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PATTERNS OF OPIOID UTILIZATION IN PREGNANCY IN A LARGE COHORT OF COMMERCIAL INSURANCE BENEFICIARIES IN THE UNITED STATES

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Abstract

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Conflicts of interest: SHD has consulted for Novartis, GlaxoSmithKlein-Biologics (Middlesex, England, United Kingdom) and AstraZeneca (London, England, United Kingdom) and JS is a consultant to Optum Insight (Eden Prairie, Minnesota, United States of America) and World Health Information Science Consultants, LLC (Newton, Massachusetts, United States of America), both for unrelated projects. The other authors declare no potential conflict of interest.

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Background—There are few data regarding the utilization of opioids during pregnancy. The objective of this study was to define the prevalence and patterns of opioid use in a large cohort of pregnant women who were commercial insurance beneficiaries.

Methods—Data for the study were derived from a de-identified research database of women from across the United States who had both medical and prescription benefits. Using diagnostic codes we defined a cohort of 534,500 women with completed pregnancies who were enrolled in a commercial insurance plan from 6 months prior to pregnancy through delivery.

Results—Overall, 76,742 (14.4%) women were dispensed an opioid at some point during pregnancy. There were 30,566 (5.7%) women dispensed an opioid during the first trimester, 30,434 (5.7%) women during the second trimester, and 34,906 (6.5%) women during the third trimester. Of these, 11,747 (2.2%) women were dispensed opioids 3 or more times during pregnancy. The most commonly dispensed opioids during pregnancy were hydrocodone (6.8%), codeine (6.1%), and oxycodone (2.0%). The prevalence of exposure at anytime during pregnancy decreased slightly during the study period from 14.9% for pregnancies that delivered in 2005 to 12.9% in 2011. The prevalence of exposure varied significantly by region, and was lowest in the Northeast and highest in the South.

Conclusions—This study demonstrated that opioids are very common exposures during pregnancy. Given the small and inconsistent body of literature on their safety in pregnancy, these findings suggest a need for research in this area.

Introduction

Approximately 2% of the US adult population use opioids regularly,¹ and 10 to 30% of patients with chronic non-cancer pain are treated with opioids.² Throughout the 1990's and early 2000's the prescription of opiate pain medications increased two to three-fold in the United States,³⁻⁵ though it may have stabilized in recent years. Despite the importance of these medications for pain control and their potential for adverse effects, there are very few data regarding their use in pregnancy in the United States.^{6,7}

While nearly all women will experience some pain during the course of pregnancy, the safety of using opioids to manage pain in pregnancy remains ill-defined. Some studies have reported an association between opioid use in the first trimester and major congenital malformations, but the findings vary.⁸⁻¹⁶ When used long-term during pregnancy, there is a known potential for neonatal opioid dependence and subsequent withdrawal symptoms in the first few days of life¹⁷, but other potential consequences for the infant of long-term maternal opioid use are less clear.

Defining how commonly opioids are prescribed in pregnancy, which opioids are preferred by physicians, what pain conditions are most frequently treated, and how patients who are chronically using opioids prior to pregnancy are managed during pregnancy are important in defining research priorities in this field. We therefore undertook a study to define patterns of utilization of opioids during pregnancy in a large cohort of pregnancies in the United States.

Materials and Methods

Definition of Cohort

Data for the patients included in this study arose from a de-identified research database InVision for Data Mart, a product of OptumInsight Life Sciences (Eden Prairie, MN). It contains compiled membership and reimbursement transactions from a nationwide US health insurer for employed people and their dependents who had both medical and prescription benefits. At the time of this study (between 2005 and 2011), the research database included claims for reimbursement of pharmacy dispensings, inpatient and outpatient services, and procedures including the associated diagnoses for an open cohort with approximately 30% annual turnover, leading to an average cohort residence time of 2.48 years (s.d., 2.36) and a cross-sectional size that ranged from 12,750,397 to 14,483,016 persons depending on the study year (approximately 4% of the US population). Demographics of people in the database are similar to the US population for all ages <65, although the geographic distribution reflects the region-specific market-share of the insurer rather than the density of the underlying population. The pharmacy benefit of the health insurer is based on an open formulary with a tiered copayment structure that incentivizes preferred medications with restrictive use of non-preferred ones.

