Maternal Drug Use and Its Effect on Neonates

A Population-Based Study in Washington State

Andreea A. Creanga, MD, PhD, Jennifer C. Sabel, PhD, Jean Y. Ko, PhD, Cathy R. Wasserman, PhD, Carrie K. Shapiro-Mendoza, PhD, MPH, Polly Taylor, MPH, Wanda Barfield, MD, MPH, Laurie Cawthon, MD, MPH, and Leonard J. Paulozzi, MD

OBJECTIVE: To estimate the effect of maternal illicit and prescription drug use on neonates in Washington State between 2000 and 2008.

METHODS: We used state-linked birth certificate and hospital discharge (mother and neonate) data to calculate prenatal drug exposure and neonatal abstinence syndrome rates, and compared state neonatal abstinence syndrome rates with national-level data from the Nationwide Inpatient Sample. We identified the drugs of exposure, examined predictors of drug exposure and neonatal abstinence syndrome, and assessed perinatal outcomes among drug-exposed and neonatal abstinence syndrome-diagnosed neonates compared with unexposed neonates.

RESULTS: Drug exposure and neonatal abstinence syndrome rates increased significantly between 2000 and 2008, neonatal abstinence syndrome rates being consistently higher than national figures (3.3 compared with 2.8 per 1,000 births in 2008; $P<.05$). The proportion of neonatal abstinence syndrome-diagnosed neonates exposed prenatally to opioids increased from 26.4% in 2000 to 41.7% in 2008 ($P<.05$). Compared with unexposed neonates, drug-exposed and neonatal abstinence syndrome-diagnosed neonates had a lower mean birth weight, longer birth hospitalization, were more likely to be born preterm, experience feeding problems, and have respiratory conditions (all $P<.001$).

CONCLUSION: Maternal use of illicit and prescription drugs was associated with considerable neonatal morbidity and significantly higher rates of drug exposure and neonatal abstinence syndrome in recent years. Data suggest that opioid analgesics contributed to the increase in prenatal drug exposure and neonatal abstinence syndrome in Washington State. In accordance with current guidelines, our findings emphasize the need for clinicians to screen pregnant women for illicit and prescription drug use and minimize use of opioid analgesics during pregnancy.

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LEVEL OF EVIDENCE: II

In utero exposure to illicit drugs, including street and prescription drugs used nonmedically, as well as methadone prescribed as treatment for opiate addiction can have negative effects on fetal development and potentially on subsequent infant, child, and adult health.[1,2] Prematurity, fetal growth restriction, and neonatal abstinence syndrome are well-established immediate effects of prenatal exposure to certain drugs.[1–3] The latter represents a constellation of behavioral and physiological signs and symptoms that occur in a newborn exposed to addictive illegal or prescription drugs while in the uterus, and, depending on exposure patterns, may require significant pharmacologic intervention.[3]

The 2009 National Survey on Drug Use and Health, the primary source of statistics on illicit drug use in the United States, estimates that 4.5% of pregnant women (15–44 years) used illicit drugs in the month before the survey.[4] Although the prevalence of illicit drug use among pregnant women does

From the Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, the Epidemic Intelligence Service, Office of Workforce and Career Development, and the Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, Centers for Disease Control and Prevention, Atlanta, Georgia; and the Washington State Departments of Health and Social and Health Services, Research and Data Analysis, Olympia, Washington.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Corresponding author: Andreea A. Creanga, MD, PhD, Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, 4770 Buford Highway, NE, Mail Stop K-23, Atlanta GA 30341-3717; e-mail: acreanga@cdc.gov.

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not appear to have changed since the early 2000s,[4,5] the types of drugs that pregnant women are using may have shifted.[4] One recent study found that prevalence of chronic medical use of prescription narcotics during pregnancy increased significantly from approximately 2.5 per 1,000 deliveries in 2000 to over 10.0 per 1,000 deliveries in 2008.[5] This is consistent with the documented increase in therapeutic and nonmedical use of prescription pain relievers in the United States.[6,7]

Rates of past-year nonmedical use of prescription pain relievers for all individuals 12 years of age or older and rates of past month illicit drug use among individuals 26 years of age or older in Washington State have consistently been among the highest in the country.[4] Moreover, trend data on drug abuse in Washington State show that numbers of overdose hospitalizations and deaths related to use of prescription opiates were four and five times, respectively, higher in 2008 than in 1999.[8] Population-based linked maternal and infant data from Washington State present an opportunity to estimate how the high drug use rate and increased abuse of prescription opiates in the state affect pregnant women and neonates. This study aims to: 1) estimate trends in prenatal drug exposure and neonatal abstinence syndrome rates in Washington State and compare the latter with corresponding neonatal abstinence syndrome rates in the United States; 2) identify the types of drugs resulting in prenatal drug exposure and neonatal abstinence syndrome; 3) estimate predictors of prenatal drug exposure and neonatal abstinence syndrome; and 4) assess perinatal outcomes among drug-exposed and neonatal abstinence syndrome-diagnosed neonates in Washington State.

