Research Article

Maternal Opioid Drug Use during Pregnancy and Its Impact on Perinatal Morbidity, Mortality, and the Costs of Medical Care in the United States

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Objective. To identify factors associated with opioid use during pregnancy and to compare perinatal morbidity, mortality, and healthcare costs between opioid users and nonusers. Methods. We conducted a cross-sectional analysis of pregnancy-related discharges from 1998 to 2009 using the largest publicly available all-payer inpatient database in the United States. We scanned ICD-9-CM codes for opioid use and perinatal outcomes. Costs of care were estimated from hospital charges. Survey logistic regression was used to assess the association between maternal opioid use and each outcome; generalized linear modeling was used to compare hospitalization costs by opioid use status. Results. Women who used opioids during pregnancy experienced higher rates of depression, anxiety, and chronic medical conditions. After adjusting for confounders, opioid use was associated with increased odds of threatened preterm labor, early onset delivery, poor fetal growth, and stillbirth. Users were four times as likely to have a prolonged hospital stay and were almost four times more likely to die before discharge. The mean per-hospitalization cost of a woman who used opioids during pregnancy was $5,616 (95% CI: $5,166–$6,067), compared to $4,084 (95% CI: $4,002–$4,166) for nonusers. Conclusion. Opioid use during pregnancy is associated with adverse perinatal outcomes and increased healthcare costs.

1. Introduction

Opioid pain medications are among the most prescribed drugs in the United States (US) [1]. In the past few decades, recent trends in increases in narcotic abuse overshadow successes in improved awareness and management of pain. Clinicians, administrators, and policymakers now face the consequential task of preventing opioid drug misuse and addiction without compromising their effective and appropriate use in the treatment of pain.

Opioid dependence in pregnancy complicates the clinical management of an already vulnerable group of patients. Dependence increases the risk of poor maternal and perinatal outcomes [2–11]. Women of reproductive age who use and abuse opioid drugs, both prescription and illegal, are more likely to have a lower socioeconomic status, family instability, receive inadequate prenatal care, and suffer from alcohol, tobacco, and illicit drug use [12, 13]. In addition to the risks associated with opioid dependence, these comorbid conditions further increase the risk of adverse perinatal outcomes [3, 14].

Increasing at an alarming rate, opioid use in pregnancy underwent an estimated 3–4-fold increase between 2000 and
The 2011 National Survey on Drug Use and Health reports of the United States found 5% of pregnant women 15 to 44 years of age report using illicit drugs [17]. These data suggest an urgent need to evaluate, on a national level, not only the negative health outcomes associated with maternal opioid use during pregnancy, but also the related economic cost burden on the US healthcare system. In this study, we leveraged a large, nationally representative hospital discharge database to identify factors that are associated with an increased likelihood of opioid use during pregnancy. We then compared selected maternal and fetal outcomes between opioid users. Finally, we computed the direct inpatient medical costs associated with maternal opioid use.

2. Materials and Methods

A cross-sectional analysis of all pregnancy-related hospital discharges from 1998 to 2009 was conducted using the National Inpatient Sample (NIS), the largest publicly available all-payer inpatient database in the US, made available by the Healthcare and Cost Utilization Project (HCUP) [18]. To create the dataset each year, HCUP stratifies all nonfederal community hospitals from participating states by five major hospital characteristics: rural/urban location, number of beds, geographic region, teaching status, and ownership. A random sample of 20% of hospitals from each stratum is then drawn using a systematic random sampling technique [18].

Hospital discharges for women who were pregnant or delivered were identified using the variable "NEOMAT" in the NIS dataset. This indicator was created by HCUP to identify maternal and/or neonatal diagnosis records on the basis of International Classification of Diseases, Ninth Revision, Clinical Modifications (ICD-9-CM) diagnosis and procedure codes for pregnancy and delivery [19]. After identifying the study population, we scanned ICD-9-CM codes (principal and secondary) in each woman’s discharge record for an indication of opioid use during pregnancy, as well as for selected maternal/fetal clinical outcomes. The complete list of ICD-9-CM codes used to characterize each condition is presented in the appendix.

