ABSTRACT

Introduction: Increasing rates of neonatal abstinence syndrome (NAS), most commonly linked to maternal opioid use, are a growing concern within clinical and public health domains.

Objectives: The study aims to describe the statewide burden of NAS and maternal substance use, focusing on opioids in Wisconsin from 2009 to 2014.

Methods: Trends in NAS and maternal substance use diagnosis rates were calculated using Wisconsin’s Hospital Discharge Data. Demographic and payer characteristics, health service utilization, and clinical outcomes were compared for newborns with and without NAS. Demographic and payer characteristics were compared between women with and without substance use identified at time of delivery.

Results: Rates of NAS and maternal substance use, most notably opioid use, increased significantly between 2009 and 2014. The majority of newborns diagnosed with NAS, and women identified with substance use, were non-Hispanic, white, and Medicaid-insured. Disproportionate rates of NAS and maternal opioid use were observed in American Indian/Alaska Native and Medicaid populations compared to white and privately insured groups, respectively. Women age 20-29 years had the highest rates of opioid use compared to the reference group (10-19 years). Odds of adverse clinical outcomes and levels of health service utilization were significantly higher for newborns with NAS.

Conclusions: Similar to trends nationally, our findings show an increase in maternal opioid use and NAS rates in Wisconsin over time, with disproportionate effects in certain demographic groups. These findings support the need for targeted interventions in clinical and public health settings aimed at prevention and burden reduction of NAS and maternal substance use in Wisconsin.

BACKGROUND

The use of drugs during pregnancy, both illicit and prescribed, can lead to negative consequences for mothers and newborns. Of particular concern amidst the current epidemic of opioid use and abuse in the United States is the increasing number of infants born with physical dependence to opioids taken by the mother. Known as neonatal abstinence syndrome (NAS), this condition encompasses a constellation of behavioral and physiological signs and symptoms characterized by neurological over-activity, feeding difficulties, and respiratory problems, which can result in significant medical treatment, prolonged hospital stays, and increased costs in the days and weeks following birth. Clinical manifestations of NAS depend on various factors influencing the newborn’s intrauterine drug exposure, including the type, dose, frequency, and metabolism of the drug used by the mother. In addition to NAS, these newborns experience higher rates of prematurity and poor fetal growth. NAS can result from in utero exposure to prescription opioid pain medications, heroin, methadone, and buprenorphine used for opioid addiction treatment, benzodiazepines, barbiturates, amphetamines, cocaine, marijuana, and alcohol. The 2012-2013 National Survey on Drug Use and Health reported that 5.4% of pregnant women age 15 to 44 years old used illicit drugs. Opioid use during pregnancy rose nearly 2.5-fold between 2001 and 2009 within a nationally representative sample of inpatient hospital discharges. Looking at all women reproductive age, on average 27.7% of privately insured and 39.4% of Medicaid-enrolled women filled a prescription for an opioid
Maternal substance use was captured causing from hospital therapies required for other complications shortly after birth and those who presented with NAS after being discharged.

The 0-28 day timeframe allowed for capturing newborns experiencing NAS shortly after birth and those who presented with NAS after being discharged.

Neonatal abstinence syndrome can occur due to iatrogenic causes in the newborn period unrelated to maternal drug use. Based on a 2012 study by Patrick et al, newborns with select diagnoses associated with iatrogenic causes of NAS were excluded. These included very low birth weight (<1,500g, ICD-9-CM 765.0, 764.01-764.05, V213.1-V213.3), gestational age less than 24 weeks (ICD-9-CM 765.21), intraventricular hemorrhage (ICD-9-CM 772.1), periventricular leukomalacia (ICD-9-CM 779.7), necrotizing enterocolitis (ICD-9-CM 777.5), spontaneous intestinal perforation (ICD-9-CM 777.6), or bronchopulmonary dysplasia (ICD-9-CM 770.7).

The comparison group of newborns without NAS included newborns born within, or en route to, the hospital during the study timeframe. The same exclusion criteria for iatrogenic causes of NAS were applied to this population to ensure comparable groups.

Delivering Mothers—Delivery hospitalizations (referred to as mothers in subsequent text) with a live birth were identified using methods described by Kuklina et al. Any record containing delivery-related procedure codes (V 720-1, V724, V726, V729, V736, V740-2, V744, V7221, V7229, V7231, V7239, V7251, V7253-54, V7271, V7279, V7322, V7359, or V7499), Medicare Severity Diagnosis-Related group codes (765-768 and 774-775 or ICD-9-CM code 650) were included. Encounters with abortive or abnormal pregnancy outcome codes (ICD-9-CM 630.x, 639.x, 750.x, 690.1x, 695.1x, and 749.1x) were excluded to ensure capture of only live births.

