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Increasing pregnancy-related use of prescribed opioid analgesics

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Abstract

Purpose—To quantify the prevalence of prescribed opioid analgesics among pregnant women enrolled in Tennessee Medicaid from 1995 to 2009.

Methods—Retrospective cohort study of 277,555 pregnancies identified from birth and fetal death certificates, and linked to previously-validated computerized pharmacy records. Poisson regression was used to estimate trends over time, rate ratios and 95% confidence intervals.

Results—During the study period, 29% of pregnant women filled a prescription for an opioid analgesic. From 1995 to 2009, any pregnancy-related use increased 1.90-fold (95% CI = 1.83, 1.98), first trimester use increased 2.27-fold (95% CI = 2.14, 2.41), and second or third trimester use increased 2.02-fold (95% CI = 1.93, 2.12), after adjusting for maternal characteristics. Any pregnancy-related, first trimester, and second or third trimester use were each more likely among mothers who were at least 21 years old, white, non-Hispanic, prima gravid, resided in non-urban areas, enrolled in Medicaid due to disability, and who had less than a high school education.

Conclusions—Opioid analgesic use by Tennessee Medicaid-insured pregnant women increased nearly 2-fold from 1995 to 2009. Additional study is warranted in order to understand the implications of this increased use.

MeSH KEYWORDS

Opioids; Pregnancy; Prescription

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INTRODUCTION

Providers and pregnant women often face difficult choices identifying safe and effective medications to use when treating maternal conditions during pregnancy. This is particularly true for commonly used drugs such as opioids [1–15]. Existing guidelines do not recommend avoiding opioids during pregnancy [16–19], but emerging data suggest that the risks of exposure to the developing fetus may warrant reexamination of current recommendations [20–33].

Ex vivo and animal studies suggest a possibility of teratogenic effects with early fetal exposure to some opioid analgesics [20–26]. A recent case control study using birth defect registry data demonstrated that early fetal exposure to prescription opioid analgesics was associated with 1.8- to 2.7-fold increased risk for specific cardiovascular and central nervous system defects [27]. The risk of neonatal abstinence syndrome with later fetal exposure is well-documented [28–33]; evidence suggests that approximately half of all babies with later fetal opioid exposure are likely to develop some signs of neonatal abstinence syndrome. [26, 34]

Little is known about the magnitude of fetal exposure to prescription opioid analgesics [28–35]. Given the potential risks of both early and later fetal opioid exposure, it is important to quantify the magnitude of exposure to these powerful medications. Thus, we conducted a large, retrospective cohort study to describe changing use of prescription opioid analgesics by women enrolled in Tennessee's Medicaid program during pregnancy from 1995 to 2009.

METHOD

Data Sources

The study was conducted using the Tennessee Medicaid Research database which includes birth, death and fetal death certificates linked to Tennessee Medicaid administrative claims and U.S. census data. Birth, death and fetal death certificates were used to identify mothers with a live birth or fetal death in Tennessee from 1995 to 2009. The date of conception was defined in one of two ways. For those births in which the date of the last menstrual period (LMP) was recorded on the birth certificate, the date of conception was defined as the LMP date [36, 37]. For those births in which the LMP date was not recorded on the birth certificate (approximately 10%), a previously-validated method of estimating the LMP was used [36–38]. Birth and fetal death certificates were also used to define the date of delivery or fetal death and maternal age (less than 21 years vs. 21 years or more), race (white vs. black vs. other), ethnicity (non-Hispanic vs. Hispanic), education level (less than high school vs. high school or more), and number of prior pregnancies (none vs. one or more).

Tennessee Medicaid data were used to identify the reason for Medicaid enrollment (not disabled vs. disabled) and filled prescriptions for opioid analgesics. Studies among non-pregnant populations demonstrate that administrative pharmacy claims data are free of recall bias and are highly concordant with patient reported medication use [38–41], although concordance may differ for pregnant populations. Medicaid pharmacy data included information about the date a prescription was filled and the number of days of medication supply for all outpatient prescriptions paid for by the Tennessee Medicaid program. All study pregnancies were classified according to opioid analgesic use during pregnancy including prescriptions for opioid agonist medications (codeine, dihydrocodeine combinations, dezocine, fentanyl, hydrocodone combinations, hydromorphone, levorphanol, meperidine hydrochloride, meperidine promethazine, methodone hydrochloride, morphine sulfate, oxycodone combinations, oxymorphone hydrochloride, propoxyphene and propoxyphene combinations, sufentanil citrate, and tramadol hydrochloride), mixed opioid