Individual-level sociodemographic factors were extracted from the NIS databases. Maternal age in years was classified into five categories: <20, 20–24, 25–29, 30–34, and ≥35. Self-reported maternal race-ethnicity was first based on ethnicity (Hispanic or non-Hispanic [NH]), and the NH group further subdivided by race (white, black, or other). Relative median household income (in quartiles) was estimated by HCUP using the patient’s zip code and served as a proxy for each woman’s socioeconomic status. We grouped the primary payer for hospital admission into three categories: government (Medicare/Medicaid), private (commercial carriers, private health maintenance organization [HMOs], and preferred provider organization [PPOs]), and other sources (e.g., self-pay and charity). We also considered several hospital characteristics including teaching status (teaching, or a ratio of full-time equivalent interns and residents to nonnursing home beds ≥0.25, versus nonteaching), location (urban versus rural), and US region (Northeast, Midwest, South, or West).

The NIS databases also contain discharge-level charges for all hospitalized patients. Reported charges, however, are not a good estimate of actual cost, since there is significant variation in markup from what it costs a hospital to provide medical care to what it charges for services rendered [20]. To adjust for variation in markup across hospitals and over time, we multiplied the total charge for a hospital stay by a time- and hospital-specific cost-to-charge ratio (CCR) available from HCUP [21]. However, even within the same facility, sizeable differences in markup exist across different departments (e.g., higher markup for operating room services compared to routine bed services). Therefore, we incorporated into the computation of cost an "adjustment factor" (AF) that attempts to account for this intradepartmental variation to yield a more accurate cost estimate for each discharge record [22, 23]. Consider

\[
\text{cost} = \left( \text{reported charges} \times \text{CCR} \times \text{AF} \right).
\]

2.1. Statistical Analysis. We calculated descriptive statistics including frequencies, percentages, and rates to describe prevalence of opioid use during pregnancy across maternal age, racial/ethnic, household income strata, primary payer, selected behavioral characteristics, and comorbidities. National rate estimates were computed by weighting the analyses with discharge-level weights provided in the NIS databases. We constructed simple and multivariable survey logistic regression models (SURVEYLOGISTIC procedure) to identify factors associated with an increased likelihood of maternal opioid use during pregnancy. Since use of the NIS databases confers a large sample size and a limited number of available covariates, the multivariable model included all factors considered in bivariate analyses. In addition to identifying predictors for maternal opioid use, we also calculated the rate of selected clinical comorbidities by maternal opioid use status. These comorbidities were selected based on a review of the literature and expert opinion and identified using ICD-9-CM codes in the discharge record. The comorbidities included anxiety, chronic renal disease, depression, HIV status, insomnia, obesity, osteopenia, and prepregnancy diabetes and hypertension.

We compared the rate of selected maternal/fetal pregnancy outcomes between opioid users versus nonusers. We used unconditional survey logistic regression to generate the odds ratios (ORs) and 95% confidence intervals (CIs) for outcomes associated with maternal opioid use. In addition to an unadjusted model, we constructed two multivariable models. In the first multivariable model, we adjusted for sociodemographic, perinatal, and hospital characteristics. In the second multivariable model, we also adjusted for tobacco, alcohol, and drug use, as well as existing medical conditions (obesity, chronic renal failure, prepregnancy diabetes, and prepregnancy hypertension) that may be related to both maternal opioid use and the selected pregnancy outcomes.

After computing the direct inpatient medical costs for each pregnancy-related discharge, we compared mean maternal direct hospitalization costs by opioid use status. Considering the strong positive skewness of the cost data, we used a multivariable generalized linear model with a gamma
distribution and a natural log link to estimate the mean
difference in cost, after adjusting for potential confounders.

All statistical analyses accounted for the complex sam-
pling design of the NIS. To account for NIS sampling design
changes, we used the NIS-Trends files, supplied by HCUP, so
that trend weights and data elements would be consistently
defined over time [24]. Statistical tests were two-sided with
level of significance set at 5%. In addition, for cost analyses, we
rewighted all discharges to account for missing cost data by
multiplying the original discharge weight provided by HCUP
by the ratio of the summed weights across all discharges to
the summed weight of discharges with nonmissing cost infor-
mation. Since hospital-level CCR data were only available
beginning in 2001, we restricted cost analyses to discharges for
the period 2001–09. Analyses were performed using SAS
software, version 9.3 (SAS Institute, Inc., Cary, NC) and Stata
statistical software, release 11 (StataCorp LP, College Station,
TX). The Institutional Review Board of the University of
South Florida determined that this study using deidentified,
publicly available data did not meet the definition of human
subjects research and was thus exempt from IRB approval.

