Opioid Abuse and Dependence during Pregnancy

Temporal Trends and Obstetrical Outcomes

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ABSTRACT

Background: The authors investigated nationwide trends in opioid abuse or dependence during pregnancy and assessed the impact on maternal and obstetrical outcomes in the United States.

Methods: Hospitalizations for delivery were extracted from the Nationwide Inpatient Sample from 1998 to 2011. Temporal trends were assessed and logistic regression was used to examine the associations between maternal opioid abuse or dependence and obstetrical outcomes adjusting for relevant confounders.

Results: The prevalence of opioid abuse or dependence during pregnancy increased from 0.17% (1998) to 0.39% (2011) for an increase of 127%. Deliveries associated with maternal opioid abuse or dependence compared with those without opioid abuse or dependence were associated with an increased odds of maternal death during hospitalization (adjusted odds ratio [aOR], 4.6; 95% CI, 1.8 to 12.1, crude incidence 0.03 *vs.* 0.006%), cardiac arrest (aOR, 3.6; 95% CI, 1.4 to 9.1; 0.04 *vs.* 0.01%), intrauterine growth restriction (aOR, 2.7; 95% CI, 2.4 to 2.9; 6.8 *vs.* 2.1%), placental abruption (aOR, 2.4; 95% CI, 2.1 to 2.6; 3.8 *vs.* 1.1%), length of stay more than 7 days (aOR, 2.2; 95% CI, 2.0 to 2.5; 3.0 *vs.* 1.2%), preterm labor (aOR, 2.1; 95% CI, 2.0 to 2.3; 17.3 *vs.* 7.4%), oligohydramnios (aOR, 1.7; 95% CI, 1.6 to 1.9; 4.5 *vs.* 2.8%), transfusion (aOR, 1.7; 95% CI, 1.5 to 1.9; 2.0 *vs.* 1.0%), stillbirth (aOR, 1.5; 95% CI, 1.3 to 1.8; 1.2 *vs.* 0.6%), premature rupture of membranes (aOR, 1.4; 95% CI, 1.3 to 1.6; 5.7 *vs.* 3.8%), and cesarean delivery (aOR, 1.2; 95% CI, 1.1 to 1.3; 36.3 *vs.* 33.1%).

Conclusions: Opioid abuse or dependence during pregnancy is associated with considerable obstetrical morbidity and mortality, and its prevalence is dramatically increasing in the United States. Identifying preventive strategies and therapeutic interventions in pregnant women who abuse drugs are important priorities for clinicians and scientists. (**ANESTHESIOLOGY 2014; 121:1158-65**)

OPIOID abuse is epidemic in the United States, especially among the young.[1] Overdose deaths from opioid pain relievers in women of all ages have increased five-fold between 1999 and 2010 and are continuing to rise.[2–6] Recent work suggests that opioids are commonly prescribed during pregnancy.[7] With its potent respiratory depressive effects and propensity to precipitate withdrawal, opioid abuse during pregnancy is detrimental to maternal and fetal well-being.

The risk of neonatal abstinence syndrome associated with *in utero* exposure to opioids is well known.[8,9] However, data on the association between opioid exposure during pregnancy and other adverse obstetrical outcomes are

What We Already Know about This Topic

- Whether the prevalence of opioid abuse and dependence has increased in women during pregnancy and, if so, whether it imparts maternal or obstetric risks are unknown

What This Article Tells Us That Is New

- In a review of over 57 million American women admitted for obstetric delivery in the Nationwide Inpatient Sample, the prevalence of opioid abuse and dependence more than doubled between 1998 and 2011
- Opioid abuse and dependence was associated with a 4.6-fold increased risk of maternal death during hospitalization and was present in 1.5% of deliveries complicated by maternal death

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This article is featured in "This Month in Anesthesiology," page 1A. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This research was presented at the Society for Obstetric Anesthesia and Perinatology 46th Annual Meeting, May 15, 2014, Toronto, Ontario, Canada.

more limited.[10,11] The aim of this study was to investigate nationwide trends in maternal opioid abuse or dependence during pregnancy and to elucidate its impact on maternal and obstetrical outcomes using the largest U.S. healthcare utilization dataset. We hypothesized that the prevalence of opioid abuse and dependence is increasing among pregnant women, and that these disorders are associated with several measures of maternal and obstetric morbidity.