The study cohort was first defined on the basis of inpatient or outpatient codes indicating infant delivery using a algorithm based on *International Classification of Diseases 9, Clinical Modification* diagnostic and procedure codes.¹⁸ We further refined the date of delivery for each pregnancy hierarchically based on either (1) delivery procedure codes, (2) the date of admission for the delivery, or (3) the date of the last outpatient visit with codes for delivery. The last menstrual period (LMP) was defined as 245 days prior to the date of delivery if the maternal record indicated that the delivery was preterm, otherwise the LMP was assigned as 273 days prior to delivery.¹⁹ Analyses were restricted to patients with continuous insurer enrollment from 180 days prior to the estimated LMP through date of delivery, allowing for up to 30-day lapses in coverage (534,500 completed pregnancies). No further restrictions or exclusions were imposed.

Definition of pregnancy periods and exposure

We examined patterns of dispensing by type of opioids in the pre-pregnancy period, during each trimester, and then in pregnancy overall. The pre-pregnancy period represented two 90 day-periods prior to the estimated LMP. The first trimester extended from the estimated LMP through day 90 of pregnancy, second trimester was the following 90 days, and the third trimester began 181 days after estimated LMP and continued to delivery. Dates of pharmacy dispensing, and expected duration of use based on days supplied for study medications were used to estimate duration of exposure during pregnancy.

The opioids considered in our analysis included hydrocodone, codeine, oxycodone, propoxyphene, tramadol, meperidine, hydromorphone, morphine, fentanyl, buprenorphine, methadone, pentazocine, tapentadol, and oxymorphone. In this analysis we allowed days supply to accumulate for patients who were dispensed opioids before the days supply from their previous dispensing was expected to be completed. We assumed continuous exposure

for patients with sequential prescriptions when the days supply expired less than 7 days prior to a new prescription. We also determined the mean number of dispensings, by type, for patients that were exposed to opioids during pregnancy.

Statistical Analyses

Analyses of patterns of dispensing, associated conditions, and temporal trends were descriptive of this commercially insured population. The results are parameters for this particular population, rather than estimates based on samples. Accordingly, we present the results without confidence intervals.

Defining patterns of opioid utilization in pre-pregnancy chronic opioid users

We defined chronic opioid users as women who received dispensings of an opioid during 3 or more separate months in the 180 days prior to pregnancy and then examined patterns of opioid dispensing during the first and second trimester for this group. We identified, by trimester, those who were dispensed the same type of opioid, dispensed a different type of opioid, or were not dispensed any opioid.

Description of associated conditions

Medical conditions that might be associated with opioid prescription were identified using *International Classification of Diseases 9 Clinical Modification* diagnosis codes in the patients' inpatient and outpatient records between 180 days before LMP and delivery. The frequency of each of these conditions was determined in (1) all patients exposed to opioids during pregnancy, (2) patients with 3 dispensings of opioids during pregnancy, (3) patients who were defined as chronic users prior to LMP, and (4) patients who were unexposed to opioids during pregnancy.

Temporal and regional trends in utilization of opioids during pregnancy

For each year in the study period (defined by the year of delivery), we examined the frequency of exposure to any opioids at anytime during pregnancy and during each of the 3 trimesters observed. We also examined trends in the frequency of exposure to the four most commonly dispensed opioids at any time during pregnancy.

We examined regional variations in opioid prescribing using a mixed-effects logistic regression model to account for random variation. The state identifier was modeled as a normally distributed random intercept. Each intercept represents the state-specific prescribing rate, defined as the proportion of pregnant women who were dispensed opioid medications at any time during pregnancy. These predicted state-specific prescribing rates are empirical Bayes estimates; that is, they have been shrunk towards the overall mean prescribing rate.²⁰

All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

The use of this de-identified database for research was approved by the Partners Institutional Review Board (Boston, Massachusetts).

Results

There were 534,500 completed pregnancies eligible for analysis (meeting criteria of enrollment in the health insurer from 6 months prior to pregnancy through delivery). The median age of the women at the time of delivery was 31 years (interquartile range: 28–35); 17,793 (3.3%) of pregnancies were multiple gestations and 37,795 (7.1%) were preterm deliveries. There were 59,405 (11.1%) pregnancies from the Northeast, 230,137 (43.1%) from the South, 147,137 (27.5%) from the Midwest, 97,771 (18.3%) from the West. There were 435,649 women who had one pregnancy during the study period, 45,389 who had two pregnancies, and 2,656 who had three or more pregnancies.

