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Neonatal Withdrawal Syndrome, Michigan, 2000–2009

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Abstract

Background—Neonatal withdrawal syndrome, which is associated most frequently with opioid use in pregnancy, is an emerging public health concern, with recent studies documenting an increase in the rate of U.S. infants diagnosed.

Purpose—This study examined neonatal withdrawal syndrome diagnosis among Michigan infants from 2000 to 2009 and hospital length of stay (LOS) between infants with and without the syndrome for a subset of years (2006–2009).

Methods—Michigan live birth records from 2000 to 2009 were linked with hospital discharge data to identify infants with neonatal withdrawal syndrome. Linked data were restricted to infants born between 2006 and 2009 to examine the difference in hospital LOS between infants with and without the syndrome. Multivariable regression models were constructed to examine the adjusted impact of syndrome diagnosis on infant LOS and fit using negative binomial distribution. Data were analyzed from July 2011 to February 2012.

Results—From 2000 to 2009, the overall birth rate of infants with neonatal withdrawal syndrome increased from 41.2 to 289.0 per 100,000 live births ($p<0.0001$). Among infants born from 2006 to 2009, the average hospital LOS for those with the syndrome was between 1.36 (95% CI=1.24, 1.49) and 5.75 (95% CI=5.41, 6.10) times longer than for infants without it.

Conclusions—Diagnosis of neonatal withdrawal syndrome increased significantly in Michigan with infants who had the syndrome requiring a significantly longer LOS compared to those without it.

Introduction

With prescription opioid use among women of reproductive age increasing since the late 1990s,[1,2] concern regarding the effect on the fetus and newborn has grown. Neonatal withdrawal syndrome is an emerging public health concern,[3–5] with recent studies documenting almost a threefold increase in the rate of U.S. infants diagnosed in the past decade.[6,7] Neonatal withdrawal syndrome risk is greatest with maternal usage of opioids

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analgesics and heroin[4,8]; however, prenatal usage of non-narcotic drugs can cause similar neonatal withdrawal symptoms.[3]

Symptoms usually relate to central nervous system irritability and gastrointestinal dysfunction such as tremors, irritability, increased muscle tone, and difficulty sleeping.[9,10] Neonatal withdrawal syndrome infants are more likely to be born preterm[6]; be admitted to a neonatal intensive care unit (NICU)[11]; and need longer hospitalization (measured as length of stay [LOS]).[4–7] Little information is available that quantifies the additional LOS of neonatal withdrawal syndrome infants compared to other infants after controlling for maternal and infant factors.[6] Therefore, the purpose of the study was to examine withdrawal syndrome diagnosis among Michigan infants from 2000 to 2009 and to compare LOS between infants with and without withdrawal syndrome for a subset of years (2006–2009). Infants with withdrawal syndrome were hypothesized to require a longer LOS than infants without withdrawal syndrome, after adjusting for factors affecting LOS.

Methods

Study Population and Data Sources

A retrospective cohort population-based study was conducted using live birth certificate and hospital discharge data for infants born to Michigan (resident) mothers. Hospital discharge data contained discharge diagnosis records for all Michigan hospitals. Live birth certificate data were linked with hospital discharge records by probabilistic, followed by deterministic, linkages performed separately for maternal and infant files. Overall, 88.5% of hospital discharge newborn records and 99.2% of maternal records are matched with birth certificate records (T Le, Michigan Department of Community Health, unpublished observations, 2005). Maternal hospital discharge records up to 1 year before and after delivery were included.

To examine maternal and infant variables related to neonatal withdrawal syndrome, most recent years of data were used (2006–2009). For withdrawal syndrome infants, the hospitalization with first withdrawal syndrome diagnosis was selected, whereas for infants without the syndrome, the first hospitalization was chosen. Hospitalizations for infants with transfers only included the first hospitalization. This study was reviewed and approved by the Michigan Department of Community Health IRB.

Measures

Live birth certificate records provided the following data: maternal age; race; education; number of named parents; tobacco use during pregnancy; Kotelchuck index (inadequate defined as <50% of expected prenatal visits[12]); Caesarean-section delivery; infant year of birth; gender; plurality; birthweight (low defined as <2500 g); and estimated gestational weeks. Maternal race was used as a proxy for infant's race; only the mother acknowledged on the birth certificate was used as a proxy for social support at home.

Hospital discharge data provided infant LOS (measured in days); NICU usage; and main payment source (private insurance, Medicaid, self-pay, other). Infants with withdrawal syndrome were identified by any diagnosis of ICD-9-CM[13] Code 779.5. Maternal morbidity

was defined by discharge diagnoses related to mental illness (ICD-9-CM=290, 293–302, 306–319, 648.4) and preexisting chronic conditions (ICD-9-CM=240–246, 250, 393–398, 435, 440–448, 451–459, 648.0–648.1, 648.5–648.6, 745–747; VIG, unpublished observations, 2005) from maternal hospitalizations during pregnancy.