MATERIALS AND METHODS

We used 2000–2008 data from the Birth Events Records Database maintained by the Washington State Department of Health. The data consist of infant birth certificates linked to birth hospitalization discharge data for infants and mothers. The Washington State Department of Health receives the data electronically with the exception of 1% of birth certificates being filed as paper forms and performs a range of data quality procedures and consistency checks before making the data available for analysis; detailed information on the data and data quality procedures can be found elsewhere.[9] The analysis was restricted to state-resident mothers who delivered in nonmilitary hospitals in Washington State. We identified prenatal drug exposure and neonatal abstinence syndrome using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes from the maternal and infant hospital discharge data as shown in Table 1. To provide a

Table 1. International Classification of Diseases, 9th Revision, Clinical Modification Codes Used to Identify Prenatal Drug Exposure

Data	Condition	ICD-9-CM Code
Maternal birth hospital discharge diagnosis	Drug dependence	304.x, 648.3
	Drug abuse	305.x
	Drug-induced mental disorders	292.x
	Drug poisoning	965.0, 965.8, 965.9, 967.x, 968.2, 968.3, 968.5, 969.x, 977.8, 977.9, E850.0, E850.1, E850.2, E850.8, E851.x-E854.x, E855.2, E950.x, E980.x
	Use of drugs causing adverse effects in therapeutic use	E935.0, E935.1, E935.2, E937.x, E938.2, E938.3, E938.5, E939.x, E940.x
	Counseling on substance use and abuse	V65.42
Maternal procedure during birth hospitalization	Drug addiction counseling	94.45
	Referral for drug addiction rehabilitation	94.54
	Drug rehabilitation	94.64, 94.67
	Drug detoxification	94.65, 94.68
	Drug rehabilitation and detoxification	94.66, 94.69
Infant birth hospital discharge diagnosis	Drug dependence	304.x
	Adverse effects of therapeutic drugs used to treat withdrawal	E935.1, E935.2, E937.0, E939.4, E940.1, E940.8, E940.9
	Fetus or newborn affected by noxious substance transmitted by the placenta	760.72, 760.73, 760.75
	Suspected damage to the fetus from drugs	655.5
	Neonatal abstinence syndrome	779.5

ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification.

comparison with neonatal abstinence syndrome rates in the United States, we used 2000–2008 Nationwide Inpatient Sample hospital discharge data obtained from the Healthcare Cost and Utilization Project.[10] We identified all records with a neonatal abstinence syndrome discharge diagnosis (Table 1) and used the algorithm proposed by Kuklina et al[11] to identify delivery hospitalizations. We calculated annual rates of drug exposure and neonatal abstinence syndrome among neonates born in Washington State and annual neonatal abstinence syndrome rates in the United States between 2000 and 2008; Cuzick nonparametric tests for trend were performed to assess the statistical significance of the observed trends.[12]

Because ICD-9-CM coding lacks the detail necessary to differentiate between illicit and prescription drug use for most drug exposure diagnoses, we can only categorize drug exposure into broad drug categories: 1) opioids and related narcotics (including heroin, opioid analgesics, and methadone); 2) cocaine; 3) other psychotropic drugs (including sedatives, hypnotics, and tranquilizers); and 4) other or unspecified drugs. To the extent possible, we separately explored opioid exposure resulting from heroin (ICD-9-CM 965.01, E850.0, E935.0) and prescription opioids including methadone (ICD-9-CM 965.02, 965.09, E850.1, E850.2, E935.1, and E935.2). The contribution of these drug categories and of multidrug use to prenatal drug exposure and neonatal abstinence syndrome in Washington State was calculated for 2000–2008. We could not conduct the same analysis using the Nationwide Inpatient Sample data and provide a meaningful Washington State–U.S. comparison due to confidentiality laws by which some data sources contributing data to Nationwide Inpatient Sample restrict discharge records indicating chemical dependency.[10]

In the absence of a unique identifier, five variables (zip code, year of birth, race, ethnicity, and education) were used to identify "repeat mothers" (women with more than one delivery or multiple births [ie, twins]). We investigated the effect of clustering from multiple records (ie, repeat mothers) using generalized estimating equations. Multivariable logistic regression models with generalized estimating equations and an exchangeable working correlation matrix were computed using pooled 2000–2008 Birth Events Records Database data to identify predictors of drug exposure and neonatal abstinence syndrome using drug-unexposed neonates as the reference group. We explored the influence of several factors reported on the birth certificate (neonatal sex, maternal age, maternal race or ethnicity, marital status, parity, education, and pregnancy trimester at onset of prenatal care) as well as presence of maternal mental health disorders (ICD-9-CM 290.x, 293.x–319.x) and the payer source for index delivery from hospital discharge data.

Generalized estimating equation methods were also used to examine perinatal outcomes among drug-exposed and neonatal abstinence syndrome-diagnosed neonates compared with drug-unexposed neonates. Specifically, we fitted univariable logistic regression models for the following perinatal outcomes: neonate's mode of delivery (vaginal or cesarean), preterm birth (gestational age less than 37 weeks), low birth weight (less than 2,500 g) as recorded on birth certificates, presence of disorders relating to short gestation and low birth weight (ICD-9-CM 765.0x, 765.1x), feeding problems (ICD-9-CM 779.3x), respiratory distress syndrome (ICD-9-CM 769.x) and other respiratory conditions (ICD-9-CM 770.x) as noted on infants' birth hospital discharge records, and univariable linear regression models for: birth weight as recorded on birth certificates and the length of birth hospitalization. Drug exposure and neonatal abstinence syndrome, respectively, were the covariates of interest in all univariable models. Because relationships between drug exposure and neonatal abstinence syndrome and neonatal feeding problems, respiratory distress syndrome, other respiratory conditions, and length of birth hospitalization may be confounded by low birth weight or prematurity, for these four outcomes, we estimated both low birth weight-adjusted models and prematurity-adjusted models. Separately, for all outcomes, we also estimated models adjusted for three proxy variables for maternal heavy drinking (ICD-9-CM 303.x, 305.0, 292.x, 980.x), heavy smoking (ICD-9-CM 305.1, 649.0), and maternal nutritional deficiencies (ICD-9-CM 648.9, 260.x–269.x, 799.4, V12.1).