Measures
Newborn Substance Exposure—The ICD-9-CM does not allow for identification of a specific substance of exposure within the 779.5 NAS code. Therefore, newborn substance exposure type was identified by searching for codes associated with a specific drug exposure in the newborn’s hospital record. If a substance exposure code was identified without a concurrent diagnosis of NAS, the newborn was excluded as a NAS case due to limitations in confirming if the newborn suffered clinical symptoms meeting criteria for NAS.

Maternal Substance Use—Maternal substance use was captured by searching for select ICD-9-CM codes associated with maternal substance use identified during the delivery hospitalization, mirroring the technique used by Creanga et al. Mothers were classified broadly as substance-using (any substance) or non-substance using. Substance-using mothers included those with ICD-9-CM codes in the hospitalization record for broad drug types, eg, opioid (including heroin, methadone, and opioid analgesic), psychotropic (sedative, hypnotic, and tranquilizers), stimulant, cocaine, cannabis, alcohol, tobacco, other, unspecified, and poly-drug. Illicit versus prescribed use could not be ascertained with ICD-9-CM coding.
**RESULTS**

**Newborn Results**

A total of 2,361 newborns were diagnosed with NAS between 2009 and 2014. The rate of NAS per 1,000 delivery hospitalizations increased significantly during this time period (P for trend <0.05), Figure 1. Ninety-two percent (n=2182) of NAS cases were diagnosed during the delivery hospitalization. ICD-9-CM codes for a specific substance of exposure were identified in only 17.4% (n=412) of NAS-affected newborns. Of these identified exposures, opioids comprised 70.9% of cases.

Mean LOS for newborns diagnosed with NAS was significantly longer compared to newborns without NAS (16.4 days, SD=16.1 vs 2.8 days, SD=4.9, P<0.001). Mean hospital charges were also significantly higher for newborns diagnosed with NAS compared to unaffected newborns ($44,929, SD=58,971 vs $5,864, SD=22,644, P<0.001).

NAS rates by demographic and payer group are presented in Table 1. The majority of newborns with a NAS diagnosis were non-Hispanic (73.8%), white (68.2%), and Medicaid-insured (82.0%). Rates of NAS were higher in males and non-Hispanic newborns. Compared to white newborns, the NAS rate was lower in black and “other” race categories, but higher in American Indian/Alaska Native newborns. Compared to privately insured newborns, the NAS rate was higher for Medicaid and other-insured groups.

The proportion of newborns with and without NAS experiencing adverse clinical outcomes is presented in Table 2. Compared to newborns without a NAS diagnosis, newborns with NAS had significantly higher odds of low birth weight, prematurity, feeding difficulties, seizures, and respiratory distress syndrome.
Maternal Results
Rates of any substance use per 1,000 delivery hospitalizations increased from 83.0 in 2009 to 96.5 in 2014. Tobacco was the leading substance identified (mean 4814 users per year [range 4658-5015]), followed by opioids, polydrug (defined as >1 substance), cannabis, unspecified substances, cocaine and alcohol (Figure 2). Opioid use rates per 1,000 delivery hospitalizations increased 3.3-fold over the study period (Figure 1, P for trend <0.001). Rates of cannabis and polydrug use were the only other substance categories to increase between 2009 and 2014, and to a smaller degree than opioids, 2.1-fold and 2.0-fold, respectively.

Maternal substance and opioid use rates by demographic and payer groups are presented in Table 3. The majority of women with any substance use were non-Hispanic (93.4%), white (79.5%), and Medicaid-insured (70.2%). Compared to women age 10 to 19, the rate of any maternal substance use was higher in women age 20 to 29, and lower in women age 30 to 39 and age 40 to 55 years. Compared to white women, rates of any maternal substance use were higher in black and American Indian/Alaska Native women, but lower in Asian/Pacific Islander and “other” race women. Medicaid-insured and “other”-insured women had higher rates of any maternal substance use versus privately insured women. Similar comparisons of rates between demographic groups were observed for maternal opioid use with the exception of age. Compared to the reference age group (10 to 19 years), the rate of maternal opioid use was higher in women age 20 to 29, and also in women age 30 to 39 and 40 to 55 years.

DISCUSSION
This study found increasing rates of NAS and maternal substance use, particularly for opioids, in Wisconsin between 2009 and 2014. Although analyzing mothers and newborns separately restricts causal inferences, the parallel rising trends for both findings is supportive of an association. There was a slight decline in the NAS rate in 2014; however, this was not statistically different from the rate in 2013. The decline could represent a true plateau in the number of cases or be an outlier within a continued upward trend. It also might signal improvements in the prenatal management of substance-using mothers, in particular given the 4% rise in maternal opioid use rates observed from 2013 to 2014.