3. Results

Of the estimated 55,781,965 pregnancy-related hospitaliza-
tions, 138,224 were associated with opioid use, a prevalence of
2.5 cases per 1,000 discharges (95% CI: 2.2–2.8). The rate of
opioid use during pregnancy initially decreased from 2.5 per
1,000 in 1998 to 1.6 per 1,000 in 2001. This decreasing trend
was followed by a 12% annual increase to a peak rate of 4.0
per 1,000 in 2009.

The rate of opioid use during pregnancy varied consid-
erably across maternal sociodemographic, perinatal, behav-
ioral, and hospital characteristics (Table 1). The highest
crude rates (per 1,000 discharges) were seen among women
using/abusing alcohol (81.0), women using tobacco during
pregnancy (21.6), women on Medicare/Medicaid (4.5)
or "Other" insurance (4.8), women in the lowest quartile of
household income (3.6), and black-NH women (3.2).
 Conversely, low rates of opioid use during pregnancy were
observed among teenage mothers (0.9), women on private
insurance (0.7), women of other-NH race/ethnicity (1.0), and
women in the highest quartile of household income (1.4).
After adjusting for other covariates, compared to women
with private insurance, women without private insurance had
9 times the odds of opioid use (Medicare/Medicaid; OR =
8.9; 95% CI: 7.7–10.3; "Other" insurance; OR = 9.2; 95% CI:
8.2–10.4). Alcohol and tobacco users were approximately
7 times as likely to use/abuse opioids, relative to
nonusers. The likelihood of opioid use during pregnancy
increased with increasing maternal age and decreased with
increasing household income (Table 1). Although black-NH
women had the highest crude rates of opioid use, after
adjustment for other sociodemographic and behavioral char-
acteristics, black-NH women were significantly less likely
than white-NH women to use opioids (OR = 0.6, 95% CI:
0.5–0.8). Similar findings were obtained in Hispanic
and other-NH women when compared to their white-NH
counterparts.

Figure 1 presents the rates of various comorbidities, by
opioid use status. Compared to nonusers, women who used
opioids during pregnancy had significantly higher rates of
depression (per 1,000 discharges) (116.7 versus 13.0), anxiety
(47.2 versus 4.8), HIV (18.1 versus 1.4), and insomnia (2.2
versus 0.2). Users were also more likely to have chronic
medical conditions such as hypertension, diabetes, and renal
disease but had a slightly lower rate of medically diagnosed
obesity (11.4 versus 14.7).