Data Analysis

Analyses were conducted from July 2011 to February 2012. Neonatal withdrawal syndrome birth rates per 100,000 live births in Michigan from 2000 to 2009 were calculated, with a chi-square test performed for linear trend analysis (Epi Info, version 7). Data from the most current years, 2006–2009, were used to measure demographic and health outcomes differences between infants with and without neonatal withdrawal syndrome using percentages (crude rate per 100) and 95% CIs.

Multivariable regression models examined the adjusted impact of withdrawal syndrome diagnosis on infant LOS and were fit using negative binomial distribution (SAS, version 9.2). Candidate covariates were included based on possible association with both withdrawal syndrome diagnosis and infant LOS and included: mother's race; maternal hospitalization related to chronic disease and mental illness; Caesarean-section delivery; low birthweight (LBW); having only the mother acknowledged on the birth certificate; insurance type; inadequate Kotelchuck index; and smoking.[14–17]

Nonsignificant (p-value ≥0.002) terms (main effects and two-way interaction effects) were dropped sequentially from the model in reverse order of significance, commencing with the two-way interaction terms and removing collinear variables, until the most parsimonious model was obtained. If a two-way interaction term was significant, the main effects included in the interaction were retained. The final multivariable regression model included infant neonatal withdrawal syndrome and the following covariates: mother's race (black, white, other); maternal hospitalization related to chronic disease and mental illness; Caesarean-section delivery; LBW; only the mother being acknowledged on the birth certificate; and inadequate Kotelchuck index. Neonatal withdrawal syndrome interaction terms included maternal hospitalization related to mental illness and LBW. Adjusted incidence rate ratios (IRRs) and 95% CIs were calculated.

Results

From 2000 to 2009, a total of 1509 infants were hospitalized with neonatal withdrawal syndrome. The syndrome birth rate per 100,000 live births increased during the study period, from 41.2 (2000) to 289.0 (2009; p<0.0001). When stratified by race, the increase was significant among white but not black infants (data not shown).

A comparison of infant and maternal characteristics and health outcomes for infants with and without withdrawal syndrome are shown in Table 1. Neonatal withdrawal syndrome infants were more likely to be white and have Medicaid as their hospital payment source. Adjusted IRRs of infant LOS for interactions between neonatal withdrawal syndrome status and LBW and maternal hospitalization related to mental illness status are shown in Table 2. Among infants with normal birthweight and whose mothers were not hospitalized because

of mental illness, those with the syndrome had 5.75 times longer LOS than those without it (95% CI=5.41, 6.10). Among LBW infants, the LOS for those with the syndrome was 1.36 times on average longer than for those without it (95% CI=1.24, 1.49), whereas for infants with a maternal mental illness hospitalization, the average LOS for syndrome infants was 4.66 times longer than it was for infants without it (95% CI=4.39, 4.96).

Discussion

Neonatal withdrawal syndrome infants had a significantly longer LOS than infants without withdrawal syndrome after adjusting for factors that could affect LOS, consistent with previous literature documenting a higher LOS among infants with withdrawal syndrome,[4,5,7] after adjusting for LBW or prematurity.[6] The current study is unique by quantifying the additional LOS of infants with withdrawal syndrome after adjusting for maternal factors in addition to infant factors. Given that infants with withdrawal syndrome are more likely to be covered by Medicaid and to require a significantly longer LOS, these findings suggest that the majority of the withdrawal syndrome financial burden falls on state and federal governmental funding streams.

Withdrawal syndrome birth rates increased significantly among Michigan infants from 2000 to 2009, consistent with other recent population-based studies.[3–7] Among infants with a maternal mental illness hospitalization, the average LOS was almost five times longer for withdrawal syndrome infants than for infants without withdrawal syndrome. Withdrawal syndrome infants with a maternal mental health illness hospitalization may have a longer LOS because of the need for a safe discharge plan to be in place before leaving the hospital.[18]

Limitations

Study limitations relate to validity and completeness of vital statistics and hospital discharge data. Identifying infants that have withdrawal syndrome by ICD-9-CM coding alone underestimates the true birth rate.[19] When infants are transferred from one hospital to another, hospitalizations are counted as separate visits, thus lowering LOS into two shorter stays, suggesting that the study LOS underestimates the true LOS for some infants with the syndrome.