The higher incidence of poor perinatal outcomes in newborns with NAS certainly contributes to the observed increased health service utilization for these newborns. These adverse outcomes must be interpreted cautiously. Some outcomes measured are clinical criteria used within symptom scoring tools to make a diagnosis of NAS, and therefore are expected to be more common in newborns with this diagnosis.3,6 Causal links between poor clinical outcomes and substance use by the mother should be considered within the context of other potential confounding risk factors, which were not explored in the present analysis. These include

Table 1. Demographic Characteristics and Payer Source for Delivery Hospitalizations of Newborns With and Without Neonatal Abstinence Syndrome (NAS) in Wisconsin, 2009-2014

<table>
<thead>
<tr>
<th>Delivery Hospitalizations</th>
<th>Delivery Hospitalizations</th>
<th>NAS Rate</th>
<th>Rate Ratio&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without NAS No. (%)</td>
<td>With NAS No. (%)</td>
<td>Per 1,000 (95% CI)</td>
<td>(95% CI)</td>
</tr>
</tbody>
</table>

Sex<sup>b</sup>
- Female: 188,589 (48.8) 1,030 (43.6) 5.4 (5.1, 5.7) Ref
- Male: 198,014 (51.2) 1,331 (56.3) 6.7 (6.3, 7.1) 1.2 (1.1, 1.3)

Ethnicity<sup>c</sup>
- Non-Hispanic: 285,121 (75.0) 1,772 (73.8) 6.2 (5.9, 6.5) 1.2 (1.1, 1.3)
- Hispanic: 27,403 (4.6) 109 (7.1) 4.0 (3.3, 4.7) Ref

Race<sup>d</sup>
- White: 258,773 (66.9) 1,612 (68.2) 6.2 (5.9, 6.5) 1.2 (1.1, 1.3)
- Black: 33,757 (8.7) 162 (6.9) 4.8 (4.1, 5.5) Ref
- American Indian/Alaskan Native: 9,936 (2.6) 148 (5.7) 4.2 (3.4, 5.0) 1.2 (1.1, 1.3)
- Other: 18,279 (4.7) 68 (2.9) 3.7 (2.8, 4.6) 1.2 (1.1, 1.3)

Payer
- Private insurance: 207,528 (53.7) 1,938 (82.0) 11.9 (11.4, 12.4) 1.2 (1.1, 1.3)
- Medicaid: 161,089 (41.7) 1,938 (82.0) 11.9 (11.4, 12.4) Ref
- Other: 20,012 (4.7) 129 (5.5) 7.1 (5.9, 8.3) 1.2 (1.1, 1.3)

<sup>a</sup>Rate ratios represent the rate of NAS in each group compared to the rate of NAS in the reference group
<sup>b</sup>Missing for 74,585 delivery hospitalizations (19.1%)
<sup>c</sup>Missing for 59,040 delivery hospitalizations (15.2%)
<sup>d</sup>Missing for 26 delivery hospitalizations (<0.5%)

Table 2. Proportions and Odds of Clinical Outcomes for Delivery Hospitalizations of Infants with NAS in Wisconsin, 2009-2014

<table>
<thead>
<tr>
<th>Delivery Hospitalizations</th>
<th>Delivery Hospitalizations</th>
<th>Rate Ratio&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without NAS No. (%)</td>
<td>With NAS No. (%)</td>
<td>Per 1,000 (95% CI)</td>
</tr>
</tbody>
</table>

Low birth weight: 18,781 (4.9) 349 (14.8) 3.4 (3.0, 3.8)
Prematurity: 27,983 (7.2) 411 (17.4) 2.7 (2.4, 3.0)
Feeding difficulties: 14,257 (3.7) 470 (19.9) 6.5 (5.9, 7.2)
Seizures: 389 (0.1) 21 (0.9) 8.9 (5.7, 13.8)
Respiratory distress syndrome: 31,815 (8.2) 677 (28.7) 4.5 (4.1, 4.9)

<sup>a</sup>Odds ratios represent the odds of a clinical outcome for NAS.
the impact of other clinical conditions from which the newborn may be suffering, as well as maternal factors such as stress, other substances used, general health, mental health disorders, socioeconomic status, and characteristics of prenatal care, which could contribute to poor newborn outcomes.1,6,17