All statistical analyses were conducted using STATA 10. Both Birth Events Records Database and Nationwide Inpatient Sample data are publicly available and do not include any personal identifiers; thus, the study was considered exempt from review by the institutional review board at the Centers for Disease Control and Prevention.

RESULTS

Between 2000 and 2008, there were 709,948 births to Washington State-resident women occurring at nonmilitary hospitals in Washington State. Of these, 669,451 records in Birth Events Records Database had complete data (ie, birth certificate, mother and infant birth discharge records) corresponding to a population-level data linkage rate of 94.3%. Our

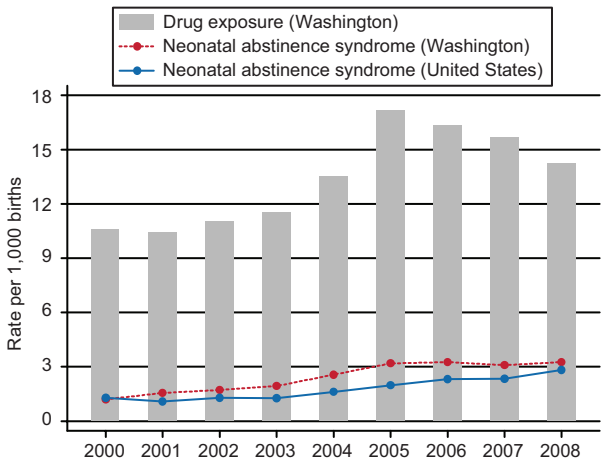

Fig. 1. Trends in prenatal drug exposure and neonatal abstinence syndrome in Washington State and the United States: 2000–2008.

Creanga. Maternal Drug Use and Neonatal Morbidity. Obstet Gynecol 2012.

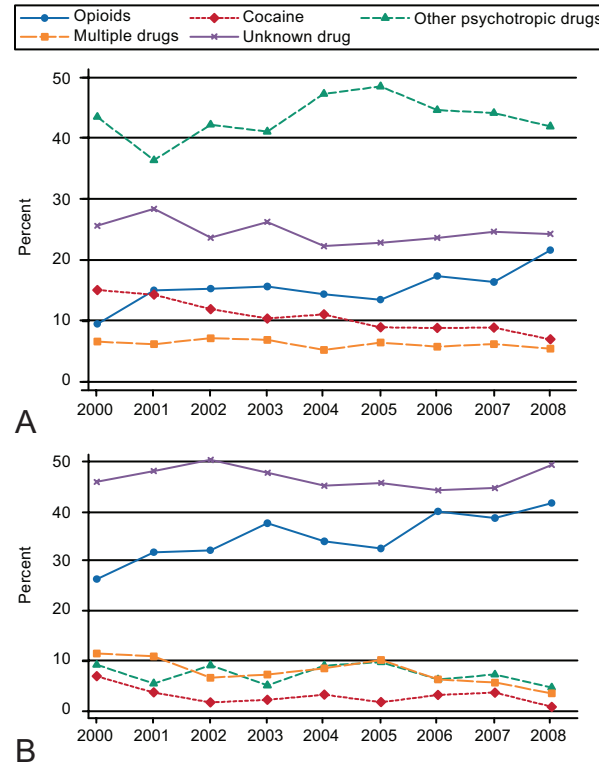

Fig. 2. Contribution of specific categories of drugs to prenatal drug exposure **(A)** and neonatal abstinence syndrome **(B)** in Washington State: 2000–2008. Note: Exclusive exposure to opioids, cocaine, and other psychotropic drugs is shown; exposure to multiple drugs includes exposure to two or more drug categories as presented in the text.

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ICD-9-CM-based algorithm identified 9,024 (1.3%) drug-exposed neonates. Drug exposure rates increased from 10.6 per 1,000 births in 2000 to 16.3 per 1,000 births in 2005 and decreased slightly to 14.3 per 1,000 births in 2008 (overall trend, $P=.021$). Almost one-fifth (18.9%) of drug-exposed neonates or 0.3% of 2000–2008 Washington State neonates were diagnosed with neonatal abstinence syndrome. Neonatal abstinence syndrome rates increased significantly both in Washington State and nationwide between 2000 and 2008, being consistently higher in Washington State ($P<.001$) (Fig. 1). By and large, neonatal abstinence syndrome rates increased monotonically from 1.2 per 1,000 births in 2000 to 3.3 per 1,000 births in 2008 (trend $P=.008$) in Washington State, and from 1.3 per 1,000 births in 2000 to 2.8 per 1,000 births in 2008 in the United States as a whole (trend $P=.011$).

