Prescription Opioid Epidemic and Infant Outcomes

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abstract

BACKGROUND AND OBJECTIVES: Although opioid pain relievers are commonly prescribed in pregnancy, their association with neonatal outcomes is poorly described. Our objectives were to identify neonatal complications associated with antenatal opioid pain reliever exposure and to establish predictors of neonatal abstinence syndrome (NAS).

METHODS: We used prescription and administrative data linked to vital statistics for mothers and infants enrolled in the Tennessee Medicaid program between 2009 and 2011. A random sample of NAS cases was validated by medical record review. The association of antenatal exposures with NAS was evaluated by using multivariable logistic regression, controlling for maternal and infant characteristics.

RESULTS: Of 112 029 pregnant women, 31 354 (28%) filled ≥1 opioid prescription. Women prescribed opioid pain relievers were more likely than those not prescribed opioids ($P < .001$) to have depression (5.3% vs 2.7%), anxiety disorder (4.3% vs 1.6%) and to smoke tobacco (41.8% vs 25.8%). Infants with NAS and opioid-exposed infants were more likely than unexposed infants to be born at a low birth weight (21.2% vs 11.8% vs 9.9%; $P < .001$). In a multivariable model, higher cumulative opioid exposure for short-acting preparations ($P < .001$), opioid type ($P < .001$), number of daily cigarettes smoked ($P < .001$), and selective serotonin reuptake inhibitor use (odds ratio: 2.08 [95% confidence interval: 1.67–2.60]) were associated with greater risk of developing NAS.

CONCLUSIONS: Prescription opioid use in pregnancy is common and strongly associated with neonatal complications. Antenatal cumulative prescription opioid exposure, opioid type, tobacco use, and selective serotonin reuptake inhibitor use increase the risk of NAS.

WHAT'S KNOWN ON THIS SUBJECT: Although opioid pain relievers are commonly prescribed in pregnancy, their association with neonatal outcomes is not well described. Further, factors associated with development of neonatal abstinence syndrome, a neonatal opioid withdrawal syndrome is inadequately understood.

WHAT THIS STUDY ADDS: Prescription opioid use in pregnancy is common and strongly associated with neonatal complications. Antenatal cumulative prescription opioid exposure, opioid type, tobacco use, and selective serotonin reuptake inhibitor use increase the risk of neonatal abstinence syndrome.

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Recently, sales of opioid pain relievers (OPRs) in the United States have surged.[1] Complications of this increase have affected a wide range of the US population, including pregnant women and their infants.[2,3] Neonatal abstinence syndrome (NAS) is a postnatal withdrawal syndrome, initially described among heroin-exposed infants,[4] that presents with a wide array of clinical signs ranging from feeding difficulties to seizures.[5] From 2000 to 2009, the number of infants in the United States diagnosed with NAS grew nearly threefold, temporally associated with a fourfold increase in OPR prescriptions.[1,6] By 2009, one US infant was born per hour with NAS, accounting for $720 million in national health care expenditures.[6] Despite this temporal association, no large population-based studies have explored the association between OPR use in pregnancy and NAS.

Factors that determine which exposed infants will develop NAS are poorly understood. Rates of NAS among infants exposed to heroin or maintenance medications are reportedly as high as 80%.[5,7] For infants exposed to maintenance medications, risk of NAS seems unrelated to opioid dose[8,9]; however, the association of cumulative opioid exposure for nonmaintenance OPRs and NAS has not been studied. Some reports suggest that the use of tobacco and coprescription of selective serotonin reuptake inhibitors (SSRIs) may also increase the likelihood of developing NAS.[10–12]

Using a large retrospective cohort of pregnant women, our objectives were to identify neonatal complications associated with antenatal OPR exposures and to determine if antenatal cumulative prescription opioid exposure, opioid type, number of cigarettes smoked daily, and SSRI use were associated with a higher likelihood of developing NAS.