Materials and Methods

Data are collected from the Nationwide Inpatient Sample (NIS) of the Healthcare Cost and Utilization Project sponsored by the Agency for Healthcare Research and Quality. The NIS is the largest inpatient healthcare utilization dataset in the United States, with information on a sample of approximately 20% of all discharges from nonfederal, acute-care hospitals. Five characteristics define which hospitals are selected for inclusion in the NIS: geographic region (Northeast, South, Midwest, and West), ownership (public, investor-owned, and not-for-profit), location (urban or rural), teaching status, and number of inpatient beds, thereby creating a sample that is representative of all U.S. hospitalizations. Hospital discharges are weighted based on the sampling scheme to account for the complex survey structure and to permit nationwide inferences and we used this weighted sample for all our analyses. For each hospital admission, patient sociodemographic and hospitalization information as well as up to 15 diagnoses and procedures coded using the *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9 CM) can be listed. Specific data elements included and other methodological information can be found elsewhere.*

The NIS data are publicly available and do not include any personal identifiers; thus, this study was exempt from the review by the Institutional Review Board (Massachusetts General Hospital, Boston, Massachusetts, and Center for Disease Control and Prevention, Atlanta, Georgia).

Inclusion and Exclusion Criteria

We identified all 1998 to 2011 delivery admissions using the algorithm described by Kuklina *et al.*[12] Hospitalizations with diagnosis codes designating delivery or a procedure code pertaining to delivery (*e.g.*, forceps, breech extraction, vacuum extraction, version and extraction, manually assisted deliveries, episiotomy, hysterotomy, or cesarean delivery) were included. Hospitalizations with diagnosis or procedure codes indicating abortion, ectopic pregnancy, or hydatidiform mole were excluded. We did not use diagnosis-related group codes for identifying deliveries because they changed during the study period. The full dataset, drawn from years 1998 to 2011, was used only for the trend analysis of the

prevalence of opioid dependence or abuse. There are many changes in obstetric practice during the 14-yr study period, including increasing cesarean delivery rates, numbers of inductions of labor, and use of neuraxial anesthesia.[13–16] In addition, there have been changes in the ways in which opioids are prescribed and dependence is managed.[17,18] The analysis of the demographic characteristic and associations with adverse maternal outcomes were therefore restricted to the last 5 yr of the study period (2007–2011), using the most contemporary data available while preserving power to explore relatively rare endpoints.

Outcomes

We determined the prevalence of maternal opioid abuse or dependence during hospitalizations for delivery annually between 1998 and 2011. Next, using the restricted dataset of 2007–2011, we characterized the demographics and medical conditions in this population and estimated the associations between maternal opioid abuse or dependence and key potentially related obstetrical complications. We first identified the women with diagnoses of opioid-type dependence (ICD-9 CM codes 304.0x, 304.7x) and nondependent opioid abuse (ICD-9 CM code 305.5x). We excluded the code for "long-term (current) use of other meds" (V58.69) used in other investigations because of its lack of specificity for opioid abuse or dependence.[8] Maternal demographic factors (age, race, primary expected payer), delivery-related factors (previous cesarean section, multiple gestations), and comorbid conditions (human immunodeficiency virus [HIV], chronic anemia, tobacco use, alcohol abuse or dependence, depression, anxiety, and nonopioid drug abuse or dependence) that could potentially confound associations between opioid abuse or dependence and maternal or obstetrical complications were selected after a review of the published literature, and these were compared between parturients with and without opioid abuse or dependence in the pooled 2007–2011 dataset. Sociodemographic data were recorded directly from the NIS dataset. Relevant maternal and obstetrical outcomes for this analysis (*i.e.*, death during hospitalization, cardiac arrest, intrauterine growth restriction, placental abruption, length of stay more than 7 days, preterm delivery, oligohydramnios, need for transfusion, stillbirth, premature rupture of membranes, cesarean delivery, severe preeclampsia or eclampsia, anesthesia complications, cerebrovascular complication, sepsis, and postpartum hemorrhage) were also defined using ICD-9 codes.