The vast majority of 2000–2008 drug-exposed neonates in Washington State were exposed prenatally to psychotropic drugs other than opioids or cocaine (Fig. 2). Similar proportions of neonates were exclusively exposed to such drugs in 2000 (43.5%) and 2008 (41.9%). Prenatal exposure to opioids (including exposure among multidrug users) more than doubled (11.5% in 2000 compared with 24.4% in 2008) during the study period (data not shown) with 21.6% of neonates being exposed exclusively to opioids in 2008 (Fig. 2). Only one case of heroin and 363 cases of prescription opioid (including methadone) poisoning were identified during the study period using the specific ICD-9-CM codes. Exposure to cocaine declined during the study period–20.5% of drug-exposed neonates were exposed to cocaine in 2000 compared with 10.5% in 2008 (data not shown, includes both exclusive and multidrug exposure). Although 15.0% of all drug-exposed neonates were exposed to cocaine alone in 2000, this proportion declined to 6.9% in 2008 (Fig. 2). A relatively smaller proportion of neonates was identified as having been exposed to multiple drugs (6.5% in 2000 compared with 5.4% in 2008). The specific category of drugs to which neonates were exposed is unknown for approximately one-fourth of all neonates each year during the study period.

The proportion of neonatal abstinence syndrome-diagnosed neonates exclusively exposed prenatally to opioids increased from 26.4% in 2000 to 41.7% in 2008 ($P<.05$; Fig. 2). In contrast, between 2000 and 2008, exclusive exposure to cocaine decreased from 6.9% to 0.8% and that to other psychotropic agents from 9.2% to 4.6%. For a considerable proportion of neonatal abstinence syndrome-diag-

nosed neonates (49.4% in 2008), the type of drugs to which they have been exposed is unknown, whereas 3.5% of them are known to have been exposed to a combination of drugs.

No difference was observed in the proportion of male and female drug-exposed neonates, but male neonates appeared to be at slightly higher risk of being diagnosed with neonatal abstinence syndrome (adjusted odds ratio [OR] 1.2, 95% confidence interval [CI] 1.1–1.3) (Table 2). Neonates born to Native American or Alaska Native women were 1.8 (95% CI 1.7–1.9) times more likely to be exposed to drugs and 2.0 (95% CI 1.7–2.3) times more likely to be diagnosed with neonatal abstinence syndrome when compared with those born to non-Hispanic white women. Interestingly, neonates of non-Hispanic African American women were as likely as those of non-Hispanic white women to be exposed to drugs but less likely to be diagnosed with neonatal abstinence syndrome. The older the age of the woman, the more likely her newborn was to be exposed to drugs and diagnosed with neonatal abstinence syndrome. On

Table 2. Predictors of Prenatal Drug Exposure and Neonatal Abstinence Syndrome Among Neonates in Washington State, 2000–2008

		Drug-Exposed (n=9,024)		Neonatal Abstinence Syndrome (n=1,642)	
Characteristics (N=669,451)	Drug-Unexposed (n=660,427) %	%	Adjusted OR (95% CI)	%	Adjusted OR (95% CI)
Sex (female [referent])	48.8	48.6	1.0	44.3	1.0
Male	51.2	51.4	1.0 (1.0–1.1)	55.7	1.2 (1.1–1.3)
Mother's race or ethnicity					
(non-Hispanic white [referent])*	71.5	72.8	1.00	77.0	1.0
Non-Hispanic African American	4.3	9.7	1.0 (0.9–1.1)	5.9	0.6 (0.5–0.7)
Native American or Alaska Native	2.3	10.7	1.8 (1.7–1.9)	12.1	2.0 (1.7–2.3)
Asian American or Pacific Islander	9.7	2.5	0.3 (0.2–0.3)	1.6	0.2 (0.1–0.3)
Hispanic	12.3	4.3	0.2 (0.1–0.2)	3.4	0.1 (0.1–0.2)
Age (y) (younger than 20 [referent])	8.8	12.4	1.0	4.1	1.0
20–24	23.6	32.5	1.3 (0.2–1.4)	26.3	3.1 (2.4–4.0)
25–29	27.8	27.1	1.4 (1.3–1.6)	32.8	5.4 (4.2–7.1)
30–34	24.4	16.7	1.4 (1.3–1.6)	21.3	5.7 (4.4–7.6)
35 or older	15.3	11.2	1.5 (1.4–1.7)	15.5	6.8 (5.1–9.1)
Education (completed years)					
(fewer than 12 [referent])*	74.6	85.7	1.0	87.9	1.0
12	9.2	9.1	0.9 (0.8–0.9)	6.5	0.6 (0.5–0.8)
More than 12	16.3	5.3	0.6 (0.6–0.7)	5.6	0.6 (0.5–0.7)
Marital status (married [referent])*	69.3	23.6	1.0	31.6	1.0
Unmarried	30.7	76.4	1.8 (1.5–2.2)	68.4	1.7 (1.2–2.5)
Number of living children (0 [referent])*	41.8	32.4	1.0	27.0	1.0
1	32.5	25.6	1.2 (1.1–1.3)	26.2	1.1 (1.0–1.3)
2	15.5	19.7	1.6 (1.5–1.8)	22.7	1.5 (1.3–1.7)
3 or more	10.2	22.3	2.2 (2.1–2.4)	24.1	1.6 (1.4–1.9)
Diagnosis of a mental health disorder					
(no [referent])	98.1	90.4	1.0	87.0	1.0
Yes	1.9	9.6	3.7 (3.4–4.0)	13.0	4.3 (3.6–4.9)
Onset of prenatal care					
(first trimester [referent])*	80.4	50.7	1.0	53.7	1.0
Second trimester	15.6	27.2	1.7 (1.6–1.8)	24.7	1.5 (1.3–1.8)
Third trimester	3.4	10.7	2.7 (2.5–3.0)	10.1	2.4 (2.1–2.9)
No prenatal care	0.7	10.5	11.0 (10.0–12.0)	11.5	8.2 (6.7–10.0)
Principal payer for delivery					
(Medicaid [referent])	39.9	79.5	1.0	80.3	1.0
HMO or third party	59.2	17.5	0.3 (0.3–0.3)	17.1	0.2 (0.2–0.2)
Self-pay	0.9	3.0	1.3 (1.2–1.5)	2.6	1.0 (0.7–1.3)

