

Associations of Prescription Opioid Use during Pregnancy with Low Birth Weight and Length of
Hospital Stay: Analysis of PRAMS Data

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Abstract

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Background: Prescription opioid use among US pregnant women, primarily used for its analgesic properties, has increased substantially over the last decades. Findings from several studies investigating associations of prescription opioid use with adverse neonatal outcomes (including preterm birth, poor fetal growth, longer hospital stays, neonatal abstinence syndrome, and birth defects) were not consistent. We examined overall and infant-sex specific associations of maternal prescription opioid use in pregnancy with infant low birth weight and prolonged hospital stay.

Methods: Data from the 2019-2020 Pregnancy Risk Assessment Monitoring System (PRAMS), a surveillance project of the CDC and state departments of health, was used for the analyses. Participants (N=35,404 mother-newborn pairs) with information on the exposure (maternal prenatal prescription opioid use) and outcomes (low infant birth weight defined as birth weight less than 2,500g, and, prolonged hospital stay defined as hospital stay longer than three days)

were included in the analyses. We used crude and adjusted (for maternal age, race, household income, maternal smoking, depression, and infant sex) logistic regression models to estimate odds ratios (ORs) and corresponding 95% confidence intervals (CIs). We also evaluated infant sex as a potential effect modifier of the associations using stratified analyses and models with interaction terms.

Results: Among study participants, 1,729 mothers (4.9%) reported prescription opioid use during pregnancy. Overall, 18.2% infants had low birth weight and 4.8% had prolonged hospital stay. In unadjusted models, mothers exposed to prescription opioids during pregnancy had 2-fold (95%CI:1.67-2.44) higher odds of delivering a low birth weight infant compared to mothers who were not exposed to prescription opioids during pregnancy. This association was attenuated but remained statistically significant after adjustment for all covariates (adjusted OR:1.70; 95%CI:1.40-2.07; p-value<0.01). We found no evidence of effect modification by infant sex (males: adjusted OR:1.65; 95%CI:1.25-2.18, and, females: adjusted OR:1.75; 95%CI:1.39-2.31) (interaction p-value>0.05). In unadjusted models, infants of mothers who reported prescription opioid use during pregnancy had 2.07-fold (95%CI:1.65-2.61) higher odds of prolonged hospital stay compared to infants of mothers who did not report prescription opioid use during pregnancy. This association remained statistically significant after adjustment for covariates (adjusted OR:1.86; 95% CI:1.47-2.36, p-value<0.01). We found no evidence of effect modification of this association by infant sex (males: adjusted OR:1.67; 95%CI:1.22-2.28, and females: adjusted OR:2.05; 95%CI:1.43-2.93) (interaction p-value>0.05).

Conclusion: In the PRAMS cohort, prescription opioid use during pregnancy was associated with both low birth weight and prolonged hospital stay. We also found that the associations were

similar among male and female infants. Our findings highlight the potential consequences of opioid use during pregnancy for further research.

Introduction

Opioids are a class of drugs used for its analgesic and euphoric properties. Prescription opioids (including codeine and hydrocodone) are used for the management of acute (e.g., joint pain) or chronic pain (e.g., back ache) (1-5). Prenatal prescription opioid use among US pregnant women has increased significantly (131%) between 2010-2017(6). An estimated 6.6% of respondents from the 2019 PRAMS survey reported prescription opioid use during pregnancy. (7) The rising prevalence of opioid use in pregnancy is concerning as it can potentially lead to various adverse neonatal outcomes (8).

Several studies have reported associations of opioid use disorder with adverse neonatal outcomes including preterm birth, poor fetal growth, prolonged hospital stay, neonatal abstinence syndrome, and birth defects (9-13). However, findings of studies examining associations of prescription opioid use in pregnancy with neonatal outcomes were not consistent (9-13). Further, this has not been investigated using nationwide data in recent years. Despite well-recognized infant-sex-specific differences in associations of maternal exposures and neonatal outcomes, studies did not examine potential differences in associations of prenatal maternal prescription opioid use with adverse neonatal outcomes among male and female infants. Finally, potential mediators of the adverse consequences of prescription opioid use on the newborn, including prematurity, have not been fully characterized (14).