Maternal opioid use during pregnancy was also asso-
ciated with pregnancy-related maternal/fetal morbidity and
mortality (Table 2). Even after adjusting for sociode-
ographic, behavioral, and chronic prepregnancy conditions,
opioid use was associated with an increased odds of threat-
ened preterm labor (OR = 1.3, 95% CI: 1.2–1.5), early onset
delivery (OR = 1.7, 95% CI: 1.6–1.9), poor fetal growth (OR
= 1.6, 95% CI: 1.5–1.8), and stillbirth (OR = 1.3, 95% CI:
1.2–1.5). Women who used/abused opioids during pregnancy
were also 4 times as likely to have a prolonged hospital
stay exceeding 5 days (95% CI: 3.4–4.7) and were almost
4 times as likely to die during their hospital stay (OR =
3.7, 95% CI: 2.3–5.9). These differences in morbidity and
mortality also translated into differences in direct inpatient
medical costs. The mean per-hospitalization cost of a woman
who used opioids during pregnancy was $5,616 (95% CI:
$5,166–$6,067), compared to $4,084 (95% CI: $4,002–$4,166)
for nonusers. The estimated per-hospitalization difference
in cost between opioid and non-opioid-related discharges
was $2,602 (95% CI: $1,931–$3,272) after adjustment for
potential confounders. With an estimated 138,224 preg-
nancy-related hospital discharges affected by opioid use
nationally from 1998 to 2009, the excess direct inpatient medical
cost associated with opioid use was estimated at $359 million,
or approximately $30 million annually.
| Characteristic                          | N | Rate of opioid use (95% CI) | OR (95% CI) | AOR (95% CI) |
|----------------------------------------|---|-----------------------------|-------------|--------------|
| Overall                                | 55,781,965 | 2.48 (2.18–2.78) | n/a | n/a |
| Maternal age (years)                    |     |                            |             |              |
| 13–19                                  | 6,198,796  | 0.93 (0.82–1.04) | 0.35 (0.31–0.38) | 0.23 (0.21–0.26) |
| 20–24                                  | 13,822,023 | 2.47 (2.16–2.77) | 0.91 (0.85–0.98) | 0.62 (0.58–0.66) |
| 25–29                                  | 15,001,057 | 2.70 (2.35–3.05) | Reference | Reference |
| 30–34                                  | 12,797,406 | 2.76 (2.37–3.15) | 1.02 (0.94–1.11) | 1.36 (1.26–1.47) |
| ≥35                                    | 7,921,464  | 2.84 (2.41–3.28) | 1.05 (0.97–1.15) | 1.37 (1.25–1.50) |
| Other/unknown                          | 41,218   | 0.37 (<0.00–0.89) | 0.14 (0.03–0.56) | 0.15 (0.03–0.66) |
| Maternal race                          |     |                            |             |              |
| White, non-Hispanic                    | 22,047,327 | 2.90 (2.52–3.28) | Reference | Reference |
| Black, non-Hispanic                    | 6,025,913  | 3.24 (2.32–4.17) | 1.12 (0.88–1.43) | 0.61 (0.48–0.78) |
| Hispanic                               | 9,444,177  | 1.33 (1.07–1.59) | 0.46 (0.37–0.56) | 0.31 (0.25–0.38) |
| Other, non-Hispanic                    | 4,079,383  | 1.02 (0.80–1.24) | 0.35 (0.28–0.44) | 0.26 (0.21–0.34) |
| Missing/unknown                        | 14,185,165 | 2.68 (2.02–3.35) | 0.93 (0.70–1.22) | 0.98 (0.78–1.23) |
| Tobacco use                            |     |                            |             |              |
| Yes                                    | 2,009,092  | 21.60 (18.71–24.50) | 12.50 (11.41–13.70) | 6.67 (6.07–7.33) |
| No                                     | 53,772,873 | 1.76 (1.56–1.97) | Reference | Reference |
| Alcohol use                            |     |                            |             |              |
| Yes                                    | 96,629    | 81.02 (71.00–91.04) | 37.56 (33.98–41.52) | 7.17 (6.42–7.99) |
| No                                     | 55,685,336 | 2.34 (2.06–2.62) | Reference | Reference |
| Hospital region                        |     |                            |             |              |
| Northeast                              | 9,516,239  | 4.47 (3.66–5.28) | 2.60 (1.88–3.60) | 2.16 (1.60–2.92) |
| Midwest                                | 12,032,900 | 2.35 (1.74–2.96) | 1.37 (0.94–1.98) | 0.88 (0.60–1.28) |
| South                                  | 20,796,015 | 2.13 (1.61–2.65) | 1.24 (0.86–1.78) | 0.87 (0.63–1.18) |
| West                                   | 13,436,811 | 1.72 (1.26–2.19) | Reference | Reference |
| Hospital location                      |     |                            |             |              |
| Rural                                  | 6,877,937  | 1.36 (1.15–1.58) | Reference | Reference |
| Urban                                  | 48,763,827 | 2.64 (2.30–2.98) | 1.94 (1.58–2.38) | 2.22 (1.80–2.74) |
| Hospital teaching status               |     |                            |             |              |
| Nonteaching                            | 29,501,465 | 1.63 (1.43–1.82) | Reference | Reference |
| Teaching                               | 26,140,299 | 3.44 (2.85–4.04) | 2.12 (1.72–2.62) | 1.68 (1.33–2.12) |
| Hospital bed size                      |     |                            |             |              |
| Small                                  | 6,100,955  | 2.39 (1.84–2.94) | 0.89 (0.63–1.28) | 0.82 (0.59–1.13) |
| Medium                                 | 14,821,822 | 2.67 (1.94–3.39) | Reference | Reference |
| Large                                  | 34,718,987 | 2.42 (2.06–2.77) | 0.91 (0.66–1.23) | 0.95 (0.72–1.26) |
| Household income                       |     |                            |             |              |
| Lowest quartile                        | 14,617,169 | 3.58 (3.06–4.10) | 2.53 (2.19–2.93) | 1.54 (1.36–1.82) |
| 2nd quartile                           | 14,070,584 | 2.50 (2.18–2.82) | 1.76 (1.58–1.97) | 1.20 (1.09–1.33) |
| 3rd quartile                           | 13,294,169 | 2.18 (1.89–2.47) | 1.54 (1.41–1.67) | 1.17 (1.08–1.26) |
| Highest quartile                       | 12,830,659 | 1.42 (1.23–1.60) | Reference | Reference |
| Missing/unknown                        | 969,383   | 3.63 (3.02–4.24) | 2.56 (2.17–3.03) | 1.43 (1.17–1.75) |
Table 1: Continued.