Statistical Analyses

Multivariable logistic regression models were then used to assess the associations of maternal opioid abuse or dependence with each obstetrical outcome adjusting for all measured demographics and comorbidities noted above. All potential confounders were defined *a priori* based on literature review and clinical plausibility (including age group, race, primary payer, previous cesarean section, multiple

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* HCUP Nationwide Inpatient Sample (NIS). Healthcare Cost and Utilization Project (HCUP). Rockville, Maryland, Agency for Healthcare Research and Quality, 1998–2007. Available at: http://www.hcup-us.ahrq.gov/. Accessed February 21, 2014.

gestations, and maternal preexisting conditions) and forced into the model as potential confounders, without further selection. Age was divided into clinically relevant categories and modeled as a categorical variable to avoid the assumption of a log-linear association between maternal age and the outcomes considered. No interaction terms were included in the model.

In addition, because obstetrical outcomes can be influenced by other factors difficult to account for in administrative data (*e.g.*, socioeconomic background, diet, nutritional status), we conducted a sensitivity analysis comparing maternal and obstetrical outcomes in women with opioid abuse or dependence *versus* women hospitalized for delivery who abuse or are dependent on other illicit drugs or prescription drugs used illicitly, including cannabis (ICD-9 CM codes 305.2x, 304.3x), hallucinogens (ICD-9 CM codes 305.3x, 304.5x), sedatives, hypnotics, or anxiolytics (ICD-9 CM codes 305.4x, 304.1x), cocaine (ICD-9 CM codes 305.6x, 304.2x), amphetamines (ICD-9 CM codes 305.7x, 304.4x), antidepressants (ICD-9 CM code 305.8x), or other mixed or unspecified drugs (ICD-9 CM codes 305.9x, 304.6x, 304.8x, 304.9x); women who were abusing or dependent on both opioids and other drugs were considered as opioid abusers in this analysis. Our assumption was that these women who used these other illicit drugs or who used prescription drugs in nonprescribed ways are likely to be more similar with respect to potentially important, unmeasured confounders than women drawn from the general parturient population. Therefore, comparing them to the opioid-dependent or -abusing patients might better facilitate the identification of adverse obstetrical outcomes that are more likely to be causally related to the opioid exposure.

Moreover, we conducted another sensitivity analysis to explore the association between nondependent opioid abuse (ICD-9 CM code 305.5x) and opioid-type dependence (ICD-9 CM codes 304.0x, 304.7x) on adverse maternal and obstetrical outcomes separately as a supplemental aim.

Although distinguishing these two entities is clinically difficult, we sought to determine whether membership in these individual groups have potentially unique associations with adverse obstetrical outcomes, because abuse is regarded more as a behavioral disorder and dependence a physiological state induced by chronic opioid administration.[19,20]

Of note, as some states do not report race in the NIS, 3,529,606 (17.2%) of the women in the dataset were missing race information. We used an indicator variable for missing race values to include race in multivariable analyses. Age was missing in 16,679 (0.1%) delivery admissions and primary expected payer was missing in 34,185 (0.2%). These patients were excluded from the multivariable analysis. Disposition was also missing in 8,219 (0.04%) and these patients were excluded from the analysis of in-hospital death. Analytical weights were applied in the analysis to account for the complexity of the NIS design. Statistical analyses were conducted using Stata Statistical Software: Release 12.1 (StataCorp LP, College Station, TX).

Results

There were 56,900,512 delivery admissions eligible for analysis from 1998 to 2011. Overall, 113,105 (0.2%) women hospitalized for delivery were identified as abusing or being dependent on opioids. The prevalence of opioid abuse or dependence during pregnancy increased by 127%, from 1.7 per 1,000 delivery admissions in 1998 to 3.9 per 1,000 delivery admissions in 2011 (*P* for trend is <0.001; fig. 1). The most substantial increase in opioid abuse or dependence occurred within the age group of 20 to 34 yr (162%; from 1.8 per 1,000 delivery admissions in 1998 to 4.5 per 1,000 delivery admissions in 2011). The prevalence rate increases within the age groups of 35 to 39 and 40-yr or older were less apparent (fig. 1).