The study's findings support anecdotal reports of increasing NAS and maternal opioid use observed by clinical and public health practitioners across the state. Further, the analysis highlights populations with the highest burden of NAS and maternal substance use (e.g., non-Hispanic, White, and Medicaid-insured newborns and women), while identifying subgroups disproportionately affected by these issues (e.g., American Indian and Alaska Native, non-Hispanic, and Medicaid-insured newborns and women; women aged 20-29 years old). Wisconsin's findings are comparable to descriptive analyses from other states, including Tennessee, Ohio, Washington, and Florida, suggesting a need for additional research, prevention and treatment investments, and nonpunitive policy initiatives targeting substance exposure during pregnancy and associated impact on newborns at the state and national levels.1,3,9,17,18

There are several limitations of this study. ICD-9-CM code limitations, as well as variations in practice across clinical settings, complicate the determination of a “best” definition of NAS for accurately identifying cases caused by maternal substance use. Some studies have included a broader array of codes to capture NAS (e.g., 760.7x, noxious influences affecting fetus or newborn via placenta or breast milk).3,18 For this analysis a more conservative definition was used to improve specificity at the risk of underestimating the true burden of NAS.

The number of NAS-diagnosed newborns lacking a specific substance exposure code, as well the newborns identified with only an opioid exposure code but no NAS code, also may be a product of coding obstacles and practice variations. The latter group may contain missed NAS cases. Further challenges arise when trying to exclude newborns with NAS due to iatrogenic causes. The array of exclusion diagnoses used in this analysis, while informed by previous studies, is not comprehensive.1,3,4,9

Without additional clinical information, there could be misclassification of newborns with and without NAS due to maternal substance use. Future studies should build upon existing analyses to improve case ascertainment for NAS, including accurate identification of substance exposure and appropriate exclusions for iatrogenic causes to ensure appropriate classification of cases.

The reliance on ICD-9-CM codes captured at time of delivery to identify maternal substance use also may underestimate the use rates. The episode of hospital care at time of delivery is only one snapshot within a longer prenatal course during which substance use may have affected pregnancy. Fear of reporting substance use due to the potential consequences, and the absence of universal substance use screening protocols during delivery hospitalization could result in missed cases. Future work using linked data sets, such as HDD and birth certificate data, and exploration of the clinical record could aid in associating newborn outcomes from specific maternal exposures, provide additional variables of interest (e.g., maternal education), and enable more complex regression analysis using continuous variables (e.g., birth weight). A better understanding of clinical coding and screening practices also may ensure more comprehensive and consistent surveillance.

Incomplete variables within the dataset, such as missing information for race (15.2%) and ethnicity (19.1%) in newborns, could misrepresent the burden and disproportionate risk of NAS across groups. Missing data is one potential explanation for the discordance in risks observed for NAS and maternal substance use within racial groups. Although black newborns had a decreased risk of NAS compared to white newborns, there was an increased risk of any maternal substance use, and specifically opioid use, in black women compared to white women. Other factors that could affect findings across different demographic groups include disparate screening, reporting, prescribing, or management practices. Previous literature, for example, has shown that providers are less likely to prescribe opioids to some minority groups compared to whites presenting with similar medical problems.1,9

Inclusion of birth certificate data in future analyses may help overcome the
Table 3. Maternal Demographic Characteristics and Payer Source for Delivery Hospitalizations With and Without Substance Use in Wisconsin, 2009-2014

<table>
<thead>
<tr>
<th>Age (years)b</th>
<th>Delivery Hospitalizations Without Substance Use No. (%)</th>
<th>Delivery Hospitalizations With Substance Use No. (%)</th>
<th>Substance Use Rate Per 1,000 (95% CI)</th>
<th>Rate Ratioa (95% CI)</th>
<th>Delivery Hospitalizations With Opioid Use No. (%)</th>
<th>Opioid Use Rate Per 1,000 (95% CI)</th>
<th>Rate Ratioa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 19</td>
<td>23,835 (6.7)</td>
<td>2,752 (8.1)</td>
<td>103.5 (99.6, 107.4)</td>
<td>Ref</td>
<td>169 (3.8)</td>
<td>6.4 (5.4, 7.4)</td>
<td>Ref</td>
</tr>
<tr>
<td>20 to 29</td>
<td>184,247 (51.9)</td>
<td>22,210 (65.0)</td>
<td>107.6 (106.2, 109.0)</td>
<td>1.0 (1.0, 1.1)</td>
<td>2,719 (61.2)</td>
<td>13.2 (12.7, 13.7)</td>
<td>2.1 (1.8, 2.4)</td>
</tr>
<tr>
<td>30 to 39</td>
<td>138,675 (39.1)</td>
<td>8,721 (25.5)</td>
<td>59.2 (58.0, 60.4)</td>
<td>0.6 (0.5, 0.6)</td>
<td>1,477 (33.2)</td>
<td>10.0 (9.5, 10.5)</td>
<td>1.6 (1.3, 1.8)</td>
</tr>
<tr>
<td>40 to 55</td>
<td>8,049 (2.3)</td>
<td>498 (1.5)</td>
<td>58.3 (53.2, 63.4)</td>
<td>0.6 (0.5, 0.6)</td>
<td>79 (1.8)</td>
<td>9.2 (7.2, 11.2)</td>
<td>1.5 (1.1, 1.9)</td>
</tr>
</tbody>
</table>