OR, odds ratio; CI, confidence interval; HMO, health maintenance organization.
Models adjusted for all neonatal/maternal characteristics shown.
* Missing data on race on 2.2% of cases, on education for 3.3% of cases, on marital status for 0.8% of cases, on the number of living children for 2.4% of cases, and on prenatal care onset for 12.3% of cases; missing data indicators for all variables with missing data were included in the regression models.

the other hand, the more educated women were, the less likely their neonates were to be exposed to or affected by maternal drug use. Neonates born to unmarried women were 1.7 times (95% CI 1.2–2.5) more likely to be diagnosed with neonatal abstinence syndrome compared with married women. Women of higher parity were more likely than their counterparts to deliver drug-exposed neonates and have neonatal abstinence syndrome-diagnosed neonates. Women with a diagnosis of mental health disorder were 3.7 (95% CI 3.4–4.0) times more likely to have drug-exposed neonates and 4.3 (95% CI 3.6–4.9) times more likely to have neonatal abstinence syndrome-diagnosed neonates.

Although women who initiated prenatal care in their second or third pregnancy trimester were between 1.5 and 2.7 times more likely to have drug-exposed and neonatal abstinence syndrome-diagnosed neonates than women who started prenatal care in their first trimester, the lack of prenatal care increased the odds of women having drug-exposed and neonatal abstinence syndrome-diagnosed neonates by more than eight times. Women with private health insurance were less likely to use drugs during pregnancy and have a neonate diagnosed with neonatal abstinence syndrome than women who were on Medicaid.

Among neonates not exposed to drugs, 28.1% were delivered by cesarean, whereas 31.0% ($P<.001$) of drug-exposed neonates and 39.8% ($P<.001$) of those diagnosed with neonatal abstinence syndrome were cesarean deliveries (Table 3). The mean length of birth hospitalization was 2.6 (standard deviation 6.3, median 2, range 0–279) days for unexposed neonates compared with 6.5 (standard deviation 12.0, median 3, range 1–274; $P<.001$) days for drug-exposed neonates and 14.4 (standard deviation 14.3, median 10, range 1–169; $P<.001$) days for those diagnosed with neonatal abstinence syndrome. Neonates exposed to drugs in utero and diagnosed with neonatal abstinence syndrome weighed on average 326.9 g and 400.5 g less than those unexposed to drugs, respectively. Relative to unexposed neonates, those exposed to drugs had 2.6–3.4 times the odds of being born preterm, low birth weight, having conditions relating to both short gestation and low birth weight, feeding problems, respiratory distress syndrome, or other respiratory conditions specific to the early neonatal period. Moreover, neonates diagnosed with neonatal abstinence syndrome were between 4.1 and 9.2 times more likely than drug-unexposed neonates to have the conditions noted previously. Importantly, these crude ORs declined by more than 10.0% for the associations between drug exposure and neonatal abstinence syndrome and birth weight, low birth weight, and feeding problems after adjusting for three important potential confounders: heavy drinking, heavy smoking, and maternal nutritional deficiencies, but their statistical significance did not change. As shown in Table 3, ORs for the associations between perinatal outcomes and drug exposure and neonatal abstinence syndrome declined after adjusting for low birth weight or prematurity, but their statistical significance persisted.

DISCUSSION

This study uses population-level data to investigate patterns of maternal drug use and its effect on neonates in a U.S. state in recent years. Rates of neonatal drug exposure and neonatal abstinence syndrome increased significantly in Washington State during the study period, the latter following a similar but consistently higher trend than the U.S. neonatal abstinence syndrome rate. Since 2005, rates of prenatal drug exposure decreased by 17.0%, whereas neonatal abstinence syndrome rates plateaued in Washington State. Because opioids are the most frequent cause of neonatal abstinence syndrome,[5,13] this finding is consistent with the observed increase in opioid exposure among neonates overall and among those diagnosed with neonatal abstinence syndrome, and supports our hypothesized shift in the types of drugs women use during pregnancy. This is not the only report that points toward a rise in opioid use by pregnant women in Washington State. Recently reported data from the Pediatric Interim Care Center in Kent, Washington, a "statewide model program" providing specialized care for drug-exposed newborns, show that the percentage of admitted neonates exposed to prescription-type opiates has doubled between 2005 and 2009.[8] This finding is consistent with a documented twofold increase in sales of opioid analgesics in Washington State in recent years (see the Appendix online at http://links.lww.com/AOG/A292)[14] and the current obstetric literature showing significant increases in use of prescription opioid analgesics among pregnant women.[5] The matching, yet slower rates of increase in both neonatal abstinence syndrome and opioid analgesic sales in the United States suggest that this practice may not be unique to Washington State.[14]