The analysis of the association between opioid abuse and dependence and adverse outcomes was restricted to deliveries between 2007 and 2011 to best reflect current obstetric
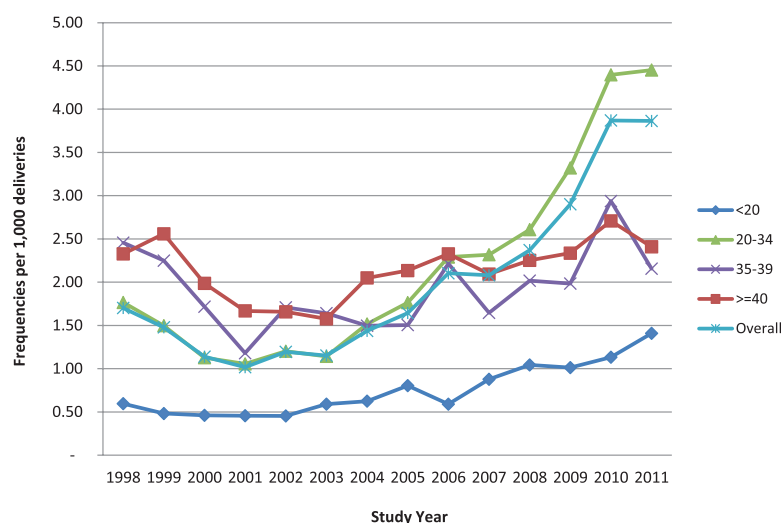
Fig. 1. Opioid abuse or dependence per 1,000 deliveries, overall and by age: United States, 1998–2011.

Table 1. Delivery Characteristics of the Study Population: United States, 2007–2011

Characteristics	Delivery Hospitalizations with Opioid Abuse or Dependence n (%)	Delivery Hospitalizations without Opioid Abuse or Dependence n (%)
Total	60,994	20,456,485
Age (yr)*		
<20	2,142 (3.5)	1,993,866 (9.7)
20–34	52,402 (85.9)	15,475,335 (75.7)
35–39	5,108 (8.4)	2,403,303 (11.7)
≥40	1,337 (2.2)	567,306 (2.8)
Race		
White	40,478 (66.4)	8,767,617 (42.9)
Black	4,108 (6.7)	2,380,322 (11.6)
Hispanic	4,481 (7.4)	3,930,820 (19.2)
Asian/Pacific Islander	207 (0.3)	875,021 (4.3)
Other	1,848 (3.0)	982,971 (4.8)
Missing	9,872 (16.2)	3,519,734 (17.2)
Primary expected payer†		
Medicare	1,658 (2.7)	138,272 (0.7)
Medicaid	46,420 (76.1)	8,748,603 (42.8)
Private	8,659 (14.2)	10,262,543 (50.3)
Self-pay	2,639 (4.3)	668,925 (3.3)
No charge	189 (0.3)	47,444 (0.2)
Other	1,316 (2.2)	556,626 (2.7)
Maternal preexisting conditions		
Previous cesarean section	11,404 (18.7)	3,302,158 (16.1)
Multiple gestation	810 (1.3)	374,453 (1.8)
HIV infection	119 (0.2)	4,926 (0.02)
Tobacco use	1,262 (2.1)	37,074 (0.2)
Chronic anemia	5,644 (9.3)	1,562,027 (7.6)
Alcohol abuse or dependence	1,283 (2.1)	20,288 (0.1)
Depression	4,734 (7.8)	306,578 (1.5)
Anxiety	2,664 (4.4)	133,840 (0.7)
Nonopioid drug abuse or dependence	13,562 (22.2)	200,074 (1.0)

* Age is missing for 16,679 (0.1%). † Primary expected payer is missing for 34,185 (0.2%).
HIV = human immunodeficiency virus.

practice (n = 20,517,479). Table 1 compares sociodemographic and medical characteristics for women hospitalized for delivery with and without opioid abuse or dependence. Parturients with opioid abuse or dependence were older, in higher proportion white, insured by Medicaid rather than by a private insurance company, with significantly higher rates of tobacco use, alcohol, or other illicit drug use, and with depression, anxiety, HIV infection, chronic anemia, and previous cesarean delivery when compared with those without an opioid abuse or dependence code ($P < 0.01$ for all).