We investigated overall and sex-specific associations of prescription opioid use during pregnancy with low birth weight and prolonged hospital stay. In a secondary analysis, we also examined the potential role of prematurity (birth prior to 37 completed weeks of gestation) as a mediator of the associations. Findings from this study can inform future research in this area,

encourage surveillance of prescription opioid use among pregnant individuals, and provide guidance to healthcare providers while making decisions related to prescribing opioids during pregnancy.

Methods

Study Design and Study Setting

This is a retrospective cohort study investigating associations of exposure to prescription opioid use among pregnant women with adverse neonatal birth outcomes, low birth weight and prolonged hospital stay. Data from the 2019-2020 Pregnancy Risk Assessment Monitoring System (PRAMS) was used in this study. PRAMS is a surveillance project of the CDC and state health departments. PRAMS collects site-specific, population-based data on maternal attitudes and experiences before, during, and shortly after pregnancy (15).

Study Participants

In PRAMS, potential study participants who had a recent live birth are identified from jurisdiction's birth certificate files. PRAMS recruits new mothers through mailed questionnaires and telephone surveys. Women are contacted 2 to 6 months after giving birth. Annually, each participating site samples 1,000 to 3,000 eligible women. Women from some groups are sampled at a higher rate to ensure adequate data are available in smaller but higher-risk populations (16). A total of 86,899 participants responded to the PRAMS phase 8 Core Questionnaire in 2019-2020. Of these, 35,499 participants opted to answer the PRAMS Opioid Supplement which included questions on prescription opioid use during pregnancy. Participants who reported the use of illicit drug use (including heroin and cocaine) (N=95) were excluded from the current analyses. The final analytic sample included 35,404 participants. The analysis was conducted on

a de-identified PRAMS data set and therefore did not need institutional review board approval nor an exemption according to guidelines by the University of Washington Institutional Review Board (17).

Data Collection

The PRAMS survey collects information from new mothers about their pregnancy and their newborn baby using a core questionnaire. Information is obtained on topics like prenatal care, obstetric history, maternal use of alcohol and cigarettes, physical abuse, contraception, economic status, maternal stress, and early infant development and health status. In 2019, an opioid supplement questionnaire and call-back survey were added to the PRAMS survey at 34 sites (18). The supplement included questions on the type of opioid use, source of the opioid, the length of opioid use, and the timing of use.

Exposure and Outcome Assessment

The primary exposure was prescription opioid exposure use during pregnancy based on maternal self-report to question on the PRAMS Opioid Supplement. Prescription opioid exposure during pregnancy was categorized as a binary variable based on “yes” or “no” response to the question “During your most recent pregnancy, did you use any of the following prescription pain relievers (hydrocodone, codeine, oxycodone, morphine, tramadol, hydromorphone, oxymorphone, morphine or fentanyl)?”. The primary outcomes, obtained from PRAMS Phase 8 Core Questionnaire, were low birthweight, defined as birth weight less than 2,500 grams, and prolonged hospital stay, defined as hospital stay of more than three days.

Covariates:

Based on previous literature, we considered other characteristics (such as sex of the newborn, maternal age, maternal race, prenatal smoking status, maternal depression, household income, and prematurity) as potential covariates for analyses. Maternal smoking and depression have been associated with the exposure (prescription opioid use during pregnancy) and outcomes (low infant birth weight and prolonged hospital stay) we considered (19-21). Studies have also shown relationships between maternal age, maternal race and household income to both prescription opioid use during pregnancy and infant birth outcomes (22-24). Accumulating research has also shown that response to prenatal exposure is dependent on infant sex and that infant sex is strongly associated with birth weight of the baby (25-26). Studies have shown associations of prescription opioid use with premature birth, which can influence infant birth weight (27).

