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Received: 06 April 2017; Accepted: 01 August 2017; Published: 08 August 2017

Abstract

Objective: To investigate the in-hospital length of stay and costs associated with observation and treatment of newborns affected by neonatal abstinence syndrome (NAS).

Methods: A retrospective chart review was conducted at University of Florida Health in Gainesville, FL with Institutional Review Board approval. Data was collected from January 1, 2012 to December 31, 2015. We investigated the in-hospital length of stay, hospital charges associated with observation and treatment of newborns affected by NAS, type of treatment required (e.g. pharmacologic, supportive), and type of opioid exposure during pregnancy.

Results: Three hundred twenty-three eligible newborns were included in the study. The average length of stay for newborns diagnosed with NAS who required only supportive measures was 4.6 days. The average length of stay for newborns diagnosed with NAS requiring pharmacologic management was 14.4 days. Over the four-year study period, hospital charges related to the diagnosis and treatment of NAS increased from $1.7 million in 2012 to $2.5 million in 2015. The percentage of newborns diagnosed with NAS requiring pharmacologic management increased from 53.8% in 2012 to 64.5% in 2015.

Conclusions: The incidence of NAS, hospital charges, and length of stay all increased over the length of the study. The length of stay was less in the infants exposed to buprenorphine in utero versus methadone.

Introduction

One of the most common causes of Neonatal Abstinence Syndrome (NAS) is in utero exposure to opioids, either pharmaceutical (e.g. oxycodone) or non-pharmaceutical opioids (e.g. heroin) [1]. The prevalence of nonmedical prescription opioid use as well as diagnosed prescription opioid disorder is increasing. A study, using 2012 through 2013 National Epidemiological Survey on Alcohol and Related Conditions data, reported a 12-month prevalence for nonmedical use of opioids as 4.1%. This represents more than double the 1.8% prevalence found in 2001 through 2002 [2]. Saha, et al. (2016) also reports that past 12-month prevalence of diagnosed opioid use disorder more than doubled from 0.4% in 2001-2002 to 0.9% by 2012-2013 [2].

Patrick et al. (2012) reported that the prevalence of antepartum maternal opioid use increased significantly from 1.19 cases in 2000 to 5.6 per 1000 hospital live births in 2009 [1]. Desai, et al. (2014) reported that approximately one fifth of pregnant women enrolled in Medicaid between 2000 and 2007 filled a prescription opioid [3]. Pregnant women are also known to abuse opioid medications from medical and non-medical sources [4]. Roughly one percent of pregnant women report nonmedical use of opioid-containing pain medications [5]. Emergency department visits related to misuse or abuse of opioid pain relievers among women more than doubled between 2004 and 2010 [6].

The mainstay of treatment for chronic opioid use or opioid dependence in pregnancy is opioid agonist treatment (OAT) with methadone or buprenorphine [7,8]. OAT has the positive effects of increasing compliance with prenatal care, decreasing opioid cravings, and decreasing symptoms of opioid withdrawal. However, chronic, pharmaceutical and/or non-pharmaceutical opioid use in pregnancy, including OAT, is known to cause NAS, a treatable but serious medical condition of the neonate manifested by tremors/jitteriness, sneezing, high-pitched cry, feeding/sucking problems, poor weight gain, irritability, disturbed sleep, hyperpnea, hypertensive deep tendon reflexes, temperature instability, seizures, and skin irritation [9]. In 2012 it was reported that the number of hospital discharges of newborns diagnosed with NAS in Florida increased more than 10-fold (from 0.4 to 4.4 discharges per 1,000 live births) from 1995 to 2008, which was higher than observed nationally [10].