METHODS

Study Design and Setting

This retrospective, longitudinal cohort study was conducted by using data from TennCare, Tennessee's Medicaid program; outpatient prescription claims were linked to vital records and hospital and outpatient administrative data. These resources have been used extensively to assess the safety of medications during pregnancy.[13–16] Medicaid serves as an ideal program to study NAS because an estimated 80% of infants with NAS nationwide are enrolled in state Medicaid programs.[6]

The present study was approved with a waiver of informed consent by the Vanderbilt University institutional review board, the State of Tennessee Department of Health, and the Bureau of TennCare.

Cohort Assembly

Maternal and infant dyads were included in the study if: (1) the mother was 15 to 44 years old at the time of delivery; (2) the mother had been enrolled in TennCare at least 30 days before delivery; and (3) the infants were enrolled in TennCare within 30 days after delivery. Last menstrual period and date of delivery were obtained from vital records.[17] Pregnancies were included if the birth occurred between January 1, 2009, and December 31, 2011. Of a total 134 450 births, 112 029 met our inclusion criteria (83.3%).

Exposures

The study's primary exposure of interest was any prescription opioid fill during pregnancy identified from TennCare pharmacy claims data. TennCare pharmacy files contain information on all outpatient prescriptions that are reimbursed by TennCare. Opioid drug types were categorized as short-acting (eg, oxycodone hydrochloride), long-acting (eg, oxymorphone hydrochloride extended release), or maintenance (eg, buprenorphine hydrochloride) medications. Opioid doses were converted to morphine milligram equivalents by using established conversion guidelines to facilitate meaningful comparisons.[18] Duration of opioid use was defined as the period between the prescription start date and the end of the days of supply (allowing up to a 5-day carryover period from previous prescriptions). SSRI prescriptions filled within 30 days before delivery were captured. Information on tobacco use during pregnancy was obtained from birth certificates and from claims by using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM),[19] diagnostic codes (tobacco: 305.1, V15.82, 989.84, and 649.0x). Data regarding the number of cigarettes smoked per day were obtained from birth certificates, and medication costs were obtained from TennCare pharmacy expenditures. Antenatal exposure to benzodiazepines[20] has been associated with more severe NAS among opioid-exposed infants and was considered in our evaluation; however, the use of these drugs was rare in the study population (167 of 112 029) due to TennCare policies and was not included.

Descriptive Variables, Demographic Characteristics, and Outcomes

Maternal Characteristics

Demographic information was obtained, including maternal age, education (number of years), birth number (parity), and race from birth certificates. Given that the literature describes opioid-using populations to be at increased risk of hepatitis B,[21] hepatitis C,[21,22] HIV,[23] depression,[24–26] and anxiety,[27] data regarding these conditions were obtained from birth certificate data and from outpatient and hospital administrative records by using diagnostic codes (hepatitis B: 070.2x and 070.3x; hepatitis C: 070.41, 070.44, 070.51, 070.54, and 070.7x; HIV: 042, 079.53, and V08;

depression: 296.2x, 296.3x, and 311; and anxiety disorder: 300.x). Acute pain, chronic pain, headache or migraine, and musculoskeletal diseases were identified by using ICD-9-CM codes (acute pain: 338.1x; chronic pain: 338.2x; headache or migraine: 339.x, 346.x, and 784.0; diseases of the musculoskeletal system and connective tissue: 710.x–739.x) as potential OPR indications. Lastly, we identified women with opioid dependency (opioid-type dependence: 304.0x; combinations of opioid type drug with any other drug dependence: 304.7x).

Outcome

Infants with NAS were identified if the ICD-9-CM code 779.5 (drug withdrawal syndrome in newborn) appeared in any diagnostic field during the birth hospitalization. To establish the accuracy of administrative coding for NAS, a chart review was performed of 228 randomly selected cases and noncases. Using a standard definition of NAS as a reference, ICD-9-CM–based identification yielded an 88.1% (95% confidence interval [CI]: 83.3–91.7) sensitivity and a 97.0% (95% CI: 93.8–98.5) specificity (Supplemental Information Appendix A). Infants were further classified as having: (1) no opioid exposure; (2) opioid exposure without NAS; or (3) NAS.