Overall, 76,742 (14.4%) women were dispensed an opioid at some point during pregnancy. Exposure occurred in 30,566 (5.7%) women during the first trimester, in 30,434 (5.7%) women during the second trimester, and in 34,906 (6.5%) women during the third trimester (Table 1). When we excluded prescriptions filled within 3 days of delivery (and thus potentially in anticipation of the need for postoperative analgesia following a Cesarean delivery or the like), the prevalence of exposure in the 3rd trimester decreased only slightly to 6.2%. The frequency of exposure during each of these periods was considerably lower than the frequency of exposure during the two 90 day-periods that preceded pregnancy (10.0% and 9.7% respectively). There were 11,747 (2.2%) women who were dispensed opioids 3 or more times during pregnancy. Of the 76,742 women exposed to opioids during pregnancy, 7,135 (9.3%) had a hospital admission with a primary procedure code indicating that they underwent a surgical procedure. The frequency of opioid exposure in the first pregnancies recorded in the database was 14.4%, in the second pregnancy was 14.1%, and in the third or greater pregnancy was 14.9%.

The most common opioid dispensed in pregnancy was hydrocodone (dispensed to 6.8% of pregnant women), followed by codeine (6.1%), oxycodone (2.0%), and propoxyphene (1.6%). The distribution of opioids types dispensed was fairly uniform across the 3 trimesters (Table 1).

Table 2 shows, for patients dispensed each type of opioids during pregnancy, the mean, median, and interquartile range for the cumulative number of days supply during pregnancy. For the most commonly used opioids (hydrocodone, codeine, oxycodone, and propoxyphene) the median duration of exposure was less than a week. In contrast, morphine, fentanyl, buprenorphine, methadone, and oxymorphone were associated with longer durations of exposure. The number of distinct dispensings for each opioid also followed this pattern.

There were 5,838 patients chronically filling opioid prescriptions prior to pregnancy. Figures 1a and 1b show patterns of opioid dispensing during the first and second trimester, respectively, for patients who were chronically exposed to opioids prior to pregnancy (note, patients can belong to more than one group if they are chronically taking more than one type of opioid prior to pregnancy). Depending on the type, between 67% and 95% of chronic users were dispensed an opioid during the first trimester, with the majority being dispensed the same opioid that they used during the pre-pregnancy period, but between 8% and 15%

were dispensed a different opioid. The frequency of opioid dispensing to chronic pre-pregnancy users generally declined in the second trimester and ranged from 53% to 90%. The proportion that was dispensed a different opioid than during the pre-pregnancy period ranged from 11% to 28% depending on the type.

Table 3 shows conditions present in patients with any opioid dispensing during pregnancy, patients with 3 or more dispensings of opioids during pregnancy, patients defined as chronic users prior to pregnancy, and in women unexposed during pregnancy. Back pain was the most commonly associated condition and was present in 37% of patients dispensed an opioid during pregnancy and 61% of those dispensed opioids 3 or more times during pregnancy. Other conditions that were most commonly associated with opioid exposure included abdominal pain, migraine, joint pain, and fibromyalgia.

Figures 2 and 3 show temporal trends in the utilization of opioids in pregnancy. As shown in figure 2, the prevalence of exposure at anytime during pregnancy decreased slightly from 14.9% for pregnancies that delivered in 2005 to 12.9% in 2011. This decrease was noted in prevalence of exposure in each of the trimesters as well. Among the 4 most commonly dispensed opioids (Figure 3), there was a decrease in the use of codeine (from 7.2% to 5.3%), an increase in the use of oxycodone (from 1.6% to 2.1%), and hydrocodone use was relatively stable. There was a notable decrease in the use of propoxyphene among pregnancies that delivered in 2011, reflecting the removal of propoxyphene from the market in the United States in late 2010.

Figure 4 shows the prevalence of opioid exposure at any point during pregnancy by state while accounting for random variation. Given the large number of pregnancies contributed by each individual state, the predicted prescribing based on the mixed effects regression analysis was very similar to the actual observed prescribing for most states. Significant regional differences were observed. Use ranged between 6.5% and 26.3%. In general, the prevalence was lowest in the Northeast and highest in the South. Arkansas, Mississippi, and Alabama all had prevalences in excess of 20%. There was about a 2-fold difference in the average prescribing rate of states in the lowest (10.2%) versus the highest (20.0%) prescribing quartile.

Discussion

In this analysis of over a half a million pregnancies among private health insurance beneficiaries drawn from across the United States from 2005 to 2011, we found that opioids were dispensed to 14% of women during the antepartum period with approximately 6% of women receiving opioids during each of the 3 trimesters. While most opioid exposure represented short courses of treatment, 2.2% of women received 3 or more opioid dispensings during pregnancy. The most frequently prescribed opioids in pregnancy included hydrocodone, codeine, and oxycodone. The overall prevalence of exposure at any time during pregnancy, while declining slightly, was in excess of 12% for each of the 7 years in the study period.