Maternal age was categorized as ≤ 17 , 18-19, 20-24, 25-29, 30-34, 35-39, ≥ 40 years. Race was categorized as non-Hispanic White, non-Hispanic Black, Hispanic, Chinese, Japanese, Filipino, other Asian, American Indian, Alaskan Native, Hawaiian, other non-white and mixed race. Household income was categorized as low if the total household income was less than 60,000 dollars (28). Prenatal smoking status of the mother was dichotomized as ‘smoker’ or ‘nonsmoker’ based on response to the question asking if the mother smoked one or more cigarettes at any time during the pregnancy. Antenatal depression was self-reported (yes/ no) to the question “ During your most recent pregnancy, did you have any of the health conditions ?” (a. Gestational diabetes b. High blood pressure c. Depression) as obtained from the Phase 8 core questionnaire. We considered infant sex (male/female), obtained from the birth certificate variables in the PRAMS research dataset codebook, as an adjustment variable and as a potential

effect modifier of the associations between prescription opioid use and low infant birth weight. Premature birth (defined as birth prior to 37 completed weeks of gestation) was evaluated as a potential mediator of the associations.

Statistical Analysis

In all analyses, we accounted for PRAMS sampling weight, a nonresponse adjustment, and a noncoverage adjustment, using information provided by the CDC (29). In descriptive analyses, the characteristics of study participants were summarized overall and by exposure status (prescription opioid use during pregnancy) using number (percentage) for categorical variables.

To address the primary aim of the study, associations of prescription opioid use during pregnancy with low birth weight, we fitted multiple logistic regression models with prescription opioid use during pregnancy as exposure and low birth weight as an outcome: unadjusted and adjusted (adjusted for infant sex, maternal age, race, income level, cigarette smoking, and depression) models. Similarly, to address the second primary aim of the study, associations of prescription opioid use during pregnancy with prolonged hospital stay, we fitted multiple logistic regression models with prescription opioid use during pregnancy as exposure and prolonged hospital stay as an outcome, with or without adjustment variables (as described above). We also conducted analyses to evaluate effect modification of both associations by infant sex using stratified analyses (stratified by infant sex) of the adjusted models and by fitting additional models that included interaction terms (interactions of infant sex with the respective exposure) along with the other variables described above. P-values of the interaction terms were used to

determine statistical significance of multiplicative interactions between infant sex and respective exposures.

Additionally, we conducted a secondary analysis to assess the role of premature birth as a potential mediator of the association between maternal prescription opioid use during pregnancy using comparison of adjusted models. We fitted adjusted models that included covariates (infant sex, maternal age, race, income level, cigarette smoking, and depression) as well as prematurity. The difference between estimates from this model, compared with previously described adjusted models, provided evidence for the potential role of prematurity as a mediator of the associations. For all analyses, a p-value < 0.05 was used as a cutoff to determine statistical significance and all analyses were conducted using the R software (version 4.0.5).

Results

Selected characteristics of study participants are shown in **Table 1**. Among 35,404 study participants, 1,729 mothers (4.9%) reported prescription opioid use during pregnancy. Overall, 22.8% participants had a low birth weight infant and 4.8% infants had a prolonged hospital stay after a delivery. Among women who reported prescription opioid use during pregnancy, 30.1% delivered a low birth weight infant and 7.5% infants had a prolonged hospital stay.

Corresponding rates for women who did not report prescription opioid use during pregnancy were 20.4% and 5.4%, respectively (both p-values < 0.05). Women who reported prescription opioid use during pregnancy were more likely to report prenatal smoking (15.6% vs 6.5%), antenatal depression (28.1% vs. 15.5%), and low household income (65.6% vs. 51.7%), when compared to women who did not report prescription opioid use during pregnancy (all p-values < 0.01). Women who reported prescription opioid use during pregnancy were less likely to be

White (51.9% vs. 56.5%), compared with women who did not report prescription opioid use during pregnancy (all p-values < 0.01).