Infant Characteristics

After establishing our cohort, our goal was to describe the clinical characteristics of each infant based a priori on the literature. NAS is characterized by respiratory symptoms, feeding difficulties, and seizures. Opioid-exposed infants and infants with NAS are also more likely to be born preterm or with a low birth weight.[5] Gender, gestational age, and birth weight data were obtained from birth certificates. Clinical signs of NAS, including transient tachypnea of the newborn (770.6), meconium aspiration syndrome (770.11 and 770.12), respiratory distress syndrome (769.x), other neonatal respiratory diagnoses (770.x, excluding the aforementioned codes and 770.7), feeding difficulty (779.3x), and seizure (779.0 and 780.3), were obtained from hospital claims. Infants with NAS might be at greater risk for concerns of sepsis (771.81) considering their clinical presentation (eg, irritability, respiratory distress), and they may also be at an increased risk of jaundice (774.x) due to feeding difficulties. We evaluated for necrotizing enterocolitis (777.5x), given that some authors have reported an association between this condition and NAS.[28] Lastly, we examined the risk of hemolytic disease (773.x) among infants with NAS because of the possibility of previous maternal intravenous drug use.

Data Analysis

The Wilcoxon rank-sum test and χ^2 tests were used where appropriate for bivariate analyses. Candidate predictors of NAS were established a priori from the literature. The level of missing data in our predictors was evaluated; <1% of missing data was found for all variables except number of cigarettes smoked per day, which had 5.6% missing. Birth weights <400 g were deemed unreliable and considered missing. To account for missing data, we used the aregImpute function for multiple imputation by using predictive mean matching[29,30] with 5 imputations. Because of the small numbers of long-acting opioids (n = 177), this group was combined with maintenance opioids for the statistical analyses. Using our entire cohort of 112 029 pregnant women, a logistic regression model was fit with NAS as the outcome and cumulative opioid exposure, opioid type (short-acting, long-acting, or maintenance), number of cigarettes smoked per day, SSRI within 30 days of delivery, infant gender, birth weight, multiple gestations, year of birth, birth number (parity), maternal age, maternal education, and maternal race (white, African American, and other) as predictors. The nonlinear relationship of continuous variables was accounted for by using restricted cubic splines for all variables except morphine milligram equivalents, which were cube root transformed and fit by using a quadratic function to account for skewness.[29] Results for nonlinear predictors are presented graphically (with P values for tests of association) because odds ratios would compare arbitrary data points and may not fully capture their nonlinear relationship with the primary outcome (ie, NAS). Interactions were tested between opioid type × cumulative opioid exposure, number of cigarettes smoked per day × cumulative opioid exposure, opioid type × number of cigarettes smoked per day, and SSRI × cumulative opioid exposure.

Because OPR use early in pregnancy would likely not result in NAS, 2 supplemental analyses restricted to opioid prescriptions were performed that continued through the final 30 and 14 days of pregnancy to determine if restriction to these subsets changed our results. Cost estimates were created by using TennCare pharmacy expenditures and previously published estimates of NAS hospitalization charges.[6] All dollars were adjusted to 2011 US dollars by using the Consumer Price Index.[31] Statistical analyses were completed by using R version 3.1.0. (R Foundation for Statistical Computing, Vienna, Austria)[32] and Stata version 13.0 (StataCorp, College Station, TX).

RESULTS

Among the 112 029 pregnant women in our sample, 31 354 (28.0%) were prescribed at least 1 OPR during pregnancy. Compared with women with no opioid exposure, women taking OPRs were more likely ($P <$ .001) to be white (72.4% vs 65.8%); have depression (5.3% vs 2.7%), anxiety disorder (4.3% vs 1.6%),

headache or migraine (8.3% vs 2.0%), and musculoskeletal disease (23.7% vs 5.8%); use tobacco (41.8% vs 25.8%); and be prescribed an SSRI within 30 days before birth (4.3% vs 1.9%) (Table 1).

Among women prescribed opioids, the majority received short-acting medications (n = 30 192 [96.2%]); fewer received maintenance treatment of opioid use disorder (n = 853 [2.7%]) or long-acting preparations (n = 177 [0.6%]) (Supplemental Table 4). Median (interquartile range) cumulative morphine milligram equivalents were higher among those using maintenance medications (18 480 [8160–37 232]) compared with those using long-acting preparations (4029 [1508–10 800]) or short-acting preparations (150 [75–373]; $P <$ .001). Median (interquartile range) amounts paid for OPRs per individual were $1317 (586–2598) for maintenance treatment, $208 (53–756) for long-acting preparations, and $8 (5–16) for short-acting preparations. Within the last 30 days of pregnancy, 8835 women were prescribed OPRs, 93.6% of whom received a short-acting preparation (Supplemental Table 5). Lastly, 12 896 women received a >7 days' supply of opioids during pregnancy (Supplemental Table 6).