While the risk of neonatal opioid dependence associated with prolonged opioid exposure is clear,²¹ other risks associated with opioid exposure remain ill-defined. The Collaborative Perinatal Project reported an increased risk of respiratory malformations associated with codeine, but not with hydrocodone, meperidine, methadone, morphine, or oxycodone.⁸ Associations between first trimester exposure to codeine and cardiovascular defects were suggested in some case-control studies not specifically designed to study opioids,^{9–12} and another study found an increased risk of oral clefts.¹³ In 2011, the National Birth Defects Prevention Study reported that opioid treatment (mainly codeine and hydrocodone) early in pregnancy is associated with greater risk of cardiac septal defects, hypoplastic left heart syndrome, spina bifida and gastroschisis.¹⁴ A recent study from the Slone Epidemiology Center Birth Defects Study found an approximately 2-fold increase risk of neural tube defects in association with periconceptual opioid use.¹⁶ However, an increased risk of malformations was not observed in a recent large European cohort study.¹⁵ Chronic opioid use in pregnancy has also been associated with Cesarean delivery, excessive postpartum hemorrhage due to uterine atony,¹⁵ low birth weight, fetal growth restriction, and other adverse neonatal outcomes. This evidence regarding teratogenesis and other risks, in addition to being inconsistent, is limited by small numbers, and multiple comparisons (increasing the probability of chance findings). Our data demonstrate that opioids are widely used in pregnancy, including during the first trimester where even a brief course could confer risk of teratogenesis.^{8–16} This suggests a need to better define the safety of opioid medications during pregnancy.

Pain syndromes, most frequently back pain, abdominal pain, joint pain, and headaches, are very common in pregnancy. Alternatives to opioids for the treatment of pain, most notably the non-steroidal anti-inflammatory drugs, also have potential safety concerns associated with their use in pregnancy.²² Thus, there is need for comparative safety and effectiveness research to determine the optimal approach to the treatment of painful conditions in pregnancy. Likewise, it will be important to develop evidence for the safest approach for treating perioperative pain in pregnant women, as up to 2% of pregnant women will undergo non-obstetric surgery.²³

When we examined patterns of management of opioids for patients that were chronically taking opioids prior to pregnancy, it was notable that substantial fractions of women continued them into the second trimester. Thus, the majority of women who are taking opioids chronically prior to pregnancy continue to do so once they become pregnant. Given the known adverse effects of prolonged exposure to opioids on the fetus, our findings suggest that it is challenging for women on these medications chronically to discontinue their use during pregnancy. This further underscores the importance of evaluating the comparative safety of treatment alternatives to inform the treatment decision for women who require continued treatment during pregnancy.

The prevalence of exposure that we report is significantly higher than what has been observed in studies in European populations during a similar timeframe.^{24,25} A population based cohort study using the Norwegian Prescription Database linked to the Medical Birth Registry reported that 2.9% of women were exposed to opioids at any time during pregnancy during 2004–2008, compared with 14.4% in our study. This lower use was

observed during all time periods: 2.6% during the 3 months before pregnancy, 1.4% during the first trimester, and 1.0% each during the second and third trimester (versus 9.7%, 5.7%, 5.7%, and 6.5% respectively in our study). Prescription of opioids during pregnancy thus appears to be 4–6 times higher in the United States compared to Norway.²⁵ Further, there were significant regional differences in the frequency of opioid exposure in our study, with several states in the South having prevalences in excess of 20%.

The number of opioid prescriptions issued nationwide has increased from 131 million in 2000 to 219 million in 2011, representing a 67% increase. The corresponding increase during our 2004–2011 study period was 30%. During this same time period, there was a 4-fold increase in the number of deaths related to opioid use.²⁶ While it is perhaps encouraging that the overall prevalence of opioid exposure during pregnancy decreased slightly during the study period (from 14.9% in 2005 to 12.9% in 2011), the overall prevalence of exposure at the most recent estimate remains extremely high relative to what was observed in the European population. Our data therefore suggest that the epidemic of opioid overutilization in the United States that is known to exist in the general population extends to pregnancy.