| Characteristic       | \( N^b \)   | Rate\(^a\) of opioid use (95% CI) | OR\(^c\) (95% CI) | AOR\(^d\) (95% CI) |
|----------------------|-------------|-----------------------------------|-------------------|-------------------|
| Primary payer        |             |                                   |                   |                   |
| Medicare/medicaid    | 22,249,834  | 4.51 (3.89–5.14)                  | 6.90 (6.07–7.84)  | 8.87 (7.66–10.27) |
| Private              | 29,701,613  | 0.66 (0.59–0.73)                  | Reference         | Reference         |
| Other                | 3,830,518   | 4.79 (4.18–5.41)                  | 7.33 (6.54–8.22)  | 9.20 (8.16–10.38) |

AOR = adjusted odds ratio, CI = confidence interval, NIS = Nationwide Inpatient Sample, OR = odds ratio.

\(^a\) Per 1,000 pregnancy-related discharges.
\(^b\) Weighted to estimate national frequency and may not add to total due to missing data.
\(^c\) Crude model comparing the odds of maternal opioid use across different levels of each characteristic, separately.
\(^d\) A single multivariable model includes all characteristics that appear in the table.

Table 2: Rates\(^a\) of selected clinical outcomes by opioid use status and odds ratios and 95% confidence intervals for the association between opioid use and each outcome among pregnancy-related discharges, NIS, 1998–2009.

| Outcomes                        | Rate\(^a\) of outcome | OR (95% CI) | Model 1\(^b\) | Model 2\(^c\) | Model 3\(^d\) |
|---------------------------------|------------------------|-------------|---------------|---------------|---------------|
| Maternal                        |                        |             |               |               |               |
| Threatened preterm labor        | 30.1                   | 22.3        | 1.36 (1.24–1.49) | 1.34 (1.22–1.47) | 1.32 (1.19–1.45) |
| Early onset delivery            | 124.0                  | 65.2        | 2.03 (1.88–2.20) | 1.92 (1.77–2.07) | 1.72 (1.59–1.85) |
| PROM                            | 38.5                   | 35.4        | 1.10 (1.00–1.20) | 1.12 (1.03–1.23) | 1.06 (0.98–1.16) |
| Wound infection                 | 7.0                    | 5.0         | 1.41 (1.18–1.68) | 1.19 (1.00–1.42) | 1.17 (0.98–1.40) |
| Acute renal failure             | 2.1                    | 0.5         | 4.10 (3.11–5.41) | 2.78 (2.09–3.72) | 2.84 (2.11–3.84) |
| Postpartum depression\(^f\)     | 24.7                   | 2.1         | 12.04 (10.83–13.40) | 2.09 (1.79–2.44) | 1.75 (1.49–2.05) |
| Hospital stay >5 days\(^e\)     | 133.4                  | 29.9        | 5.00 (4.16–6.02) | 4.83 (4.10–5.69) | 4.02 (3.41–4.74) |
| In-hospital maternal mortality  | 0.8                    | 0.1         | 5.89 (3.74–9.28) | 3.63 (2.32–5.68) | 3.69 (2.32–5.87) |
| Fetal                           |                        |             |               |               |               |
| Poor fetal growth               | 35.9                   | 15.9        | 2.31 (2.10–2.55) | 2.21 (2.00–2.44) | 1.61 (1.46–1.77) |
| Stillbirth                       | 10.0                   | 6.3         | 1.60 (1.39–1.83) | 1.41 (1.23–1.62) | 1.32 (1.15–1.51) |