In our cohort, a total of 1086 infants were diagnosed with NAS, 701 (65%) of whom had mothers with at least 1 OPR prescription during pregnancy. Between 2009 and 2011, the quarterly rate of NAS among infants in TennCare rose from 6.0 to 10.7 per 1000 births ($P <$ .001) (Fig 1). NAS occurred more frequently among infants exposed to maintenance opioids (29.3%) and long-acting opioids (14.7%) than in those exposed to short-acting preparations (1.4%) (Supplemental Table 4). Infants with NAS were more likely than other opioid-exposed and nonopioid-exposed infants to be born with a low birth weight (21.2% vs 11.8% vs 9.9%; $P <$ .001) and preterm (16.7% vs 11.6% vs 11.0%; $P <$ .001). Consistent with the characteristics of the syndrome, when comparisons were made between nonopioid and opioid-exposed infants, those with NAS were more likely ($P <$ .001) to have respiratory diagnoses (28.7% vs 10.1% vs 8.8%), feeding difficulties (13.1% vs 2.6% vs 2.3%), and seizures (3.7% vs 0.4% vs 0.3%). Rates of necrotizing enterocolitis were similar among all groups (Table 2). Every $1 spent on short-acting and long-acting opioids (excluding maintenance) was associated with $52 and $12, respectively, in hospital charges for infants with NAS.

After adjusting for maternal age, education, race, infant gender, birth weight, multiple births, birth number (parity), year of birth, the interaction of opioid type × cumulative opioid exposure, opioid type × number of cigarettes smoked per day, and number of cigarettes smoked per day × cumulative opioid exposure, the following factors were independently associated with an increased odds of NAS: cumulative opioid exposure for short-acting OPRs ($P <$ .001), opioid type ($P <$ .001), number of cigarettes smoked per day ($P <$ .001), and SSRI use within 30 days of delivery (odds ratio: 2.08 [95% CI: 1.67–2.60]) (Fig 2). For pregnant women exposed to maintenance/long-acting opioids, the risk of NAS was consistently higher than in other exposure groups, but the risk did not vary with cumulative opioid exposure (P = .16). In supplemental analyses, restricting assessments to women who filled OPR prescriptions through 30 and 14 days before delivery, our results were similar to the findings from our primary analysis (Supplemental Tables 7 and 8, respectively).

TABLE 1 Maternal Characteristics According to Opioid Exposure in Tennessee Medicaid, 2009–2011

Characteristic	No Opioid (n = 80 675)		Any Opioid (n = 31 354)		P
	Median	IQR	Median	IQR	
Age, y	23	20–27	24	21–27	<.001
Education, y	12	12-13	12	11–13	<.001
Birth number	1	1–2	1	1–2	<.001
	N	%	*N*	%	
Race					<.001
Black	25 986	32.2	8362	26.7	
White	53 074	65.8	22 699	72.4	
Other	1298	1.6	188	0.6	
Maternal comorbidities					
Pain					
Musculoskeletal disease	4430	5.8	7439	23.7	<.001
Headache or migraine	1636	2.0	2593	8.3	<.001
Chronic pain	40	0.0	187	0.6	<.001
Acute pain	72	0.1	132	0.4	<.001
Infectious					
Hepatitis C	328	0.4	358	1.1	<.001
Hepatitis B	91	0.1	39	0.1	.61
HIV	144	0.2	43	0.1	0.13
Psychiatric					
Depression	2185	2.7	1672	5.3	<.001
Anxiety disorder	1279	1.6	1361	4.3	<.001
Opioid dependency	154	0.2	262	0.8	<.001
Additional substances used					
Tobacco	20 785	25.8	13 097	41.8	<.001
SSRI (last 30 d of pregnancy)	1529	1.9	1335	4.3	<.001

Percentages may not add to 100% because of rounding.
IQR, interquartile range.