Our study is subject to certain limitations. While our data are drawn from claims of a private health insurer that includes beneficiaries from across the United States, a substantial fraction of deliveries in the United States occur to patients that are covered by Medicaid;²⁷ it is unclear whether our findings are generalizable to these patients. As a consequence, the state specific prescribing patterns only reflect those of the commercially insured population under study and cannot be used to extrapolate to the frequency of opioid exposure in the general obstetric population. Additionally, our measure of exposure is based on pharmacy dispensing of medications, and not whether the medication was actually taken by the women. In light of the ongoing debate about opioid overprescribing, we recognize a value in documenting the prescribing patterns themselves during pregnancy. Of course, this analysis does not include exposure to opioids that are obtained illicitly. Accounting for such illicit exposure to opioids in pregnancy (or in the general population) would be a challenge for any study, irrespective of its data source or design. We also would not capture exposure to methadone at free-standing clinics. Further, the health insurer database does not include most of the medications received by patients while hospitalized, which would lead to some degree of underestimation of opioid exposure in our study, especially since women might be in greater need of analgesics during a hospital stay. Our analysis is performed at the level of individual pregnancies, not women. This approach was taken as the effects of opioid exposure are likely most significant for the individual fetuses which are exposed in-utero. While this may lead to correlated exposures in individual women who had more than one pregnancy included in the analysis, we found a similar frequency of exposure in first pregnancies (14.4%), second pregnancies (14.1%), or third or greater pregnancies (14.9%). Finally, when using insurance claims data to study exposures during pregnancy, the LMP needs to be imputed based on claims for preterm labor and delivery. While this approach has been shown to result in generally accurate estimation of gestational age,¹⁹ some degree of misclassification is likely.

In conclusion, the use of opioid analgesics in pregnant women in the United States is high and is dominated by treatments of short duration. The proportion of women exposed is relatively stable across trimesters and over time. Given this continued high use during all phases of pregnancy and the small and inconsistent body of literature on their safety, there is a need for research on the comparative safety of these medications during pregnancy to help inform clinical practice and treatment guidelines.

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Final Boxed Summary

What we already know about this topic

- Opioid prescribing has increased in the US, with approximately 2% of the populations regularly using prescription opioids
- In contrast to the general population, opioid use during pregnancy has been little studied

What this article tells us that is new

- In a review of over 500,000 women enrolled in an insurance plan from 6 months prior to pregnancy through parturition, 14% received at least one dose of an opioid during pregnancy
- Over 1 in 20 women received an opioid during the first trimester, and prevalence of opioid exposure varied several-fold across states, being generally lowest in the Northeast and highest in the South