CI = confidence interval, NIS = Nationwide Inpatient Sample, OR = odds ratio, PROM = premature rupture of membranes.

\(^a\) Per 1,000 pregnancy-related discharges.
\(^b\) Crude model with maternal opioid use as the only independent variable.
\(^c\) Model 1 + adjustment for maternal age, household income, multiple birth, primary payer, and rural/urban status.
\(^d\) Model 2 + adjustment for tobacco, alcohol, maternal obesity, chronic renal failure, diabetes mellitus, and existing hypertension.
\(^e\) Model also adjusts for disposition at discharge.
\(^f\) Model also adjusts for history of depression.

4. Discussion

Consistent with previous studies, this multiyear population-based study found an increasing prevalence of opioids use/abuse among pregnant women in the US [1, 3–5, 7, 10, 17, 25, 26]. In our previous investigation of national trends of opioid use among pregnant mothers in the US, we discuss the alarming overall increase, as well as geographic, regional, and sociodemographic differences in both the rate and trends of opioid use over 12 years [16]. Due to concern for adverse effects on the mother and developing fetus, opioid abuse in pregnancy continues to be a major source of concern [1, 5–7, 13, 14]. As rates of opioid abuse in pregnancy are increasing the incidence of neonatal abstinence syndrome is rising [15]. This syndrome leads to prolonged neonatal hospitalizations, which in turn increase overall hospital costs among these mothers and their infants.

The current study builds on the existing literature by looking at the impact of opioid use and abuse during pregnancy on a wide range of maternal and infant birth outcomes. We found that pregnant women who used or abused opioids during pregnancy were more likely to have other comorbidities, including depression, anxiety, insomnia, diabetes, hypertension, renal diseases, and HIV infection. This finding was expected due to the association between these comorbid conditions and the development of chronic pain, poor response to pain medications, or experiencing the clinical condition during opioid withdrawal [26–28]. In our study, pregnant women who used or abused opioids were also more likely than nonusers to have a prolonged hospital stay; develop acute renal failure; and suffer mortality prior to hospital discharge. Their infants suffered from increased rates of growth restriction and stillbirth. Our findings were consistent with previous reports [29–31]. The source of worsening perinatal outcomes is likely multifactorial.

Opioid dependent women are more likely to have multiple comorbidities including mental health disorders such as depression and anxiety [32, 33]. Studies also associate...
Table 3: List of International Classification of Diseases, Ninth Edition, Clinical Modification Codes used to identify selected perinatal conditions.

| Condition                  | International Classification of Diseases, 9th Edition, Diagnosis Code |
|----------------------------|---------------------------------------------------------------------|
| **Exposure**               |                                                                     |
| Opioid use                 | 304.0x, 304.7, 305.5, 965.00, 965.01, E850.0, E935.0                |
| **Comorbidities**          |                                                                     |
| Anxiety                    | 300.0x, 309x                                                   |
| Chronic renal disease      | 581x, 582x, 583x, 585x, 587x, 646.2x                              |
| Depression                 | 296.2x, 296.3x, 298.0, 300.4, 301.12, 309.0, 309.1, 311            |
| HIV                        | 042, V08, 795.3                                                |
| Insomnia                   | 780.51, 780.52, 327.0x, 327.15, 307.41                            |
| Obesity                    | 278.00, 278.01, 278.03, 649.1x, V85.3x, V85.4x, V85.54, 793.91    |
| Osteopenia                 | 733.90                                                        |
| Prepregnancy diabetes      | 249x, 250x, 648.0x                                             |
| Prepregnancy hypertension  | 401x, 402x, 403x, 404x, 405x, 642.0x, 642.1x, 642.2x, 642.7x        |
| **Perinatal outcomes**     |                                                                     |
| Threatened preterm labor   | 644.0x                                                       |
| Early onset delivery       | 644.2x                                                       |
| Premature rupture of membranes | 658.1x                                                   |
| Wound infection            | 674.1x, 674.3x, 998.3x, 998.5x                                     |
| Acute renal failure        | 584x, 669.3x                                             |
| Postpartum depression      | 648.40, 648.42, 648.44                                       |
| Poor fetal growth          | 656.5x                                                       |
| Stillbirth                 | 656.4x, V271, V273, V274, V276, V277                              |