NAS cases may be attributed to medical sources alone or in combination with non-pharmaceutical opioid use. A study of three Florida health centers in 2010 through 2011 found that 99.6% of NAS mothers were using pharmaceutical opioids while 0.8% were using heroin, which suggests that Florida NAS cases tend to result from pharmaceutical opioid use [3]. However, it should be noted that opioid usage trends change quickly. Baseline data from Roussos-Ross, et al. (2015) showed an increasing incidence of NAS, in-hospital LOS, and cost of treating affected newborns from 2008 to 2011 [9]. Given the changes in opioid policy (e.g., the implementation of a prescription drug monitoring program, the tightening of pain clinic regulations, and the designation of NAS as a mandatory reportable condition) and epidemiology in Florida from 2011 to 2015 [3,11-13], we examined the incidence, in-hospital length of stay (LOS), substances of exposure, and cost of treating NAS infants at a Florida academic health science center from January 1, 2012 through December 31, 2015.

Materials and Methods

A retrospective chart review was conducted at University of Florida Health Shands Hospital (“UF Health”), a tertiary care center, at the University of Florida in Gainesville, Florida with IRB approval. Data, including LOS, hospital charges associated with treatment, type of treatment required (e.g. pharmacologic, supportive), and maternal pharmaceutical OAT opioids used, were collected for newborns diagnosed with NAS after birth at UF Health from January 1, 2012 to December 31, 2015. Newborns from outside hospitals and transferred to UF Health within five days of birth were also included.

The hospital database was used to identify neonates and pregnant women with the following codes from the International Classification of Diseases, ninth revision [14], and/or International Classification of Diseases, tenth revision [15]:

- Drug withdrawal syndrome in newborn (ICD-9 CM 779.5)
• Narcotics affecting fetus or newborn via placenta or breastmilk (ICD-9-CM Code 760.72)
• Drug withdrawal (ICD-9-CM Code 292.0)
• Newborn (suspected to be) affected by maternal use of drugs of addiction (ICD-10-CM Code P04.49)
• Neonatal withdrawal symptoms from maternal use of drugs of addiction (ICD-10-CM Code P96.1)

A total of 436 charts were identified and accessed for analysis based on the search criteria.

Newborns were excluded from the study if they (1) were preterm (less than 36 weeks and 0 days of gestation); (2) had co-existing conditions that affected in-hospital LOS independent of NAS, such as congenital malformations; or (3) they developed sepsis during the initial hospitalization.

Non-parametric statistical analysis was performed using SPSS software to identify relationships and assess significance of the variables over the length of our study period. These variables included LOS, hospital charges associated with treatment, and substances of exposure, particularly buprenorphine and methadone. A priori significance was set at 0.05.

Results

Of the 436 subjects initially identified for the study, 340 were delivered at UF Health, and 96 were delivered elsewhere and transferred to UF Health within 5 days of delivery. A total of 324 subjects met the criteria for eligibility. Data were stratified by year: 2012 (n=66); 2013 (n=94); 2014 (n=71); and 2015 (n=93). Of the 324 newborns included in this study, 149 had documented in utero exposure to methadone, 59 had documented in utero exposure to buprenorphine, and 3 had documented in utero exposure to both methadone and buprenorphine. For 26 neonates, the opioid of exposure was not specified. The remaining 90 subjects were exposed in utero to various short-acting opioids.

Table 1 illustrates LOS and hospital charge data for each year of the study.

Neonates diagnosed with NAS requiring pharmacologic intervention with morphine were: in 2012, 35 of 66; in 2013, 42 of 94; in 2014, 43 of 71; and in 2015, 60 of 93, which represents a total of 180 neonates requiring pharmacologic care during the study period (Figure 1). Pharmacologic intervention via treatment with morphine was not required for the remaining 144 infants based on Modified Finnegan Scale scoring [16].

Over the course of the study, the cost of treatment for infants diagnosed with NAS receiving non-pharmacologic treatment and observation totaled $1,356,505, with an average of $9,486 per infant. Cumulative charges for treatment of neonates diagnosed with NAS treated pharmacologically totaled $6,895,793 over the four-year study period, at an average of $38,310 per infant.