Several factors associated with drug exposure and neonatal abstinence syndrome in Washington State are identified here. Male neonates are slightly more likely to be diagnosed with neonatal abstinence syndrome than females. Although based on administrative data, this finding is in line with results from

Table 3. Associations Between Prenatal Drug Exposure and Neonatal Abstinence Syndrome and Perinatal Health Among Neonates in Washington State, 2000–2008

Perinatal Health Outcomes (N=669,451)	Drug-Unexposed (n=660,427) Mean (SD) or %	Drug-Exposed (n=9,024) Mean (SD) or %	Crude OR (95% CI)*	LBW-Adjusted OR (95% CI)†	Prematurity-Adjusted OR (95% CI)‡
Delivery-related associations					
Cesarean delivery	28.1	31.0	1.2 (1.0–1.3)		
Preterm delivery†	8.4	21.1	3.0 (2.8–3.1)		
Birth weight (g)†	3,385.9 (567.5)	3,062.6 (650.1)	−326.9 (−338.7 to −315.1)		
LBW†	5.7	16.6	3.4 (3.2–3.6)		
Disorders relating to short gestation and LBW	6.5	17.0	3.0 (2.9–3.2)		
LBW- or prematurity-confounded associations					
Length of birth hospitalization (d)	2.6 (6.3)	6.5 (12.0)	3.8 (3.7–4.0)	2.4 (2.3–2.6)	2.6 (2.5–2.8)
Feeding problems	3.4	10.4	3.4 (3.1–3.6)	2.2 (2.0–2.3)	2.2 (2.0–2.3)
Respiratory distress syndrome	1.3	3.4	2.7 (2.4–3.1)	1.2 (1.0–1.3)	1.2 (1.1–1.4)
Other respiratory conditions	6.7	15.6	2.6 (2.4–2.7)	1.8 (1.7–2.0)	1.8 (1.7–1.9)

SD, standard deviation; OR, odds ratio; CI, confidence interval; LBW, low birth weight.
The reference group for dichotomous outcomes in all models comprises neonates with a vaginal delivery, without LBW, delivered at or after term, without disorders relating to short gestation and LBW, feeding problems, respiratory distress syndrome, other respiratory conditions, respectively.
* Unadjusted model.
† Model adjusted only for LBW (birthweight data missing for 0.3% of cases).
‡ Model adjusted only for prematurity (gestational age data missing for 0.7% cases).

studies finding higher neonatal abstinence syndrome scores and need for higher doses and longer neonatal abstinence syndrome treatment course for male than for female infants.[15] Neonates born to Native American and Alaska Native women are significantly more likely to be drug-exposed and diagnosed with neonatal abstinence syndrome than those born to non-Hispanic white women. This finding is consistent with National Survey on Drug Use and Health data showing higher rates of drug use among Native American and Alaska Native men and women.[4] Neonates born to non-Hispanic African American women appear to be as likely as those born to non-Hispanic white women to be exposed to drugs prenatally but less likely to be diagnosed with neonatal abstinence syndrome. It may be that non-Hispanic African American women are more likely to use nonnarcotic drugs during pregnancy than non-Hispanic white women, as previously shown by Muhuri and Gfroerer.[16] Findings related to higher maternal education,[13,17] age,[18] parity[13,18] and marital status[3,13,17] and the lower prenatal drug exposure and neonatal abstinence syndrome rates are in line with those found by other studies. Although not the first study to show a relationship between drug use during pregnancy and mental health disorders,[3,13,19,20] our study also ascertains the corresponding high use of psychotropic drugs like sedatives, hypnotics, and tranquilizers by pregnant women.

This study is not without limitations. Underascertainment of drug exposure, neonatal abstinence syndrome, perinatal outcomes, maternal risk factors, and Medicaid coverage is possible with use of administrative data.[21] Of note, we assess maternal drug exposure using hospital discharge diagnosis codes at the time of delivery. Ebrahim and Gfroerer[17] used National Survey on Drug Use and Health data and estimated that 93.0% of women reporting illicit drug use early in pregnancy abstained by the third trimester. Thus, when compared with the 4.5% of all pregnant women reporting illicit drug use for National Survey on Drug Use and Health,[10] our capturing of 1.3% drug-using women at the time of delivery is highly plausible. Also, the algorithm developed for drug exposure and neonatal abstinence syndrome identification is a comprehensive ICD-9-CM-based algorithm but has not yet been validated against any other drug exposure and neonatal abstinence syndrome identification methods. Underestimation of drug exposure and neonatal abstinence syndrome may lead to conservative estimates of the associations of interest.