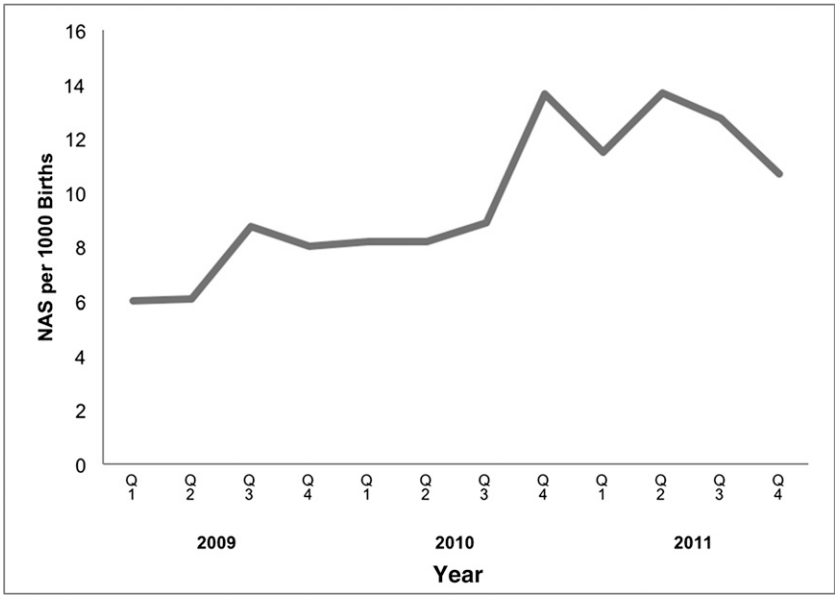

FIGURE 1
Rate of NAS in Tennessee Medicaid according to quarter, 2009 through 2011. $P < .001$.

Based on our regression model, the predicted probability of NAS among mothers who received OPRs during pregnancy varied greatly depending on drug type, cumulative opioid exposure, and number of cigarettes smoked per day. As an example, a woman who took oxycodone hydrochloride 10 mg every 6 hours for 5 weeks with no tobacco or SSRI use had a probability of delivering an infant with NAS of 0.011 (95% CI: 0.008–0.016). In contrast, a woman prescribed buprenorphine hydrochloride 24 mg daily for 25 weeks, who smoked 20 cigarettes (ie, 1 pack) per day and took an SSRI, had a 0.366 (95% CI: 0.270–0.474) probability of her infant having NAS (Table 3).

TABLE 2 Infant Characteristics for Infants With and Without NAS in Tennessee Medicaid, 2009–2011

Characteristic	No Opioid (No NAS) (n = 80 292)		Opioid (No NAS) (n = 30 651)		NAS (n = 1086)		P
	N	%	*N*	%	*N*	%	
Female	39 064	48.7	14 986	48.9	502	46.2	.2
Preterm (<37 wk)	8868	11.0	3549	11.6	181	16.7	<.001
Low birth weight (<2500 g)	7940	9.9	3615	11.8	230	21.2	<.001
Clinical conditions							
Respiratory diagnoses	7052	8.8	3083	10.1	312	28.7	<.001
Transient tachypnea of the newborn	2192	2.7	964	3.1	146	13.4	<.001
Respiratory distress syndrome	2170	2.7	1045	3.4	76	7.0	<.001
Meconium aspiration syndrome	321	0.4	106	0.3	36	3.3	<.001
Other respiratory diagnoses	4517	5.6	1965	6.4	177	16.3	<.001
Jaundice	13 963	17.4	5503	18.0	393	36.2	<.001
Feeding difficulty	1809	2.3	788	2.6	142	13.1	<.001
Sepsis	1515	1.9	692	2.3	78	7.2	<.001
Seizure	240	0.3	117	0.4	40	3.7	<.001
Hemolytic disease	1051	1.3	342	1.1	28	2.6	<.001
Necrotizing enterocolitis	136	0.2	56	0.2	**	0.1	.7

Comparisons made among mutually exclusive groups of no opioid exposure and no NAS, opioid exposure and no NAS, and NAS. Percentages may not add to 100% because of rounding.
**Value suppressed given n <10 in cell.