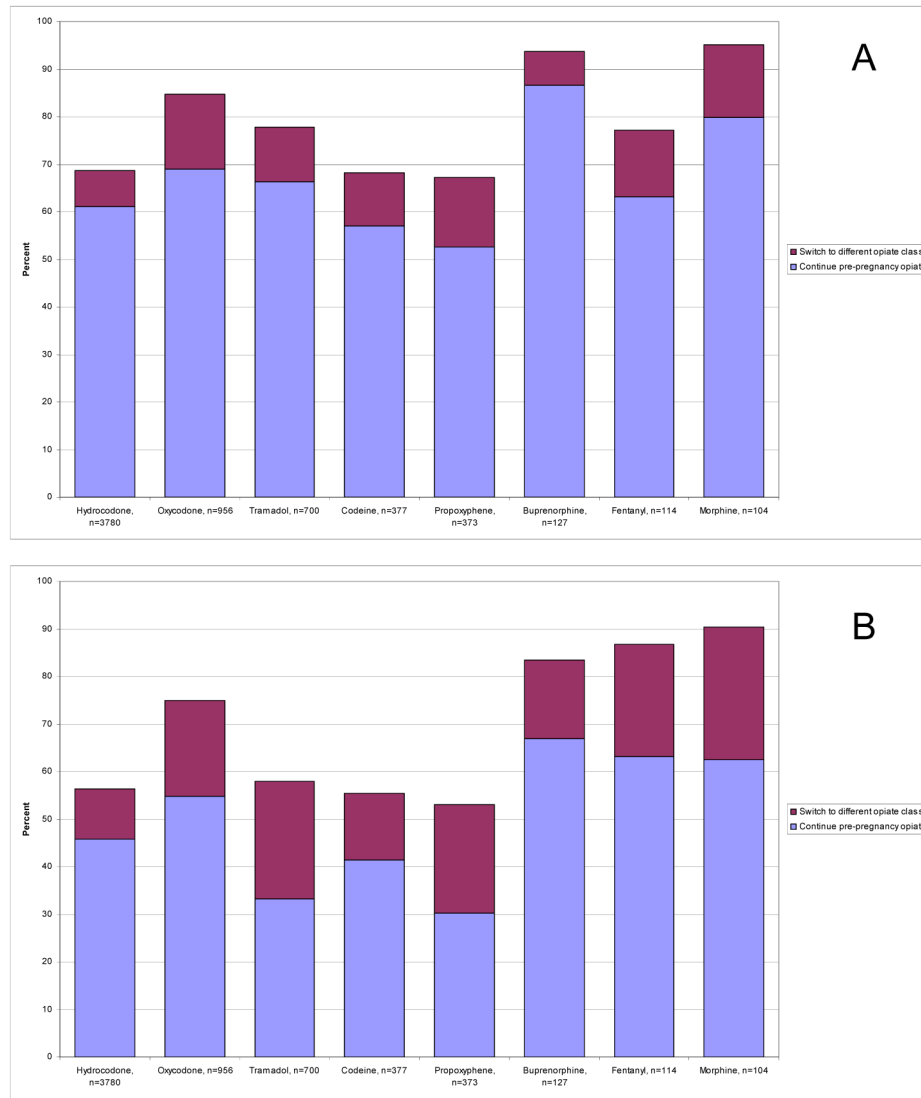


Figure 1. Among Patients Chronically Taking Opioids Prior to Pregnancy*, Patterns of Opioid Dispensing during (A) the First Trimester and (B) the Second Trimester. n=5,838

*Defined as patients who received 3 or more dispensings of an opioid pre-pregnancy (from -180 days to day prior to last menstrual period) during 3 separate months; analysis restricted to types of opioids with >100 pre-pregnancy chronic users

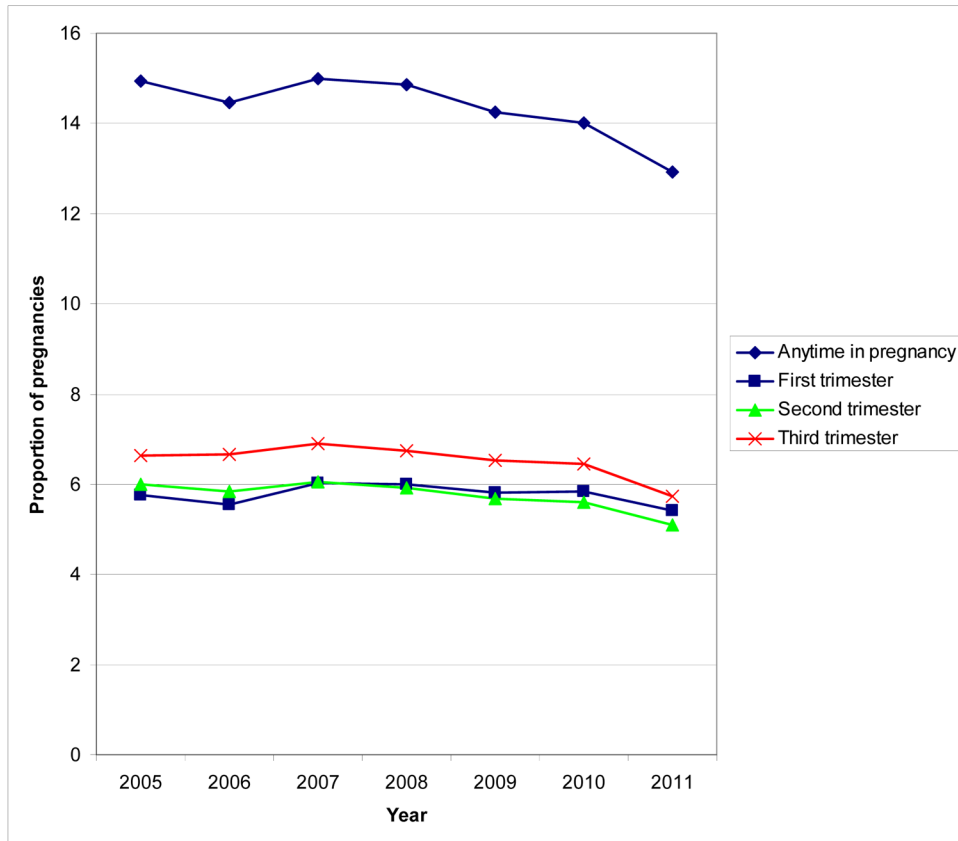


Figure 2.
Temporal Trends in Opioid Dispensing During Pregnancy (overall) and by Trimester.