Table 2 displays the frequency of maternal and obstetrical complications among parturients with and without opioid abuse or dependence from 2007 to 2011 and the associations of maternal opioid abuse or dependence with these outcomes after adjusting for age group, race, primary payer, previous cesarean section, multiple gestation, and maternal preexisting conditions (HIV infection, chronic anemia, tobacco use, alcohol abuse or dependence, depression, anxiety, and nonopioid drug abuse or dependence). Opioid abuse or dependence during pregnancy markedly increased the odds of major obstetrical morbidity and mortality, including in-hospital mortality (adjusted odds ratio [aOR], 4.6; 95% CI, 1.8 to 12.1), maternal cardiac arrest (aOR, 3.6; 95% CI, 1.4 to 9.1), intrauterine growth restriction (aOR, 2.7; 95% CI, 2.4 to 2.9), placental abruption (aOR, 2.4; 95% CI, 2.1 to 2.6), length of stay more than 7 days (aOR, 2.2; 95% CI, 2.0 to 2.5), preterm labor (aOR, 2.1; 95% CI, 2.0 to 2.3), oligohydramnios (aOR, 1.7; 95% CI, 1.6 to 1.9), transfusion (aOR, 1.7; 95% CI, 1.5 to 1.9), stillbirth (aOR, 1.5; 95% CI, 1.3 to 1.8), and premature rupture of membrane (aOR, 1.4; 95% CI, 1.3 to 1.6). Maternal opioid abuse or dependence was also associated with an increased odds of cesarean delivery (aOR, 1.2; 95% CI, 1.1 to 1.3). Conversely, the odds of severe preeclampsia or eclampsia was significantly lower among these parturients than without opioid abuse or dependence (aOR, 0.8; 95% CI, 0.7 to 0.9). The odds of anesthesia complications increased by twofold although the result did not reach statistical significance (aOR, 2.1; 95% CI, 0.8 to 5.3). Opioid abuse or dependence was present in 1.5% of deliveries complicated by maternal death.

Table 3 shows the frequency of various maternal and obstetrical complications among parturients with opioid abuse or dependence compared with those who abuse or are dependent on nonopioid illicit drugs. The increased odds of key obstetrical complications after opioid abuse or dependence persisted, specifically for length of stay more than 7 days (aOR, 1.4; 95% CI, 1.2 to 1.6), intrauterine growth restriction (aOR, 1.4; 95% CI, 1.3 to 1.5), oligohydramnios (aOR, 1.3; 95% CI, 1.2 to 1.5), transfusion (aOR, 1.3; 95% CI, 1.1 to 1.5), cesarean delivery (aOR, 1.2; 95% CI, 1.1 to 1.3), and preterm labor (aOR, 1.1; 95% CI, 1.1 to 1.2). We were unable to analyze in-hospital mortality, cardiac arrest, anesthesia complications, and cerebrovascular complications in this sensitivity analysis as the total number of outcomes precludes fitting a multivariable model that included all the prespecified confounding variables. There was again an apparent decrease in the odds of severe preeclampsia or eclampsia (aOR, 0.7; 95% CI, 0.6 to 0.9).