DISCUSSION

In this large retrospective cohort study of >100 000 pregnancies, cumulative OPR exposure for short-acting OPRs, opioid type, tobacco, and SSRI use during pregnancy was associated with an increased risk of NAS. In the study cohort, nearly 1 in 3 women used at least 1 OPR during pregnancy; 96% were nonmaintenance prescription opioids. Although NAS has previously been associated with illicit opioid use, we found that 65% of infants with NAS were exposed to legally obtained OPRs in pregnancy. These associations provide compelling evidence that OPRs and other concurrent antenatal exposures have a measurable deleterious impact on infants who are more likely than others to be born with NAS and related complications.

Maintenance medications were categorized separately, given that women using maintenance medications have different risks and different reasons for using opioids. For women with heroin dependency especially, maintenance medications have been shown to improve both maternal and neonatal outcomes, including improved fetal growth and decreased preterm birth.[33,34]

Neonatal Complications

Rates of NAS nearly doubled in TennCare during our 3-year study period, reaching 10.7 per 1000 births, exceeding previously reported rates of 3.4 per 1000 births.[6] Compared with nonopioid-exposed infants, those with NAS were more likely to have neonatal complications. Opioid-exposed infants and those with NAS were more likely than nonopioid-exposed infants to be born preterm and have low birth weight. Preterm birth imparts risk to the infant for clinical comorbidities, including respiratory distress syndrome, feeding difficulties, and jaundice (as we have shown).

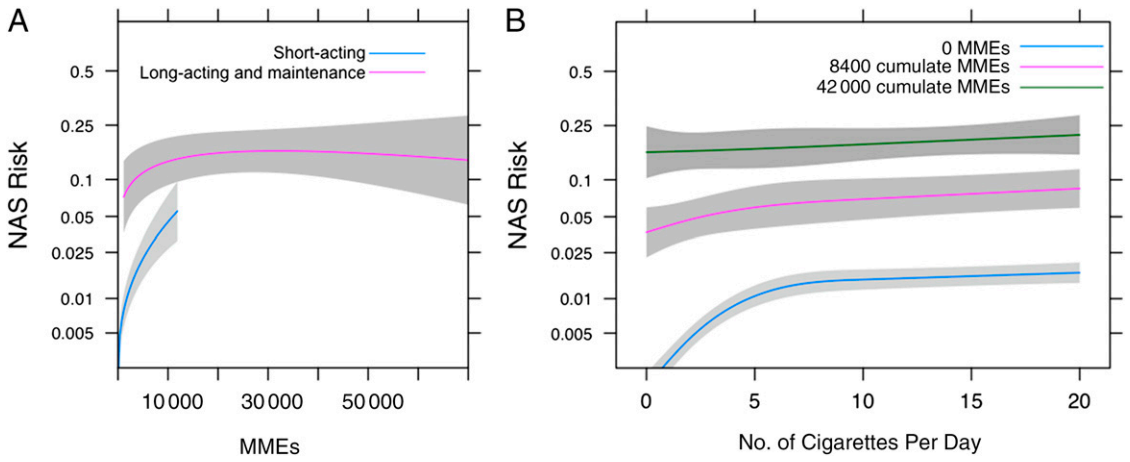

FIGURE 2

Probability of NAS. A, Opioid type and cumulative morphine milligram equivalents (MMEs). B, Number of cigarettes smoked per day and cumulative MMEs after adjusting for maternal characteristics, infant characteristics, and birth characteristics. Graph A: Cumulative MMEs and risk of NAS for short-acting opioid preparations ($P < .001$) and long-acting/maintenance opioid preparations ($P = .16$). Graph B: An increasing number of cigarettes raised the risk of NAS among women with 0 cumulative MME (ie, receiving no legal opioids; $P < .001$) receiving a cumulative total of 8400 MMEs, which equals oxycodone 10 mg q6h × 20 weeks ($P < .001$), and 42 000 MMEs, which equals buprenorphine 24 mg daily × 25 weeks ($P < .001$). The absolute risk and 95% CIs of NAS have been adjusted for cumulative opioid dose in MMEs, maternal age, maternal education, birth number, infant birth weight, year of birth, maternal race, infant gender, multiple gestations, and interaction effects of drug type × cumulative opioid dose ($P = .002$), number of cigarettes smoked per day × cumulative opioid dose ($P < .001$), and drug type × number of cigarettes smoked per day. Total sample = 112 029 mother–infant dyads, 30 651 mothers with OPR use, and 1086 infants with NAS.