In the unadjusted model (**Table 2**), participants who reported prescription opioid use during pregnancy had a 2.02-fold higher odds (95%CI:1.67-2.44) of delivering a low birth weight infant compared with participants who did not report prescription opioid use during pregnancy. This association was attenuated but remained statistically significant after adjustment for covariates (adjusted OR:1.70; 95%CI:1.40-2.07; p-value<0.01). Associations of prenatal prescription opioid use during pregnancy with having a low birth weight infant were similar among participants who delivered male or female infants (males: adjusted OR:1.65; 95%CI:1.25-2.18, and, females: adjusted OR:1.75; 95%CI:1.39-2.31; interaction p-value>0.05).

In the unadjusted model, participants who reported prescription opioid use during pregnancy had a 2.07-fold (95%CI:1.65-2.61) higher odds of prolonged hospital stay, compared with participants who did not report prescription opioid use during pregnancy (**Table 3**). This association was attenuated but remained statistically significant after adjustment for covariates (adjusted OR:1.86; 95%CI:1.47-2.36; p-value<0.01). Associations of prenatal prescription opioid use during pregnancy with prolonged hospital stay were similar among participants who delivered male or female infants (males: adjusted OR:1.67; 95%CI:1.22-2.28, and, females: adjusted OR:2.05; 95%CI:1.43-2.93; interaction p-value>0.05).

In secondary analyses, we examined whether prematurity affected observed associations. Adding prematurity to adjusted models evaluating associations of prescription opioid use during pregnancy with delivering low birth weight infant resulted in an estimate that was attenuated and became statistically insignificant (low birth weight: adjusted OR:1.32; 95%CI:0.96-1.82; p-value> 0.05). On the other hand, adding prematurity to adjusted models evaluating associations

of prescription opioid use during pregnancy with prolonged hospital stay resulted in an estimate that was attenuated but was still statistically significant (adjusted OR:1.61; 95%CI:1.17-2.21; p-value< 0.05).

Discussion

In the current study, we found that prescription opioid use during pregnancy was associated with delivering a low birth weight infant and prolonged hospital stay of the infant. Participants who reported using prescription opioids during pregnancy had 1.70 and 1.86-fold higher odds of delivering a low birth weight infant and prolonged hospital stay of the infant, respectively, compared with participants who did not report using prescription opioids during pregnancy, after adjustment for covariates. These associations were similar among participants who delivered male or female infants. The associations were however attenuated and became statistically insignificant after adjustment for prematurity.

Among our study participants, 4.9% of women self-reported prescription opioid use during pregnancy. This number is slightly below the 6.6% reported in a previous PRAMS study done in 2019 (7). The lower proportion of prescription opioid use among pregnant women reported may be due to the fact that data was based on self-report and may have underestimated prenatal opioid use. However another population study on a large national cohort of Medicaid enrolled women showed that one in five women (21.6%) filled an opioid prescription during pregnancy (30). Our results are consistent with some, but not all, studies that investigated associations of prescription opioid use during pregnancy with low birth weight (9). One study done using data from the Tennessee Medicaid Program (in 2015) showed that opioid exposed infants are more likely to have low birth weight than non-exposed infants (11.8% vs 9.9%

respectively) (31). Another study by Norgaard et al reported a higher prevalence of having low birth weight infants in women exposed to methadone and buprenorphine during pregnancy (PR:4.3; 95%CI: 3.0-6.1) (32). Other studies reported null associations between prescription use in pregnancy and low birth weight (33-35). A study on Swedish birth cohorts between 1996-2011 concluded that opioid analgesic use in pregnancy had no effect on birth weight (33). Similarly, a study on the National Birth Defects Prevention Study, by Julia et al., showed that prescription opioid use in pregnancy was not significantly associated with term low birth weight (34). Our study findings of association of prescription opioid use during pregnancy with low birth weight has potential implications on the life course health of the infant, given the early life and developmental origins of health and disease.