Table 1, Supplemental Digital Content 1, http://links.lww.com/ALN/B102, presents the sensitivity analysis comparing the associations of maternal and obstetrical outcomes with nondependent opioid abuse and opioid dependence as separate groups. Most identified complications remained statistically significant for each group examined individually

Table 2. Associations between Opioid Abuse or Dependence during Pregnancy and Obstetrical Outcomes: United States, 2007–2011

	Delivery Hospitalizations with Opioid Abuse or Dependence	Delivery Hospitalizations without Opioid Abuse or Dependence	Multivariable Odds Ratio* (95% CI)
	n (%)	n (%)	
Total	60,994	20,456,485	
Died during hospitalization	20 (0.03)	1,311 (0.006)	**4.6 (1.8–12.1)**
Cardiac arrest	24 (0.04)	1,873 (0.01)	**3.6 (1.4–9.1)**
Intrauterine growth restriction	4,157 (6.8)	431,032 (2.1)	**2.7 (2.4–2.9)**
Placental abruption	2,315 (3.8)	215,057 (1.1)	**2.4 (2.1–2.6)**
Length of stay >7 days	1,837 (3.0)	235,738 (1.2)	**2.2 (2.0–2.5)**
Preterm	10,538 (17.3)	1,506,941 (7.4)	**2.1 (2.0–2.3)**
Oligohydramnios	2,736 (4.5)	564,410 (2.8)	**1.7 (1.6–1.9)**
Transfusion	1,205 (2.0)	208,073 (1.0)	**1.7 (1.5–1.9)**
Stillbirth	727 (1.2)	124,607 (0.6)	**1.5 (1.3–1.8)**
Premature rupture of membranes	3,499 (5.7)	778,157 (3.8)	**1.4 (1.3–1.6)**
Cesarean delivery	22,130 (36.3)	6,768,679 (33.1)	**1.2 (1.1–1.3)**
Severe preeclampsia or eclampsia	722 (1.2)	289,668 (1.4)	**0.8 (0.7–0.9)**
Anesthesia complications	20 (0.03)	3,123 (0.02)	2.1 (0.8–5.3)
Cerebrovascular complications	37 (0.06)	5,079 (0.02)	2.0 (0.9–4.4)
Sepsis	273 (0.4)	79,169 (0.4)	1.3 (1.0–1.7)
Postpartum hemorrhage	1,866 (3.1)	589,811 (2.9)	1.1 (0.9–1.2)

Statistically significant values are indicated in bold.

* Adjusted for age group, race, primary payer, previous cesarean section, multiple gestation, and maternal preexisting conditions shown in table 1.

Table 3. Associations between Opioid *vs.* Nonopioid Abuse or Dependence during Pregnancy and Obstetrical Outcomes: United States, 2007–2011

	Delivery Hospitalizations with Opioid Abuse or Dependence	Delivery Hospitalizations with Other Drug Abuse or Dependence	Multivariable Odds Ratio* (95% CI)
	n (%)	n (%)	
Total	60,994	200,074	
Intrauterine growth restriction	4,157 (6.8)	9,701 (4.8)	**1.4 (1.3–1.5)**
Placental abruption	2,315 (3.8)	7,411 (3.7)	1.1 (1.0–1.2)
Length of stay >7 days	1,837 (3.0)	4,571 (2.3)	**1.4 (1.2–1.6)**
Preterm	10,538 (17.3)	32,863 (16.4)	**1.1 (1.1–1.2)**
Oligohydramnios	2,736 (4.5)	6,785 (3.4)	**1.3 (1.2–1.5)**
Transfusion	1,205 (2.0)	3,754 (1.9)	**1.3 (1.1–1.5)**
Stillbirth	727 (1.2)	3,042 (1.5)	0.9 (0.7–1.1)
Premature rupture of membranes	3,499 (5.7)	11,284 (5.6)	1.1 (1.0–1.2)
Cesarean delivery	22,130 (36.3)	63,280 (31.6)	**1.2 (1.1–1.3)**
Severe preeclampsia or eclampsia	722 (1.2)	3,937 (2.0)	**0.7 (0.6–0.9)**
Sepsis	273 (0.4)	988 (0.5)	1.1 (0.8–1.5)
Postpartum hemorrhage	1,866 (3.1)	6,493 (3.2)	1.0 (0.9–1.1)

We do not present an analysis of in-hospital mortality, cardiac arrest, anesthesia complications, and cerebrovascular complications in this sensitivity analysis as the total number of outcomes precludes fitting a multivariable model that includes all the prespecified confounding variables. Statistically significant values are indicated in bold.