In this study cohort, opioid dose for short-acting opioids, tobacco use, and SSRI use were strongly associated with NAS. Similar to previous smaller studies, we found that dose of maintenance opioids did not modify the risk of NAS.[8,9] Furthermore, our findings provide important information that builds on previous studies of OPR use in pregnancy[3,35,36] and several publications describing tobacco and SSRI use in the context of opioid maintenance.[10–12] Both tobacco and SSRIs have been described in the literature as having individual withdrawal syndromes and unique toxidromes.[5] Nevertheless, these exposures could also be associated with a constellation of other risk factors that may be difficult to measure directly (eg, substance abuse) and account for in our analyses. Polysubstance exposure is common among infants with NAS, raising the possibility that observable clinical signs (eg, hypertonia) may not be solely attributable to opioids. In many instances, clinical signs compatible with NAS may be due to multiple withdrawal syndromes and toxidromes occurring simultaneously.

State Policies

The association of increasing use of OPR, overdose deaths, and NAS garnered the attention of many state and federal policymakers.[37] States license and regulate prescribers and pharmacists, and they are financially responsible for the care received by ~80% of infants with NAS through Medicaid programs.[6,38] Nearly all states have implemented prescription drug monitoring programs[39] that aim to reduce diversion and misuse of OPR by identifying high users and high-risk behavior (eg, "doctor and pharmacy shopping"). Tennessee's program began in 2006 as an optional resource for providers and pharmacists. In 2013, the state instituted a requirement that the program must be queried before prescribing most controlled substances.[40] Our study found that ~30% of pregnant women in TennCare were prescribed at least 1 opioid before these policy changes. It will be important moving forward to evaluate the impact of new state policies on reducing opioid use in pregnancy and the incidence of NAS. Furthermore, innovative strategies to enhance prescription drug monitoring databases by including risk predictions of adverse outcomes such as NAS and overdose deaths[41] should be piloted and evaluated.

Variable Risk

The American Academy of Pediatrics recommends that all opioid-exposed infants be observed in the hospital for 4 to 7 days after birth.[5] However, our data suggest there was a wide variability in an infant's risk of drug withdrawal based on opioid type, dose, SSRI use, and number of cigarettes smoked per day by the mother (Fig 2, Table 3). Future studies should evaluate new care models for opioid-exposed infants at different risk levels of developing NAS. For instance, some low-risk infants may be safely discharged from the hospital sooner, whereas high-risk infants may require longer hospital observation.

Limitations

Our study does have several important limitations to consider, similar to other studies that rely on accurate coding of

TABLE 3 Probability of NAS According to Varying Exposures of Short-Acting Opioids and Maintenance Opioids, Tobacco, and SSRI Use

Variable	Short-Acting (eg, Oxycodone Hydrochloride) 10 mg q6h	Maintenance (eg, Buprenorphine Hydrochloride Tablet) 24 mg q24h
	Probability (95% CI)	Probability (95% CI)
5-wk duration	0.011 (0.008–0.016)	0.132 (0.085–0.199)
No cigarette use, SSRI use	0.023 (0.016–0.034)	0.241 (0.157–0.351)
5 cigarettes/d, no SSRI	0.026 (0.020–0.033)	0.165 (0.123–0.219)
5 cigarettes/d, SSRI	0.053 (0.039–0.071)	0.293 (0.217–0.383)
20 cigarettes/d, no SSRI	0.037 (0.029–0.047)	0.179 (0.137–0.231)
20 cigarettes/d and SSRI use	0.074 (0.056–0.098)	0.314 (0.239–0.399)
25-wk duration	0.048 (0.028–0.081)	0.163 (0.103–0.247)
No cigarette use, SSRI use	0.095 (0.055–0.158)	0.289 (0.188–0.416)
5 cigarettes/d, no SSRI	0.073 (0.045–0.115)	0.172 (0.123–0.236)
5 cigarettes/d, SSRI	0.141 (0.088–0.220)	0.303 (0.218–0.404)
20 cigarettes/d, no SSRI	0.104 (0.068–0.156)	0.216 (0.156–0.291)
20 cigarettes/d and SSRI use	0.196 (0.129–0.285)	0.366 (0.270–0.474)