Neonatal Abstinence Syndrome (n=1,642)			
% or Mean (SD)	Crude OR (95% CI)*	LBW-Adjusted OR (95% CI)†	Prematurity-Adjusted OR (95% CI)‡
39.8	1.7 (1.5–1.9)		
26.3	4.1 (3.7–4.6)		
2,989.3 (618.3)	−400.5 (−428.1 to −373.0)		
20.6	4.6 (4.1–5.2)		
24.2	4.9 (4.4–5.5)		
14.4 (14.3)	11.8 (11.5–12.1)	9.9 (9.6–10.1)	10.2 (9.9–10.5)
24.1	9.2 (8.2–10.3)	6.6 (5.7–7.5)	6.5 (5.6–7.4)
5.1	4.2 (3.4–5.3)	1.5 (1.2–2.0)	1.6 (1.3–2.0)
27.7	5.4 (4.8–6.0)	3.9 (3.5–4.5)	3.8 (3.3–4.3)

Lack of information on maternal drinking and smoking patterns in Birth Events Records Database prevents us from providing conclusive evidence of the associations between drug exposure and neonatal abstinence syndrome and perinatal outcomes. Adjustment for proxy variables for heavy drinking, heavy smoking, and maternal nutritional deficiencies did not change the significance of the crude associations. However, separate adjustment for either low birth weight or prematurity reduced the magnitude of observed relationships, especially of those with neonatal abstinence syndrome. Given the many behavior factors associated with drug use, pregnancy, and perinatal outcomes, disentangling direct effects of drug use is challenging.[22]

Like other studies that rely on administrative data, we were limited to routinely collected data; the accuracy and completeness of these data may depend on the variable under study.[23] For example, our inability to examine associations between specific types of drugs and perinatal outcomes is the result of the proportion of drug-exposed and neonatal abstinence syndrome cases with an "unknown" type of drug. Moreover, it is impossible to determine from these data how many women used prescription drugs and whether they were using them medically (eg, chronic pain, methadone treatment) or nonmedically. Thus, data are also prone to over-ascertainment (ie, diagnosis suspicion bias) of drug exposure (ie, women using drugs therapeutically and those perceived to be at "high risk" for drug use may be more likely to receive a drug use diagnosis at hospital discharge) and neonatal abstinence syndrome (ie, diagnosis differences between health care providers); this may have led to overestimation of assessed associations. Research has shown that the timing, duration, and amount of drug exposure can greatly affect perinatal outcomes,[24] and we were not able to control for these exposure patterns. Future studies should include objective measures of specific drugs and drug exposure patterns, assess outcomes among women on methadone maintenance separately, and explore timing and dose–response relationships.

This study has important clinical, societal, and public health implications. Clinicians should screen reproductive-aged women for drug use and refer them for treatment as recommended by the American College of Obstetricians and Gynecologists.[25] Also, their understanding of maternal drug use patterns is essential to tailoring peripartum care plans for drug-exposed women and neonates. Management of pregnant drug-abusing patients may involve not only

management of the primary abuse, but also of the use of multiple substances and of comorbid mental health or other medical conditions. As noted by Chou et al,[26] long-term use of opioid analgesics during pregnancy should be minimized. Treatment of substance abuse during pregnancy has been shown to increase fetal growth[27] and decrease the risk of poor outcomes[28] but is commonly associated with neonatal abstinence syndrome.[29] Multidrug use appears to be associated with greater and longer need of neonatal abstinence syndrome treatment[29,30]; thus, long-term monitoring of the health effects of some drug-exposed neonates may be needed. Programs tailored for drug-using pregnant women need to address factors contributing to their drug abuse and adverse perinatal outcomes such as women's reticence to access substance abuse treatment and prenatal care, their lack of medical insurance and social support, and poverty, especially in rural areas. Washington State has specialized programs providing comprehensive medical and recovery support for drug-abusing women and their neonates, which have been shown to improve medical and social outcomes[31] and lead to cost-savings for the health care system[32]; programs like these need to continue. Evidence demonstrates that punitive measures are ineffective in reducing illicit drug use among pregnant women.[33,34] Integrated prenatal care and drug abuse treatment may deliver benefits for both mothers and neonates,[35] but reducing drug use before conception and starting treatment early in pregnancy are paramount to reducing maternal drug abuse and its negative effects.