We also found associations between prenatal prescription opioid use and prolonged hospital stay in our study after adjusting for several covariates. Our finding is similar to a Washington State-based study that used state-linked birth certificate and hospital discharge data from 2000-2008 and concluded that increased use of prenatal illicit or prescription opioid drugs was associated with higher length of hospitalization (36). Neonates exposed to prenatal illicit or prescription drugs had a longer hospital stay compared to those not exposed (6.5 days versus 2.6 days, respectively). Another study conducted among participants identified in Florida between 2010-11 showed that infants with neonatal abstinence syndrome had prolonged hospital stays (37). Longer hospital stay is usually an indication of maternal and child health issues post-pregnancy. It also indicates potentially higher healthcare costs that could burden the family, health care resources, and taxpayers (38).

We did not find statistically significant effect modification of associations of prescription opioid use during pregnancy with low birth weight or prolonged hospital stay by infant sex.

While the estimates were not significantly different (interaction p -values > 0.05), it can be noted that the associations were stronger for both outcomes among females. Future research in this area is needed. In adjusted models that also included prematurity, both associations of prescription opioid use during pregnancy with low birth weight or prolonged hospital stay were attenuated and associations of prescription opioid use during pregnancy with low birth weight became statistically insignificant. This is a potential indication that prematurity may be mediating, at least in part, the associations. Among mothers who used prescription opioids, 27.2 percent had premature infants, in contrast with 17.8 percent of mothers who were not exposed to prescription opioids. Premature birth has health implications for the newborn including low birth weight, respiratory distress, hypothermia, and intraventricular hemorrhages, which may also be related to prolonged hospital stay. Our findings suggest that prevention of prematurity may reduce effects of prescription opioid use during pregnancy on low birth weight or prolonged hospital stay.

The current study has several strengths. To our knowledge, this is the first multi-state population study to investigate the association between prescription opioid use during pregnancy with low birth weight or prolonged hospital stay in recent years. Generalizability of the PRAMS data set, adjustment for potential confounding variables, and examination of potential effect modification by infant sex are additional strengths of the study. On the other hand, several limitations deserve mention. The use of the PRAMS data with maternal self-reported use of prescription opioids is potentially affected by recall bias. Some variables used in the study are from the opioid questionnaire which is not part of the core questionnaire and has fewer participants than the original survey. In addition, there may be selection bias related to this lower number of participants included in the analyses. The prescription opioid use data was only

available starting from the year 2019. Hence, it is not possible to compare the results with prior years. Our study did not account for the type of opioid prescribed or dosage responsible for observed adverse neonatal health outcomes.

In sum, we found significant associations of prenatal prescription opioid use with both delivering a low birthweight infant and prolonged hospital stay of the infant. Associations were similar among male or female infants and were significantly attenuated after adjustment for prematurity. Findings from our study, if supported by other studies, suggest that healthcare providers should exert caution while prescribing opioids to pregnant women. Patients who use opioids during pregnancy should be counseled by their practitioners about this and other potential risks associated with opioid use in pregnancy. Besides replication of our study findings, future studies need to examine potential mechanisms for the observed associations, dose-response relationships, specific opioid drugs related to these adverse outcomes, and long term health implications on children.

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Table 1 Selected characteristics of study participants