Results shown after adjustment for maternal age, education, race, infant gender, birth weight, year of birth, interaction drug type and cumulative opioid exposure (0.0002), interaction of number of cigarettes smoked per day and cumulative opioid exposure ($P < .001$), and interaction of drug type and number of cigarettes smoked per day.

Probability can be interpreted as 1 = 100% certainty that an event will occur, and 0 = 0% certainty that an event will occur. As an example, a probability of an outcome equal to 0.37 can be interpreted as among a sample of 100 patients, 37 will have the predicted outcome.

As an example, a woman taking oxycodone hydrochloride 10 mg every 6 hours for 5 weeks with no tobacco or SSRI use had a probability of delivering an infant with NAS of 0.011 (95% CI: 0.008–0.016). In contrast, a woman prescribed buprenorphine hydrochloride 24 mg daily for 25 weeks smoking 20 cigarettes (ie, 1 pack) per day and taking SSRIs had a 0.366 (95% CI: 0.270–0.474) probability of delivering an infant with NAS.

hospital administrative and vital statistics data. Both errors of omission and commission are possible, leading to misclassification bias; however, our medical record review suggested that potential misclassification of outcomes was likely to be small. Next, we did not directly observe women in our cohort taking the prescribed OPR. It is possible that OPR medications were not taken as prescribed, resulting in a bias toward the null hypothesis. Next, we were unable to capture other exposures (eg, illicit drugs) that may have influenced our primary outcome (NAS). Opioids obtained by other legal sources not paid for by TennCare (ie, cash payments) were not captured in our sample, which could bias our results toward the null hypothesis. Conversion to morphine milligram equivalents, although the accepted standard, may not create perfect comparisons of various OPRs. Finally, it is possible that opioid prescribing is a surrogate for other unmeasured risk factors for NAS; residual confounding cannot be completely ruled out.

CONCLUSIONS

The use of commonly prescribed, nonmaintenance OPRs in pregnancy increased the infant's risk of developing NAS. Nearly 27% of our cohort of pregnant women was prescribed at least 1 short-acting OPR. Furthermore, NAS risk varied widely based on antenatal cumulative opioid exposure, opioid type, number of cigarettes smoked per day, and SSRI use. Public health efforts should focus on limiting inappropriate OPR and tobacco use in pregnancy. Prescribing opioids in pregnancy should be done with caution because it can lead to significant complications for the neonate.

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THE HIGH COST OF WORKING: *My daughter has begun the search for a summer job or internship. Last year, she was quite fortunate as she found a paid internship in a city only 5 hours from where we live. The company, a provider of wellness packages, seemed a great fit given my daughter's interest in athletics and communication. That she was actually paid to rotate through the different departments and assist in a variety of functions made the experience all the more remarkable. One of my sons, looking for a position overseas, has not been so fortunate.*

As he has found out, and as reported in The New York Times *(Education Life: February 5, 2015), few paid overseas internships exist. Students either volunteer or pay someone else for the opportunity to do an internship. The demand for overseas positions is high. During the 2012-13 year, approximately 40,000 Americans participated in for-credit internships or interned, worked, or volunteered abroad for no credit. Given the demand for positions, companies have sprung up to arrange for internships in a wide array of industries across the globe. While the experiences can be quite gratifying and many students report that the experience helped them find a job back home in the US, the costs of obtaining the internship can be high. Students may have to pay between $8,000 and $15,000 for a 6- to 8-week experience. The cost of the flight and food are additional. While I am supportive of overseas learning experiences, I am having a bit of trouble digesting the concept of paying so much money for the opportunity. I am hoping that my children find summer internships close to home.*

Noted by WVR, MD