agonist and antagonist medications (buprenorphine, butorphanol tartrate, nalbuphine hydrochloride, and pentazocine hydrochloride), opioid and barbiturate combinations (codeine butalbital, oxycodone and barbiturates), and narcotic and non-steroidal anti-inflammatory drug (non-acetylsalicylic acid) combinations (hydrocodone ibuprofen). Cough preparations were excluded by identifying combinations with cough and cold medicines and reviewing trade names. For women with evidence of first trimester opioid use, filled prescriptions for other medications and ICD codes associated with medical claims paid within 30 days before and 7 days after the first qualifying opioid prescription were classified into four mutually exclusive, hierarchical diagnoses categories (e.g., cancer, opioid abuse or dependence, non-cancer pain, or other diagnoses).

U.S. Census data were used to define residence at time of delivery as in a rural, suburban or urban standard metropolitan statistical area. Permission to perform the study was obtained from the Vanderbilt University Institutional Review Board, the State of Tennessee Health Department, and the TennCare Bureau (e.g., the Tennessee Medicaid program).

Cohort Construction

Pregnancies were included in the cohort if the date of delivery or fetal death was between January 1, 1995 and December 31, 2009, the mother was listed as a Tennessee resident on the birth certificate, and the mother was enrolled in the Tennessee Medicaid program from 30 days prior to the LMP date through the date of delivery or fetal death, allowing for gaps in enrollment less than 30 days. The final cohort included 277,555 pregnancies. The number of mothers enrolled in the cohort increased from 14,448 in 1995 to 17,434 in 2009 (Table 1), which reflects nationwide Medicaid expansions over time [42].

A fetus was considered to have first trimester exposure if the mother filled a prescription between the date of the LMP and the date of LMP plus 90 days, or if a prescription was filled in the 30 days before the LMP with at least one days' supply extending past the LMP date into the first trimester. At least 1 day of exposure was also necessary for second and third trimester exposure, with the exception that possible delivery-related prescriptions (e.g., those filled within 3 days before the date of delivery or fetal death) were excluded.

Analysis Plan

Study outcomes were any pregnancy-related exposure to an opioid analgesic, first trimester exposure to an opioid analgesic with or without exposure later in pregnancy, and second or third trimester exposure to an opioid analgesic with or without exposure in the first trimester. Poisson regression was used to estimate trends over time, adjusted rate ratios (aRR), and 95% confidence intervals (95% C.I.) adjusting for maternal covariates. Year of delivery or fetal death was defined as a categorical variable, except in analyses to test for linear trend. From the regression models, marginal prediction was used to compute rates for each calendar year, again adjusting for maternal covariates [43]. For first trimester use, Poisson regression models were also built to estimate aRR and 95% CI in 2009 compared to 1995 for the four most commonly used individual opioid medications and all other opioid medications. To account for autocorrelation due to mothers with more than one pregnancy during the study period, the robust Huber-White sandwich variance estimator was used to provide correct standard errors and confidence intervals of the estimated rate ratios [44]. To guard against the possibility that results are due to cough preparations even after the removal of individual medications that were likely to be cough preparations, a sensitivity analysis was conducted excluding all codeines and trends remained statistically significant (data not shown). Analyses are complete case analyses and were performed with R version 2.15.1 [45].

RESULTS

Cohort Description

Of the 277,555 pregnant women included in the cohort, 80,608 (29.0%) filled a prescription for an opioid analgesic with at least 1 day supply at any time during pregnancy. Early fetal exposure occurred in 40,305 (14.5%) and later fetal exposure occurred in 59,127 (21.3%) of pregnancies. The median opioid analgesic supply was 4 days in the first trimester (range = 1–91 days; IQR = 2–10) and in the second or third trimester (range 1–115 days; IQR = 2–9). Characteristics of opioid-exposed and unexposed pregnancies are shown in Table 2. In comparison to non-users, users were more likely to be 21 years of age or older, white, prima gravid, residing in a non-urban area and enrolled in Medicaid due to disability.

Changes in Opioid Analgesic Use

Figure 1 shows the adjusted prevalence of any pregnancy-related use of an opioid analgesic, first trimester use, and second or third trimester use. Linear tests for trend were significant for any pregnancy-related use ($\beta = 0.052$; 95% CI = 0.051, 0.053), first trimester use ($\beta = 0.067$; 95% CI = 0.065, 0.069), and second or third trimester use ($\beta = 0.057$; 95% CI = 0.055, 0.059).

