrease the duration of the hospital stay and length of pharmacologic treatment for NAS (Velez et al., 2008; Logan et al., 2013), but were not included as controls for this study.

Polysubstance use, although not extracted from the database for this study, should be addressed because of its high prevalence in opioid users. Several alternative illicit or prescribed substances used during pregnancy can lead to neonatal withdrawal signs and symptoms, of which neonatal exposure to nicotine, cocaine, and selective serotonin reuptake inhibitors can lead to withdrawal signs that mimic NAS. Maternal nicotine use has been shown to cause neonatal excitability and hypertonicity in the postnatal period (Law et al., 2003). Neonatal withdrawal from cocaine can cause irritability, hyperactivity, tremors, and a high-pitched cry that peaks at 2 to 3 days and can last around 7 days (Hudak & Tan, 2012). The use of selective serotonin reuptake inhibitors in pregnancy has been shown to cause neonatal signs of persistent crying, irritability, jitteriness, restlessness, and hypertonicity that can last several days (Hudak & Tan, 2012).

Currently, universal drug screening and/or testing during pregnancy is not the standard of care, although it is recommended. Although only 9 mothers of those included in the study showed documentation of positive screening for additional substances (6 patients screening positive for cocaine use, 2 patients positive for marijuana use, and 3 patients positive for alprazolam use), in a population of opioid-dependent users, there is a possibility of additional unreported substance use. However, women enrolled in opioid maintenance programs in our area are typically required to undergo routine urine drug testing in order to continue receiving the prescribed opioid maintenance. Therefore, it is possible that the data presented are accurate. We were unable to determine the number of patients who were enrolled in maintenance programs versus the number of patients who were self-prescribing, as that information was not available in the chart reviews. In one study by Mayes & Carroll (1996), the effect of concomitant cocaine use by mothers on methadone-maintenance therapy led to higher initial NAS withdrawal scores, but did not increase the morphine dose required for treatment, or treatment duration in days. Gestational exposure to benzodiazepines, on the other hand, has been shown to increase the length of hospital stay in infants admitted with NAS (Seligman et al., 2008; Pritham et al., 2012; Logan et al., 2013). Exposure in utero to marijuana has not been shown to lead to signs of withdrawal in the postnatal period, but can result in long-term neurobehavioral outcomes (Campolongo et al., 2009).

Women who are pregnant and dependent on opioids are encouraged to begin treatment with methadone (in a licensed methadone-maintenance treatment program) or buprenorphine (in a licensed buprenorphine-maintenance program or in an office-based setting by a physician with a waiver to treat opioid-addicted patients). The management of pregnant mothers with opioid dependence, ideally, includes treatment at the lowest effective dose to avoid opioid cravings and relapse. Women with opioid dependence should receive prenatal care from obstetricians knowledgeable in the care and management of high-risk pregnancies. It is also important that the patient be personally involved in her treatment plan so that she can receive individual and/or group counseling and education while undergoing pharmacologic management, all of which have been shown to be effective in treating opioid dependence.

To reduce the incidence of NAS in newborns, the prevalence of drug use among women of reproductive age must be decreased. Physicians must be more diligent in utilizing nonopioid (eg, nonsteroidal anti-inflammatory drugs) and nonpharmacologic treatment (eg, physical and rehabilitative therapies, interventional techniques, and complementary and alternative therapies) for chronic pain. Before initiating treatment with opioids, physicians should exhaust other reasonable options, obtain appropriate pain management or other specialty consultations, stratify risk (eg, current or past history of substance use disorders or psychiatric comorbidities), and, perhaps, perform drug testing (DuPont, et al., 2009; Reisfield et al., 2010). Ongoing monitoring for the development of other opioid-related problems is essential. Patients who require chronic opioid medications, such as patients in OAT programs, should be educated on the adverse effects to the fetus, including risks for NAS, preterm labor, and small-for-gestational-age infants. Obstetricians should consider universal drug abuse screening as part of routine prenatal care. In fact, the American College of Obstetricians and Gynecologists (2012) has recently published Committee Opinion #524, which states that screening for substance abuse should be part of a complete obstetric care plan. Patients who screen positive for illicit drugs or unauthorized prescription medications should be educated on the associated maternal and fetal risks, and referred for substance abuse treatment. Approximately 50% of patients who initially refused drug treatment eventually accepted it after a latent period during which they often tried their own solutions.

The American Society of Addiction Medicine (ASAM, 2011) released a public policy statement in 2011 pertaining to drug use in pregnancy. Recommendations included the following:

- Education of the public regarding the effects of alcohol and other drugs during pregnancy
- Prenatal education about alcohol and other drugs for all pregnant women as part of adequate prenatal care
• Public prevention programs targeted at educating society at large on the dangers of alcohol and other drug use during pregnancy
• Appropriate education of health care professionals regarding pregnancy planning, preconception planning, and perinatal care
• Early intervention programs designed to reach parents who may manifest risky or harmful use of drugs
• Universal screening tools for at-risk women

The ASAM recommends that (1) pregnant women be given the highest priority for admission to available treatment facilities, (2) all women of reproductive age should receive basic counseling regarding pregnancy prevention and planning, and (3) women of reproductive age receiving treatment for a substance use disorder should receive counseling regarding the effects of drugs on reproductive function.

CONCLUSIONS

This study demonstrates the enormous financial cost of treating newborns with NAS. At our institution, costs associated with treating women with NAS are exponentially higher than the costs associated with infants not affected. During a recent 3-year period, hospital charges for treatment of NAS increased from $1.1 million per year to $1.8 million per year. If the burden of the societal costs of treating NAS is to be reduced, and the symptomatology experienced by infants with NAS diminished, definitive steps will need to involve strong proactive measures, such as screening pregnant women for drug use, offering substance treatment for those who need it, and encouraging women on chronic opioid therapy for pain and those receiving OAT for dependence to actively engage in family planning and contraception. In addition, implementing standardized management protocols at birth may lead to greater efficiency and effectiveness in the treatment of NAS, and, subsequently, could reduce both societal costs and the infant symptomatology attributed to NAS. Further research investigating outcomes of methadone maintenance versus buprenorphine maintenance in pregnancy is needed, as some preliminary data suggest improved fetal outcomes with buprenorphine in pregnancy.

REFERENCES