Misclassification of iatrogenic withdrawal infants as those with withdrawal syndrome is possible, but it appears to be uncommon. A recent study by Patrick et al. found that iatrogenic cases comprised less than 5% of all withdrawal syndrome births in their nationally representative sample (2000–2009).[7] Although the present study cannot identify maternal drugs used to treat opioid dependence, differentiation in pharmacologic treatment may influence infant's postneonatal LOS. Although methadone is considered standard treatment for opioid dependence during pregnancy,[20,21] a recent study found infants of mothers treated with buprenorphine had a significantly shorter hospitalization.[22]

Conclusion

This study examined the increased LOS of neonatal withdrawal syndrome infants compared to other infants and adds to the literature by providing an estimate that adjusts for available

maternal factors. Additionally, the increasing withdrawal syndrome trend with infants who are more likely to be covered by Medicaid suggests a large public financial burden. The estimated hospitalization charges in Michigan for infants with the syndrome born between 2000 and 2009 totaled more than $35 million.

Raising provider awareness is necessary to promote appropriate evaluation and treatment. The use of universal screening questions, brief intervention, and referral to treatment[23] may help target and decrease drug abuse among women of childbearing age. Further research linking prescription drug monitoring data with maternal and infant hospital discharge data could identify scheduled drugs prescribed during pregnancy.

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Table 1

Comparison of infant and maternal characteristics by neonatal withdrawal syndrome diagnosis, Michigan infants, 2006–2009

	Infants with neonatal withdrawal syndrome (*n*=935)[a]		Infants without neonatal withdrawal syndrome (*n*=470,329)[a]	
	% (95% CI)	Count	% (95% CI)	Count
Infant demographics				
Male	55.4 (50.7, 60.4)	518	51.2 (51.0, 51.4)	240,858
White	83.9 (78.1, 90.0)	780	76.1 (75.9, 76.4)	356,737
Black	13.7 (11.4, 16.2)	127	18.5 (18.4, 18.6)	86,724
Other race	2.5 (1.6, 3.7)	23	5.4 (5.29, 5.42)	25,093
Medicaid hospital payment source	78.5 (72.9, 84.4)	732	42.3 (42.2, 42.5)	198,341
Delivery/infant outcomes				
Mode of delivery Caesarean-section	37.0 (33.1, 41.2)	331	31.4 (31.3, 31.6)	140,669
Low birthweight (<2500 g)	23.2 (20.2, 26.5)	215	8.0 (7.96, 8.12)	37,648
Premature (<37 weeks)	24.5 (21.5, 27.9)	228	10.3 (10.2, 10.4)	48,121
Small for gestational age (<10th percentile)	15.9 (13.4, 18.7)	146	4.8 (4.7, 4.9)	22,096
NICU admission	29.6 (25.7, 33.9)	204	5.9 (5.8, 6.0)	19,969
Maternal demographics				
<High school graduate	29.1 (25.7, 32.9)	256	16.5 (16.3, 16.6)	72,895
Age at delivery <21 years	7.9 (6.2, 9.9)	73	14.5 (14.4, 14.6)	68,277
Only mother acknowledged on birth certificate	34.2 (30.6, 38.2)	320	15.4 (15.3, 15.6)	72,583
Maternal health variables				
Inadequate Kotelchuck index	35.8 (32.0, 40.0)	315	11.4 (11.35, 11.55)	51,551
Smoking during pregnancy	69.6 (64.4, 75.3)	640	17.5 (17.3, 17.6)	81,771
Chronic disease–related hospitalization	6.6 (5.1, 8.5)	62	4.8 (4.7, 4.9)	22,582
Mental illness–related hospitalization	50.7 (46.2, 55.5)	473	6.4 (6.3, 6.5)	30,097

[a] In all calculations for percentages, missing values were excluded from the calculation in both the numerator and denominator. NICU, neonatal intensive care unit.

Table 2

IRRs (95% CIs) of infant hospital length of stay for interactions terms, for infants with neonatal withdrawal syndrome, Michigan, 2006–2009

	Unadjusted	Adjusted[a]
Low birthweight		
Yes	1.13 (1.04, 1.23)	1.36 (1.24, 1.49)
No	5.27 (5.04, 5.52)	5.75 (5.41, 6.10)
Maternal hospitalization related to mental illness		
Yes	2.73 (2.52, 2.95)	4.66 (4.39, 4.96)
No	4.21 (3.90, 4.55)	5.75 (5.41, 6.10)

Note: N=426,030. The referent is infants without neonatal withdrawal syndrome.

[a]Adjusted for mother's race (black, white, other); maternal hospitalization related to chronic disease; maternal hospitalization related to mental illness; Caesarean-section delivery; low birthweight; inadequate Kotelchuck index; and having only the mother acknowledged on birth certificate.

IRR, incidence rate ratio.