Table 3 shows results of the multivariate regression models for any pregnancy-related, first-trimester, and second- or third-trimester opioid analgesic use. Compared to opioid use in 1995, any pregnancy-related (aRR = 1.90; 95% CI = 1.83, 1.98), first trimester (aRR = 2.27; 95% CI = 2.14, 2.41), and second or third trimester (aRR = 2.02; 95% CI = 1.93, 2.12) opioid analgesic use increased significantly by 2009 after adjusting for maternal covariates. Any pregnancy-related use, first trimester use, and second or third trimester use were each more likely among mothers who were 21 years or older, white, non-Hispanic, and prima gravid with less than a high school education who were residing in a non-urban area and enrolled in Medicaid due to disability.

First Trimester Exposures

From 1995 to 2009, the proportion of women prescribed an opioid analgesic during the first trimester with evidence of opioid abuse or dependence diagnoses increased from 0.18 to 0.63% (249.26% increase) and with evidence of non-cancer pain diagnoses increased from 53.57 to 71.73% (33.90% increase), while the proportion of women prescribed an opioid analgesic during the first trimester with evidence of a cancer diagnosis decreased from 0.63 to 0.42% (33.47% decrease) and with evidence of other diagnoses decreased from 45.61 to 27.21% (40.34% decrease).

Figure 2 shows the adjusted prevalence of first trimester opioid analgesic use by individual medication for the four most commonly used individual opioid medications (hydrocodone, codeine, oxycodone and propoxyphene) and all other opioid medications. In comparison to 1995, use in 2009 increased significantly for all other opioid medications (aRR = 17.81, 95% CI = 12.88, 24.63), oxycodone (aRR = 4.03, 95% CI = 3.17, 5.11), and hydrocodone (aRR = 3.66, 95% CI = 3.32, 4.02), and use of codeine (aRR = 0.92, 95% CI = 0.82, 1.03) and propoxyphene (aRR = 1.04, 95% CI = 0.89, 1.21) did not significantly change.

DISCUSSION

Results from this large, retrospective cohort of Tennessee Medicaid-insured pregnant women demonstrate roughly 2-fold increases in both early and later fetal exposure to opioid analgesics in the 15-year study period. Overall, more than 14% of pregnant women filled at least one prescription for an opioid analgesic with at least one days supply during the first

trimester and approximately 21% of pregnant women filled at least one prescription for an opioid analgesic with at least one days supply in the second or third trimester. Women more likely to use an opioid analgesic during pregnancy were 21 years of age or older, white, non-Hispanic and prima gravid, with less than a high school education, residing in non-urban areas, and enrolled in Medicaid due to disability. First trimester use increased dramatically among women with opioid abuse or dependence diagnoses and with non-cancer pain diagnoses. Hydrocodone, codeine and oxycodone were the three most commonly used individual opioid analgesics during the first trimester.

Existing studies of opioid analgesic use in the United States have not specifically focused on use during pregnancy. The current study reports prevalence estimates in the 14–29% range and 2-fold increases over the 15-year study time period reported that were higher than expected but generally similar to what has been reported in other cohorts of Medicaid-insured patients. For example, one existing study using administrative claims data from the Arkansas Medicaid program reported that roughly 30% of patients with non-cancer pain conditions received opioids and that opioid analgesic use increased significantly from 2000 to 2005 [14]. Prescription opioid analgesic use in commercially-insured cohorts appears to be less prevalent than it is in cohorts of Medicaid enrollees but also to have increased significantly [5, 7, 14, 46].

Results of the current study are also generally consistent with previous studies identifying socio-demographic characteristics associated with opioid analgesic use in the general population. The current study and existing research have reported increased use among older persons, whites [47–50], individuals with less than a high school education [51, 52], patients residing in different geographic areas [1, 2, 15, 53–55], and persons with disabilities [12, 56]. Future research is needed to better understand the relationship between maternal socio-demographic characteristics, prescription opioid analgesic use, and adverse neonatal and maternal health outcomes.

The use of Medicaid data in the current study limits concern about the potential for selection bias, recall bias, and differential misclassification that often plagues retrospective cohort studies. Although one-third to one-half of all births in Tennessee and across the nation are Medicaid-insured events [38, 57–59], women continuously enrolled in Medicaid throughout pregnancy are typically younger, have fewer years of education, and have higher rates of disability and racial minority representation than pregnant women more generally [57]. Classifying medication use based on records of filled prescriptions does not allow for assessment of medication adherence, though pharmacy records have been shown to be concordant with patient self-reported medication use [38–40], use of common over-the-counter analgesics such as non-steroidal anti-inflammatory drugs, or illicit activities such as obtaining opioids without a prescription or filling opioid prescriptions for non-medical purposes including the intent to distribute.