Characteristics	All Participants N=35,404	Prescription Opioid Use During Pregnancy*		P value**
		No N=33675	Yes N=1729	
Infant sex				0.67
Male	17727	16870 (50.1)	857 (49.6)	
Female	17675	16803 (49.9)	872 (50.4)	
Premature birth***				<0.01
Yes	6452	5984 (17.8)	468 (27.1)	
No	28921	27660 (82.1)	1261 (72.9)	
Maternal smoking				<0.01
Yes	2474	2205 (6.5)	269 (15.6)	
No	32688	31244 (92.8)	1444 (83.5)	
Maternal depression				<0.01
Yes	5692	5206 (15.5)	486 (28.1)	
No	29429	28208 (83.8)	1221 (70.6)	
Maternal Race				<0.01
Other Asian	1681	1580 (4.7)	101 (5.8)	
White	19921	19022 (56.5)	899 (51.9)	
Black	5925	5598 (16.6)	327 (18.9)	
American Indian	1695	1556 (4.6)	139 (8.0)	
Chinese	470	462 (1.4)	8 (0.4)	
Japanese	54	53 (0.2)	1 (0.1)	
Filipino	223	211 (0.6)	12 (0.7)	
Hawaiian	19	19 (0.1)	0 (0)	
Other Non-White	1865	1784 (5.3)	81 (4.6)	
Mixed Race	1720	1606 (4.8)	114 (6.5)	
Household Income				<0.01
Low (<\$60,000)	18549	17415 (51.7)	1134 (65.6)	
Not Low (≥\$60,000)	14436	13911 (41.3)	525 (30.3)	
Maternal Age (year)				0.06
≤17	356	343 (1.0)	13 (0.8)	
18-19	1031	985 (2.9)	46 (2.6)	
20-24	5814	5533 (16.4)	281 (16.3)	
25-29	9942	9398 (27.9)	544 (31.4)	
30-34	11050	10546 (31.3)	504 (29.1)	
35-39	5852	5581 (16.6)	273 (15.8)	
≥40	1357	1289 (3.8)	68 (3.9)	

* Number (percentage)

** Chi-square p-value comparing groups defined by prenatal prescription opioid use

*** Premature birth defined as birth before 37 completed weeks of gestation

Table 2 Association of prescription opioid use during pregnancy with low birth weight

Prescription Opioid Use	Low Birth Weight*		Unadjusted		Adjusted**	
	No N=27,281	Yes N=8,073	OR (95% CI)	P-Value	OR (95% CI)	P-value
All Infants						
No	26,760 (79.5)	6,865 (20.5)	Reference		Reference	
Yes	521 (30.1)	1,208 (69.9)	2.02 (1.67 - 2.44)	< 0.01	1.70 (1.40-2.07)	<0.01
Male Infants						
No	3,161 (18.8)	13,679 (81.2)	-----	-----	Reference	
Yes	235 (27.5)	621 (72.5)			1.65 (1.25-2.18)	<0.01
Female Infants						
No	3,700 (22.1)	13,081 (77.9)	-----	-----	Reference	
Yes	285 (31.7)	585 (68.3)			1.75 (1.39-2.31)	<0.01

*Low birth weight defined as birth weight less than 2,500 grams

**Adjusted for maternal race, smoking, depression, age, sex of the child, and household income

Note: P-value for prescription opioid use and infant sex interaction >0.05

Table 3 Association of prescription opioid use during pregnancy with prolonged hospital stay

Prescription Opioid Use	Prolonged Hospital Stay*		Unadjusted		Adjusted**	
	Yes N=5635	No N=29,499	OR (95% CI)	P-Value	OR (95% CI)	P-value
All Infants						
No	5,217 (15.6)	28,208 (84.4)	Reference		Reference	
Yes	418 (24.5)	1,291 (75.5)	2.07 (1.65 - 2.61)	< 0.01	1.86 (1.47-2.36)	<0.01
Male Infants						
No	2,733 (16.4)	14,003 (83.6)	-----	-----	Reference	
Yes	211 (25.0)	634 (75.0)			1.67 (1.22-2.28)	<0.01
Female Infants						
No	2,484 (14.9)	14,205 (85.1)	-----	-----	Reference	
Yes	207 (24.0)	657 (76.0)			2.05 (1.43-2.93)	<0.01

*Prolonged hospital stay defined as hospital stay greater than three days.

**Adjusted for maternal race, smoking, depression, age, sex of the child, and household income

Note: P-value for prolonged hospital stay and infant sex interaction >0.05