* The code suffix “x” represents all possible codes that follow the stated code prefix.
† Procedure codes, no diagnostic codes were used to define Cesarean section.

maternal anxiety during pregnancy with poor neurological development in the fetus [34]. In addition to mental health disorders, opioid dependent women are more often from socially disadvantaged backgrounds [35], lack healthy nutritional habits, have inadequate prenatal care, and engage in risky sexual practices [36]. These comorbid conditions may explain the adverse infant birth outcomes observed in our study. However, the association between opioid abuse during pregnancy and adverse maternal and infant birth outcomes persisted even after controlling for potential confounders. In addition to associated comorbidities, women with opioid abuse may have irregular menses leading to unintended pregnancy [37, 38]. Adverse perinatal outcomes occur at higher rates among unintended pregnancies alone [39]. Despite possible confounding due to associated comorbidities, the increase in hospital costs and adverse perinatal outcomes in the current study is likely due to neonatal abstinence syndrome and preterm deliveries as was seen in prior investigations [7, 15, 31, 40–42]. Due to a lack of sufficiently detailed data, this hypothesis could not be tested in our study.

This strength of the current study includes the large sample size and length of study. We used an extremely large multiyear hospital discharge database that enabled us to investigate a range of maternal/fetal outcomes. To our knowledge, this is the first study to report the impact of opioid dependence during pregnancy on maternal/fetal outcomes using over a decade of nationally representative data. We also looked at the distribution of comorbidities by maternal opioid dependence status to provide clinicians and other healthcare providers a broader understanding of the complexities surrounding opioid use/abuse during pregnancy.

Despite the noted strengths, our results need to be considered in light of the following limitations. First, the analyses were based on a database of inpatient hospitalizations and, therefore, cases of maternal opioid use not captured during pregnancy-related inpatient admissions were not included in this study. The missed cases are likely limited to home births which occurs in <1% of the US population [43]. Second, our operational definition of opioid use during pregnancy relied exclusively on ICD-9-CM codes documented in the NIS databases. These diagnostic codes lack the specificity to distinguish between use and abuse of prescription versus prescribed opioids. Thus, our analyses were not able to directly address the increasing concern for overprescription of opioids. Third, the deidentified nature of the publicly available NIS datasets do not permit linkage of maternal delivery and infant birth hospitalizations. Therefore, we were only able to investigate a small number of fetal outcomes and could not assess birth-related events available in the infant’s birth record. Third, due to the lack of a unique patient identifier, we were unable to link hospitalizations for the same woman over time and may count the same woman more than once over time leading to an overestimation of opioid use in pregnancy. Finally, hospital discharge summaries have
suboptimal sensitivity to capture all instances of maternal opioid use and may lead to underreporting. However, when compared to self-reports of substance abuse, discharge data contain greater objectivity [44]. Finally, our cost analyses were conducted from a third-party payer perspective and were only able to estimate direct medical care costs from the institutional portion of the hospital stay [45]. The NIS does not contain information on physician costs or indirect costs (e.g., lost wages).

In summary, we found increased rates of maternal comorbidities, prolonged hospital stays, in-hospital mortality, and poor fetal growth and survival among women who used or abused opioids during their pregnancy. These adverse pregnancy outcomes translated into significantly increased direct costs of inpatient care. The information provided in this study will be critical to the development and implementation of appropriate services for this high-risk group of women.

Appendix

See Table 3.

Conflict of Interests

The authors have no conflicts of interest to declare regarding the publication of this paper.

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