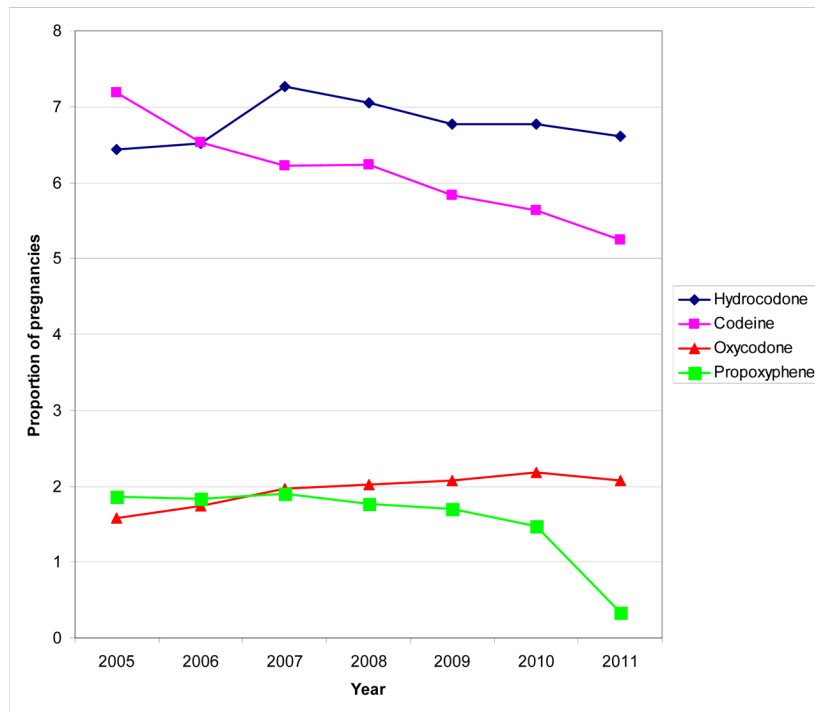


Figure 3.
Temporal Trends in Opioid Dispensing During Pregnancy For the Four Most Commonly Prescribed Types.

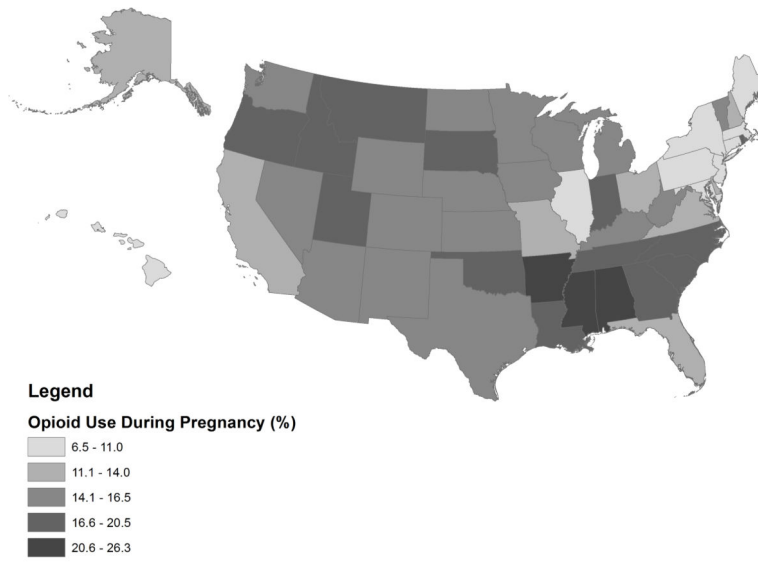


Figure 4.
Prevalence of Opioid Dispensing During Pregnancy (overall) by State.

Table 1

Prevalence of Opioid Dispensing Before and During Pregnancy

	Exposure window						
	-180 days to -91 days	-90 days to LMP	First trimester	Second trimester	Third trimester	Anytime during pregnancy	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
Any opioid	53587 (10.03)	51595 (9.65)	30566 (5.72)	30434 (5.69)	34906 (6.53)	76742 (14.36)	
Specific opioid							
Hydrocodone	30131 (5.64)	29712 (5.56)	15906 (2.98)	12879 (2.41)	15079 (2.82)	36234 (6.78)	
Codeine	10592 (2.00)	10516 (1.97)	9347 (1.75)	12972 (2.43)	13949 (2.61)	32755 (6.13)	
Oxycodone	9755 (1.83)	8509 (1.59)	3795 (0.71)	3718 (0.70)	4962 (0.93)	10402 (1.95)	
Propoxyphene	6083 (1.14)	5674 (1.06)	3014 (0.56)	2980 (0.56)	3424 (0.64)	8347 (1.56)	
Tramadol	3109 (0.58)	3306 (0.62)	1695 (0.32)	742 (0.14)	857 (0.16)	2526 (0.47)	
Meperidine	507 (0.09)	563 (0.11)	284 (0.05)	282 (0.05)	352 (0.07)	853 (0.16)	
Hydromorphone	242 (0.05)	222 (0.04)	144 (0.03)	184 (0.03)	267 (0.05)	512 (0.10)	
Morphine	197 (0.04)	190 (0.04)	149 (0.03)	148 (0.03)	186 (0.03)	299 (0.06)	
Fentanyl	174 (0.03)	177 (0.03)	162 (0.03)	138 (0.03)	143 (0.03)	249 (0.05)	
Buprenorphine	151 (0.03)	176 (0.03)	170 (0.03)	134 (0.03)	131 (0.02)	209 (0.04)	
Methadone	116 (0.02)	129 (0.02)	125 (0.02)	107 (0.02)	115 (0.02)	180 (0.03)	
Pentazocine	41 (0.01)	35 (0.01)	20 (0.00)	22 (0.00)	18 (0.00)	49 (0.01)	
Tapentadol	20 (0.00)	30 (0.01)	12 (0.00)	11 (0.00)	17 (0.00)	35 (0.01)	
Oxymorphone	26 (0.00)	24 (0)	31 (0.01)	26 (0.00)	27 (0.01)	49 (0.01)	