REFERENCES

1. Havens JR, Simmons LA, Shannon LM, Hansen WF. Factors associated with substance use during pregnancy: results from a national sample. Drug Alcohol Depend 2009;99:89–95.
2. Greenfield SF, Manwani SG, Nargiso JE. Epidemiology of substance use disorders in women. Obstet Gynecol Clin North Am 2003;30:413–46.
3. Azuma SD, Chasnoff IJ. Outcome of children prenatally exposed to cocaine and other drugs: a path analysis of three-year data. Pediatrics 1993;92:396–402.
4. Substance Abuse and Mental Health Services Administration. Results from the 2009 National Survey on Drug Use and Health: Volume I. Summary of national findings. 2010. Available at: www.oas.samhsa.gov/2k8State/Ch2.htm#2.7. Retrieved January 31, 2012.
5. Kellogg A, Rose CH, Harms RH, Watson WJ. Current trends in narcotic use in pregnancy and neonatal outcomes. Am J Obstet Gynecol 2011;204:259.e1–4.
6. Okie S. A flood of opioids, a rising tide of deaths. N Engl J Med 2010;363:1981–5.
7. Manchikanti L, Fellows B, Ailinani H, Pampati V. Therapeutic use, abuse, and nonmedical use of opioids: a ten-year perspective. Pain Physician 2010;13:401–35.
8. Washington State Department of Social and Health Services 2010 Report. Tobacco, alcohol, & other drug abuse trends in Washington State. 2010. Available at: www.dshs.wa.gov/dbhr. Retrieved January 31, 2012.
9. Washington State Department of Health. The Health of Washington State. Appendix B: primary data sources. 2007. Available at: www.doh.wa.gov/HWS/doc/AppendixB2007.pdf. Retrieved January 31, 2012.
10. Healthcare Cost and Utilization Project Databases. Rockville (MD): Agency for Healthcare Research and Quality; 2010. Available at: www.hcup-us.ahrq.gov/nisoverview.jsp. Retrieved January 31, 2012.
11. Kuklina EV, Whiteman MK, Hillis SD, Jamieson DJ, Meikle SF, Posner SF, et al. An enhanced method for identifying obstetric deliveries: implications for estimating maternal morbidity. Matern Child Health J 2008;12:469–77.
12. Cuzick J. Wilcoxon-type test for trend. Stat Med 1985;4:87–90.
13. O'Donnell M, Nassar N, Leonard H, Hagan R, Mathews R, Patterson Y, et al. Increasing prevalence of neonatal withdrawal syndrome: population study of maternal factors and child protection involvement. Pediatrics 2009;123:e614–21.
14. Drug Enforcement Administration. Automation of Reports and Consolidated Orders System. Retail drug summary. Available at: www.deadiversion.usdoj.gov/arcos/retail_drug_summary/index.html. Retrieved January 31, 2012.
15. Jansson LM, Dipietro JA, Elko A, Velez M. Maternal vagal tone change in response to methadone is associated with neonatal abstinence syndrome severity in exposed neonates. J Matern Fetal Neonatal Med 2007;20:677–85.
16. Muhuri PK, Gfroerer JC. Substance use among women: associations with pregnancy, parenting, and race/ethnicity. Matern Child Health J 2009;13:376–85.
17. Ebrahim SH, Gfroerer J. Pregnancy-related substance use in the United States during 1996–1998. Obstet Gynecol 2003;101:374–9.
18. Burns L, Mattick RP. Using population data to examine the prevalence and correlates of neonatal abstinence syndrome. Drug Alcohol Rev 2007;26:487–92.
19. Bucholz KK. Nosology and epidemiology of addictive disorders and their comorbidity. Psychiatr Clin North Am 1999;22:221–40.
20. Wachman EM, Byun J, Philipp BL. Breastfeeding rates among mothers of infants with neonatal abstinence syndrome. Breastfeed Med 2010;5:159–64.
21. Preen DB, Holman CD, Lawrence DM, Baynham NJ, Semmens JB. Hospital chart review provided more accurate comorbidity information than data from a general practitioner survey or an administrative database. J Clin Epidemiol 2004;57:1295–304.
22. Cleary BJ, Donnelly JM, Strawbridge JD, Gallagher PJ, Fahey T, White MJ, et al. Methadone and perinatal outcomes: a retrospective cohort study. Am J Obstet Gynecol 2011;204:139.e1–9.
23. Lydon-Rochelle MT, Holt VL, Nelson JC, Cárdenas V, Gardella C, Easterling TR, et al. Accuracy of reporting maternal in-hospital diagnoses and intrapartum procedures in Washington State linked birth records. Paediatr Perinat Epidemiol 2005;19:460–71.
24. Lester BM, ElSohly M, Wright LL, Smeriglio VL, Verter J, Bauer CR, et al. The Maternal Lifestyle Study: drug use by meconium toxicology and maternal self-report. Pediatrics 2001;107:309–17.

25. At risk drinking and illicit drug use: ethical issues in obstetric and gynecologic practice. ACOG Committee Opinion No. 422. American College of Obstetricians and Gynecologists. Obstet Gynecol 2008;112:1449–60.
26. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, et al. Clinical guidelines for the use of chronic opioid therapy for chronic noncancer pain. J Pain 2009;10:113–30.
27. Little BB, Snell LM, Van Beveren TT, Crowell RB, Trayler S, Johnston WL. Treatment of substance abuse during pregnancy and infant outcome. Am J Perinatol 2003;20:255–62.
28. Cox S, Posner SF, Kourtis AP, Jamieson DJ. Hospitalizations with amphetamine abuse among pregnant women. Obstet Gynecol 2008;111:341–7.
29. Dryden C, Young D, Hepburn M, Mactier H. Maternal methadone use in pregnancy: factors associated with the development of neonatal abstinence syndrome and implications for healthcare resources. BJOG 2009;116:665–71.
30. Seligman NS, Salva N, Hayes EJ, Dysart KC, Pequignot EC, Baxter JK. Predicting length of treatment for neonatal abstinence syndrome in methadone-exposed neonates. Am J Obstet Gynecol 2008;199:396.e1–7.
31. Farmer Y, Cawthon L, Salazar E. Comprehensive program evaluation project report. 2000. Available at: www.dshs.wa.gov/pdf/ms/rda/research/4/36/a.pdf. Retrieved January 31, 2012.
32. Estee S, Norlund D. Washington State Supplemental Security Income (SSI) Cost Offset Pilot Project: 2002 progress report. 2003. Available at: www.dshs.wa.gov/pdf/ms/rda/research/11/109.pdf. Retrieved January 31, 2012.
33. Armstrong EM. Drug and alcohol use during pregnancy: we need to protect, not punish, women. Womens Health Issues 2005;15:45–7.
34. Substance abuse reporting in pregnancy: the role of the obstetrician-gynecologist. ACOG Committee Opinion No. 473. American College of Obstetricians and Gynecologists. Obstet Gynecol 2011;117:200–1.
35. Goler NC, Armstrong MA, Taillac CJ, Osejo VM. Substance abuse treatment linked with prenatal visits improves perinatal outcomes: a new standard. J Perinatol 2008;28:597–603.