* Adjusted for age group, race, primary payer, previous cesarean section, multiple gestation, and maternal preexisting conditions shown in table 1.

with only fairly modest differences in magnitude, including intrauterine growth restriction, placental abruption, length of stay more than 7 days, preterm delivery, oligohydramnios, transfusion, and premature rupture of membranes. However, compared with the opioid dependence group, there were higher odds for death during hospitalization reaching statistical significance among opioid abusers (aOR, 6.2; 95% CI, 1.5 to 25.8 *vs.* aOR, 3.5; 95% CI, 1.0 to 12.9) and significantly reduced odds for severe preeclampsia or eclampsia for opioid abusers (aOR, 0.7; 95% CI, 1.0 to 1.2 *vs.* aOR, 0.9; 95% CI, 0.7 to 1.1). Moreover, the odds were statistically significantly higher in the opioid dependence group compared with the opioid abuse group for cardiac arrest (aOR, 4.1; 95% CI, 1.3 to 13.1 *vs.* aOR, 2.7; 95% CI, 0.6 to 11.7, respectively), stillbirth (aOR, 1.7; 95% CI, 1.4 to 2.1 *vs.* aOR, 1.3; 95% CI, 1.0 to 1.8, respectively), and cesarean delivery (aOR, 1.2; 95% CI, 1.1 to 1.4 *vs.* aOR, 1.1; 95% CI, 1.0 to 1.2, respectively).

Discussion

In our analysis of approximately 57 million delivery admissions across the United States from 1998 to 2011, we found that the prevalence of opioid abuse or dependence during pregnancy substantially increased, particularly among women aged 20 to 34 yr. Our analysis revealed that the opioid-dependent or -abusing pregnant population had a higher odds of in-hospital mortality, as well as an extended length of delivery hospitalization (>7 days), transfusion, and oliogohydramnios. In addition, we corroborated previous findings of a higher risk for cesarean delivery,[11] preterm birth,[21,22] and intrauterine growth restriction[21] in this substance abusing population.

There are several possible explanations for the adverse obstetrical outcomes in opioid-dependent or -abusing pregnant women. Although the American College of Obstetricians and Gynecologists highly recommends medically supervised opioid maintenance programs, substituting oral methadone or buprenorphine for the opioid of abuse,[6] enrollment in such a program, maintenance of care continuity, adequate dose adjustments, and outpatient follow-up can be challenging. Not all women are able to avail themselves of these services. Women who continue to abuse opioids during pregnancy tend to seek prenatal care late in pregnancy or not at all and exhibit poor adherence to their medical appointments.[6] These behaviors can interfere with preventive care necessary for maternal and fetal well-being throughout pregnancy.

Opioid tolerance and hyperalgesia develop in women who are dependent on or abuse opioids, and they often experience more postpartum pain than the general obstetric population.[23–27] Although these women are tolerant to the analgesic effects of opioids and often require higher doses, they have been found to be just as vulnerable to the sedative effects of opioids, which can result in oversedation and respiratory compromise.[24,25,27] Benzodiazepines and other sedatives, which are often used in opioid-dependent or -abusing parturients to manage insomnia and anxiety, are synergistic in their respiratory depressant effects[28–30] and can lead to further respiratory compromise. The increased odds of anesthesia complications (although not reaching the threshold for statistical significance), cardiac arrest, and death during hospitalization observed in our analysis of this opioid-dependent or -abusing population may be a result of this effect. Additional insight can be gained from the studies analyzing the root cause of opioid-related deaths in the general population in United States: physician error in converting opioid equivalents and an association between sleep apnea and chronic opioid use may also contribute to these outcomes.[31] As such, consultation with pain-trained anesthesiologist experts as needed, maximizing multimodal perioperative pain management, and more intensive peridelivery respiratory monitoring in these patients may help to prevent these complications. Withdrawal from opioids, in general, and heroin, in particular, can cause significant physiological

disruption, thereby leading to additional maternal and perinatal morbidity.[6,32,33] The difficulty of achieving adequate pain management in these opioid-dependent or -abusing women, the efforts to transition or maintain them in medically supervised maintenance therapy programs, and the delayed discharge of their infants who develop neonatal abstinence syndrome may all contribute to the increased odds of prolonged maternal length of stay found in our analysis. Finally, any adverse outcomes of opioid abuse or dependence that cause maternal or fetal distress can increase the odds of cesarean delivery,[34] which, in turn, can explain the increased risk of transfusion in these women.[35]