Abbreviations: LMP, last menstrual period

Table 2

For Opioids Dispensed During Pregnancy, the Number of Days of Exposure Overlapping with Pregnancy by Type.

	Days of exposure during pregnancy				Distinct Prescriptions	
	Mean, Std deviation	Median	25 th percentile	75 th percentile	Mean, Std deviation	
Hydrocodone	15.2 ± 36.5	5	3	10	1.9±2.8	
Codeine	7.3 ± 12.4	5	3	8	1.3±1.2	
Oxycodone	18.9 ± 46.9	4	3	9	2.0±2.9	
Propoxyphene	9.1 ± 18.6	5	3	8	1.4±1.4	
Tramadol	32 ± 52.6	10	5	30	2.3±3.6	
Meperidine	7.8 ± 14.1	5	3	7	1.3±1.3	
Hydromorphone	19.7 ± 41.5	5	3	14	1.9±2.0	
Morphine	84.2 ± 92.4	32	14	146	4.3±4.9	
Fentanyl	105.4 ± 93.2	71	30	199	4.8±5.1	
Buprenorphine	131.6 ± 98.7	116	30	235	6.5±5.3	
Methadone	118.9 ± 95.9	94	30	209	5.2±4.1	
Pentazocine	24.3 ± 47.2	7	3	22	1.8±1.8	
Tapentadol	28.7 ± 45.2	11	7	30	1.7±1.5	
Oxycodone	88.3 ± 88.2	45	29	141	4.2±3.9	

Table 3

Recorded Maternal Conditions for Stratified by Opioid Exposure During Pregnancy.

	Exposed to opioids during pregnancy (n=76,742)	>=3 dispensings of opioids during pregnancy (n=11,747)	Chronic users prior to LMP (n=5,838)	Unexposed to opioids during pregnancy (n=457,758)
	N (%)	N (%)	N (%)	N (%)
Back pain	28189 (36.7)	7160 (61.0)	3956 (67.8)	84003 (18.4)
Abdominal pain	24515 (31.9)	5025 (42.8)	2414 (41.3)	70415 (15.4)
Migraine	7817 (10.2)	2542 (21.6)	1264 (21.7)	12819 (2.8)
Joint Pain	9258 (12.1)	2712 (23.1)	1623 (27.8)	24499 (5.4)
Fibromyalgia and or pain in multiple sites	4690 (6.1)	1559 (13.3)	1038 (17.8)	12939 (2.8)
Cough	8521 (11.1)	1682 (14.3)	820 (14.0)	21585 (4.7)
Myalgia	4696 (6.1)	1560 (13.3)	1039 (17.8)	12973 (2.8)
Malignancy	1200 (1.6)	316 (2.7)	155 (2.7)	4617 (1.0)
Renal calculus	3217 (4.2)	914 (7.8)	315 (5.4)	2872 (0.6)
Rheumatoid arthritis	613 (0.8)	238 (2.0)	168 (2.9)	1622 (0.4)
Opioid dependence	422 (0.5)	335 (2.9)	280 (4.8)	185 (0.0)
Other headache syndromes	7967 (10.4)	73 (0.6)	38 (0.7)	22790 (5.0)
Opioid abuse	123 (0.2)	90 (0.8)	66 (1.1)	68 (0.0)
Sickle cell anemia	87 (0.1)	22 (0.2)	13 (0.2)	373 (0.1)
Peripheral neuropathy	66 (0.1)	40 (0.3)	27 (0.5)	71 (0.0)
Chronic pancreatitis	63 (0.1)	29 (0.2)	22 (0.4)	66 (0.0)

Abbreviations: LMP, last menstrual period