Ethnicityc
Non-Hispanic 309,075 (87.1) 31,935 (93.4) 93.6 (92.6, 94.6) Ref 4,124 (92.8) 12.1 (11.7, 12.5) Ref.
Hispanic 32,333 (9.1) 1,050 (3.1) 31.5 (29.6, 33.4) 0.3 (0.3, 0.4) 211 (4.8) 6.3 (5.4, 7.2) Ref.

Raced
White 270,777 (76.3) 27,178 (79.5) 91.2 (90.1, 92.3) Ref 3,746 (78.2) 11.7 (11.3, 12.1) Ref.
Black 35,934 (10.1) 4,225 (12.4) 105.2 (102.0, 108.4) 1.2 (1.1, 1.2) 558 (12.6) 13.9 (12.7, 15.1) 1.2 (1.1, 1.3)
Asian or Pacific Islander 15,453 (4.4) 421 (1.2) 26.5 (24.0, 29.0) 0.3 (0.3, 0.3) 45 (1.0) 2.8 (2.0, 3.6) 0.2 (0.2, 0.3)
American Indian/Alaskan Native 3,864 (1.1) 1,066 (3.1) 216.2 (203.2, 229.2) 2.4 (2.2, 2.5) 134 (3.0) 27.2 (22.6, 31.8) 2.3 (2.0, 2.8)
Other 18,249 (5.1) 592 (1.7) 31.4 (28.9, 33.9) 0.3 (0.3, 0.4) 114 (2.6) 6.1 (5.0, 7.2) 0.5 (0.4, 0.6)

Payer
Private insurance 211,382 (59.6) 8,696 (25.4) 39.5 (38.7, 40.3) Ref 1,400 (31.5) 6.4 (6.1, 6.7) Ref.
Medicaid 131,440 (37.1) 23,985 (70.2) 154.3 (152.3, 156.3) 3.9 (3.8, 4.0) 2,858 (64.3) 18.4 (17.7, 19.1) 2.9 (2.7, 3.1)
Other 11,988 (3.4) 1,500 (4.4) 111.2 (105.6, 116.8) 2.8 (2.7, 3.0) 186 (4.2) 13.8 (11.8, 15.8) 2.2 (1.9, 2.5)

Notes:
- Rate ratios represent the rate of substance use or opioid use in each group compared to the rate of substance use or opioid use in the reference group.
- Missing for 9 women with no substance use (<0.5%) and 9 women with no opioid use (<0.5%).
- Missing for 13,401 women with no substance use (3.8%), 1,197 women with substance use (3.5%), and 109 women with opioid use (2.5%).
- Missing for 10,533 women with no substance use (3.0%), 700 women with substance use (2.1%), and 117 women with opioid use (2.6%).

gaps in newborn demographic information observed in this study.

Despite these limitations, this study describes the growing burden of NAS and maternal substance use, particularly of opioids, in Wisconsin. The findings, supplemented by a growing body of literature showing the potential negative impacts of NAS and maternal opioid use during and beyond the perinatal period, provide evidence for targeted investments in clinical, public health, and policy initiatives aimed at all levels of prevention and care for mothers and newborns, paying particular attention to those populations with the highest burdens and risks. Early interventions, ideally preventing an opioid-affected pregnancy in the first place, should be top priority.

The ever-growing public health conversation and heightened clinical awareness of NAS and maternal opioid use may help overcome some of the aforementioned challenges of this study through increased diligence in screening, diagnosis, and documentation. Some states have developed universal substance screening procedures for delivering mothers and infants, mandated reporting policies, and statewide real-time surveillance mechanisms to better capture maternal substance use and subsequent newborn impacts. Wisconsin has not implemented such strategies, making up-to-date and accurate monitoring more challenging. Conversations between clinical providers, policy decision-makers, public health professionals, and community organizations can lead to improved surveillance approaches, better interventions for substance-using mothers and their children, and prevention strategies that will be essential to ensure the best birth outcomes possible in light of increasing opioid use in Wisconsin and across the nation.

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