There are conflicting published findings regarding the association between maternal illicit drug use and placental abruption.[11,21,36,37] The higher odds of placental abruption found in our primary analysis was attenuated when we compared the opioid and other illicit drug-dependent or -abusing parturients. It may be that the important risk factors for abruption are in part related to trauma, inadequate nutrition, and other lifestyle factors rather than to the specific drugs of abuse. Similarly, the associations between opioid abuse or dependence, intrauterine growth restriction, preterm birth, oligohydramnios, stillbirth, and premature rupture of membranes were also attenuated, suggesting that these obstetric complications may be heavily influenced by lifestyle factors that cannot be accounted for in this administrative dataset.

The apparent protective effect of opioid abuse or dependence on severe preeclampsia or eclampsia may be due to a limitation inherent to our data. Smoking is common in the illicit drug-using population and smoking decreases the risk of hypertensive disorders of pregnancy.[38–42] However, smoking behavior is underreported in the NIS data.[38] As such, the apparent relationship between opioid abuse or dependence and severe preeclampsia or eclampsia may be due to inadequate capture of smoking data, rather than to a true association.

Although our study benefits from the analysis of a large population of pregnant women that is representative of all U.S. delivery admissions, it is subject to several limitations. Because the NIS contains administrative data that are deidentified and collected for billing purposes, we could not confirm diagnoses and comorbidities with chart review.[43] We neither exclude the possibility of reporting errors, inaccuracy, or underreporting in coding leading to an underestimation or overascertainment of maternal opiate abuse or dependence nor control for exposure patterns such as the timing, duration, and amount of drug exposure or classes of opioid drugs.[43,44] We were not able to distinguish between women who were dependent on or abuse prescription opioids, those who were enrolled in opioid maintenance programs (*e.g.*, with methadone or buprenorphine), and those who abused heroin. The decision to combine opioid abuse or dependence for this analysis was in acknowledgement of the difficulty that often occurs in distinguishing between the two in the clinical setting. This challenge is further highlighted by the 5th

Edition of the Diagnostic and Statistical Manual of Mental Disorders which combines these two disorders into one official diagnosis of "Opioid Use Disorder."[45,46] Our sensitivity analysis comparing the two codes, "opioid abuse" and "opioid dependence," revealed that most outcomes remain significant and results are similar across both groups. These data are presented as supplementary material (Supplemental Digital Content 1, http://links.lww.com/ALN/B102).

Information on other key covariates, such as gestational age, maternal weight, or body mass index, are also unavailable in this dataset. It is possible that if an adverse outcome occurred, then the woman's medical history may have been better documented, which, in turn, may have strengthened the observed associations between maternal opioid abuse or dependence and adverse outcomes; however, there was some specificity in the observed associations, suggesting that this does not fully explain our findings. We also assessed for the association between opioid abuse or dependence and multiple outcomes, which introduces some threat of type-I error. Readers should interpret with some caution those associations, which were marginally significant in our analyses. Finally, we conducted a sensitivity analysis in an effort to overcome the confounding effect of lifestyle, nutrition, and other factors that are difficult to account for in the NIS data. This approach rests on the assumption that the lifestyle factors that confound the associations between opioid abuse or dependence and adverse outcomes are also found with similar frequency in women that abuse other drugs.

Our study demonstrates that the prevalence of opioid abuse and dependence during pregnancy is dramatically increasing in the United States and is independently associated with considerable obstetrical morbidity and maternal mortality. As opioid dependence or abuse emerges as the growing area of drug abuse, it is vital for clinicians to be knowledgeable about the attendant maternal morbidity and mortality and other obstetrical outcomes. Preventive strategies and therapeutic interventions in women who continue to abuse opioids during pregnancy are important priorities for clinicians and scientists.

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Competing Interests

The authors declare no competing interests.

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