A total of 51 infants were hospitalized for NAS following in utero exposure solely to buprenorphine, for a cumulative cost of treatment of $1,108,497. A total of 113 infants were hospitalized with a diagnosis of NAS following in utero exposure solely to methadone, for a cumulative cost of treatment of $3,260,592. Average cost associated with treatment of newborns diagnosed with NAS following in utero exposure to buprenorphine was $21,735 per infant, compared to an average cost of treatment for newborns exposed in utero to methadone of $28,855 per infant. A p-value of 0.119 was calculated for this relationship, indicating no statistical significance. Average in-hospital LOS for neonates exposed in utero to buprenorphine was 8.8 days, compared to an average LOS of 12.3 days for neonates exposed in utero to methadone. This was noted to be a statistically significant difference in LOS, p-value 0.034.

NAS-diagnosed newborns exposed in utero to buprenorphine required an average LOS of 3.5 days fewer than those exposed to methadone (Figure 2). Average total cost of treatment of newborns exposed to buprenorphine in utero was $7,120 less than that calculated for newborns exposed to methadone. The distribution of methadone-exposed infants diagnosed with NAS indicate longer LOS intervals compared to those exposed to buprenorphine in utero (Figure 3).

Discussion

Societal costs associated with NAS are well-documented and acknowledged. A national study determined a 35% increase from 2000-2009 in costs per infant diagnosed with NAS [1]. The standard of care for pregnant women with opioid dependence is OAT, which

### Table 1: Summary of Length of Stay and Hospital Charges Per Study Year.

<table>
<thead>
<tr>
<th>Year</th>
<th># Infants Meeting Criteria</th>
<th>Total Days in Hospital</th>
<th>Average LOS</th>
<th>Cumulative Charges ($)</th>
<th>Average Charges per Infant ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>66</td>
<td>752</td>
<td>11.4</td>
<td>1,736,403.69</td>
<td>26,309.15</td>
</tr>
<tr>
<td>2013</td>
<td>94</td>
<td>743</td>
<td>7.9</td>
<td>1,639,706.70</td>
<td>17,443.69</td>
</tr>
<tr>
<td>2014</td>
<td>71</td>
<td>768</td>
<td>10.8</td>
<td>2,267,774.01</td>
<td>31,940.48</td>
</tr>
<tr>
<td>2015</td>
<td>93</td>
<td>974</td>
<td>10.5</td>
<td>2,541,418.60</td>
<td>27,327.08</td>
</tr>
</tbody>
</table>

most frequently utilizes either buprenorphine or methadone as opioid
agonists to minimize use of other opioids by pregnant women.
Reportedly, the use of buprenorphine has resulted in shorter hospital
stays as well as smaller amounts of morphine required for effective
treatment than when methadone was utilized [17]. Our analysis
showed a similar result for the study period and population, indicating
that buprenorphine treatment is associated with shorter stays compared
to methadone.

Recommendations for the use of buprenorphine by pregnant
women as first-line treatment rather than methadone are being
considered [18,19]. Based on our data, adopting buprenorphine as
first-line treatment may shorten LOS and decrease the cost associated
with the treatment of NAS. Regardless of which long-acting opioid is
used, it is critical to increase access to substance treatment facilities
and continue treatment with long-acting opioids to prevent maternal
relapse. The American College of Obstetricians and Gynecologists and
the American Society of Addiction Medicine continues to recommend
that pregnant women stay on opioid maintenance treatment throughout
pregnancy to decrease the risks to mother and fetus associated with
opioid cravings and withdrawal [7,8].

Notably, many infants exposed in utero to pharmaceutical or non-
pharmaceutical opioids are exposed to additional non-opioid substances
as well, such as alcohol, tobacco products, or illicit substances. In
our population, self-reported drug use during pregnancy or positive
drug screening was documented in 59 cases (11 amphetamine use, 27
cocaine use, and 19 marijuana use). It is important to note that the
exposure to these substances and others may have contributed to the
length of stay, although these drugs typically do not result in prolonged
NAS symptomatology.

Prevention of NAS begins with minimizing the use of opioids
by women of reproductive age. Physicians should be thoughtful
and cautious when prescribing opioids to this particular population,
and should educate women on the potentially negative effects to
the fetus. Discussions regarding contraceptive options should also
be emphasized, especially the benefits of long-acting reversible
contraceptives (LARC).

In October 2011, Florida implemented a prescription drug
monitoring program (PDMP) to centralize patient controlled substance
dispensing histories [20]. However, it is unclear as to the extent to
which Obstetricians and Gynecologists (OBGYNs) are registered and
utilizing the voluntary Florida PDMP implemented during our study
period. Preliminary results from a Florida PDMP user survey indicate
that perceived utility of the PDMP may be lower among OBGYNs than
family practitioners (unpublished). In 2013, the Statewide Task Force
on Prescription Drug Abuse and Newborns highlighted the need for
Florida to use federal, state, and local funds to properly prevent and
treat NAS [21]. Recommendations included prevention programs to
provide awareness of the risks of opioid use in pregnancy, screening
of pregnant women for potential drug abuse, and appropriate treatment
in a substance abuse program. As of June 2014, NAS is a mandatory
reportable condition in Florida [4].

The cost of treating newborns affected by NAS over the four-year
study period rose from $1.7 million to $2.5 million, and the average
LOS showed no marked improvement. This trend is consistent with the
trend noted from 2008-2011, with costs of treating newborns affected
by NAS rising from $1.1 million to $1.8 million [9].

There are several limitations with the study design. First, the
epidemiology of opioid use, NAS diagnosing, and medical care for
pregnant women is likely not generalizable. The high incidence of NAS
currently observed in Florida is substantially above the national rate,
and our sample may be subject to case selection bias. Additionally, reliance
on diagnosis codes for the retrospective identification of patients may
be susceptible to under-reporting NAS cases. This study design also
does not allow for the causal attributions of Florida’s policy changes,
such as the implementation of the Florida PDMP, on NAS incidence
during the study period. Lastly, it is unclear whether socio-demographic
characteristics played a role in treatment types available to or selected
by the patients in this study. These characteristics may have influenced
LOS or other measures in ways unable to be meted out by this study
design.

In order to reduce the societal cost associated with treatment of NAS-
affected newborns, further steps should be taken beyond those currently
in place. This can be accomplished by preventing the unnecessary
exposure of opioids to women of reproductive age by providing only
short-term prescriptions for opioids and using alternatives, such as
nonsteroidal anti-inflammatory drugs and physical/massage therapy,
as first-line treatments for pain. Additionally, increasing the number of
available beds for inpatient and outpatient treatment programs

Citation: Triplett K, Goodin A, Delcher C, et al. Opioid Drug Exposures and Health Care Utilization Measures Associated with Neonatal
throughout the US, with preference given to pregnant women, would be impactful. Providing access to contraceptive care for those who desire it, specifically long-acting reversible contraceptives to women with opioid dependence and women in substance treatment facilities, may decrease the incidence of unintended pregnancy in these groups, consequently decreasing the incidence of NAS. Finally, efforts should be undertaken to improve the uptake of PDMP usage among Florida’s OB/GYNs [22,23].

Acknowledgement

Work for this study was accomplished at UF Health at the University of Florida, Gainesville, Florida.

Dr. Delcher was supported by a grant from the Bureau of Justice Assistance Harold Rogers Prescription Drug Monitoring Program: Data-Driven Responses to Prescription Drug Abuse (2016-PM-BX-K005).

A poster of this work has been presented at the 2017 ACOG Annual Clinical and Scientific Meeting, San Diego, CA, May 6-9, 2017.

References


15. International Classification of Diseases, Tenth Revision (ICD-10).