Both early and later fetal exposure to prescription opioid analgesics may be associated with risk for mothers and their babies. Possible risks of opioid analgesic exposure to babies include birth defects with early fetal exposure [20–27, 60–65] and neonatal abstinence syndrome with later fetal exposure [28–34]. Prescribing opioid analgesics to treat medical conditions during pregnancy requires balancing the benefits to the mother with the potential risks to the developing fetus. Although the FDA does not require manufacturers to include on drug labels a recommendation against prescribing opioids to women during early pregnancy or specifically warn against potential risks of pregnancy-related use in patient-oriented educational materials [16, 17, 66], better information about the benefits and risks of pregnancy-related use are needed to guide clinical care. Given the increasing magnitude of pregnancy-related opioid analgesic use reported in the current study and the infeasibility of

studying this issue via randomized clinical trials, future epidemiologic examination of potential risks associated with fetal exposure to opioid analgesics is warranted.

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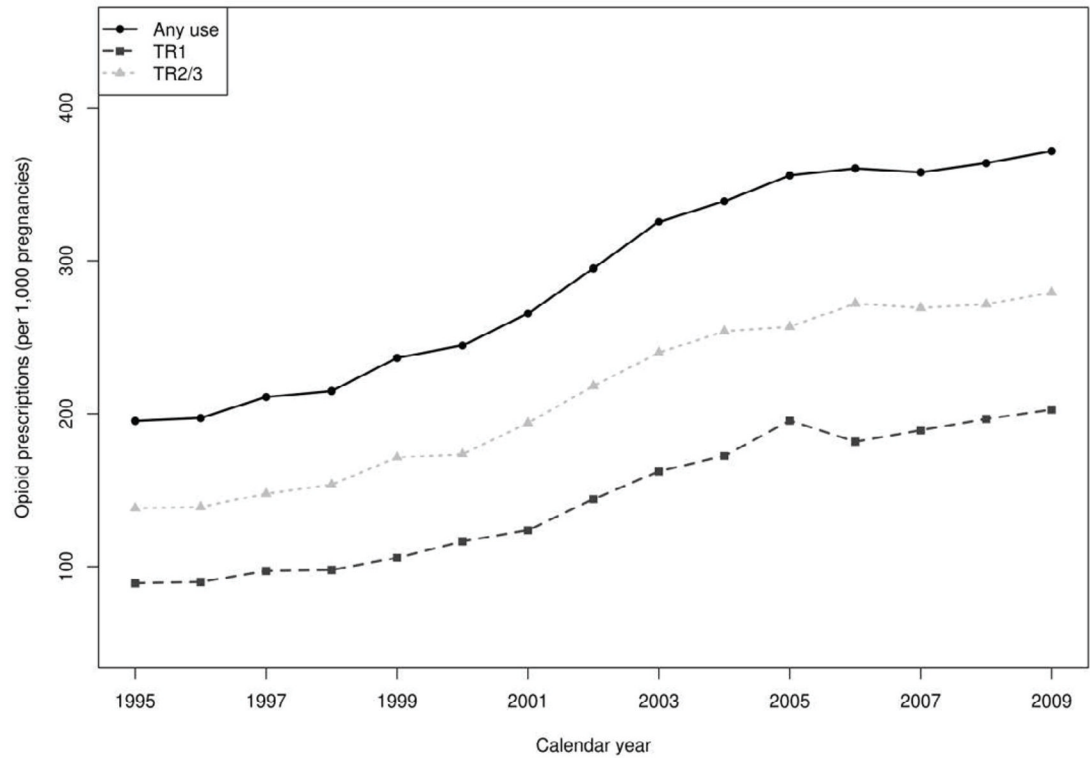
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	1995	1997	1999	2001	2003	2005	2007	2009
# preg	14448	17090	19421	20839	18308	18367	19100	17434
# any use	2751	3590	4617	5584	6002	6605	6784	6416
# TR1	1246	1651	2067	2615	3011	3645	3586	3489
# TR2/3	1942	2515	3347	4079	4424	4772	5094	4816

Figure 1. Opioid analgesic use during pregnancy: Tennessee Medicaid, 1995–2009
 TR1 = First trimester use (with or without second or third trimester use); TR2/3 = Second or third trimester use (with or without first trimester use)

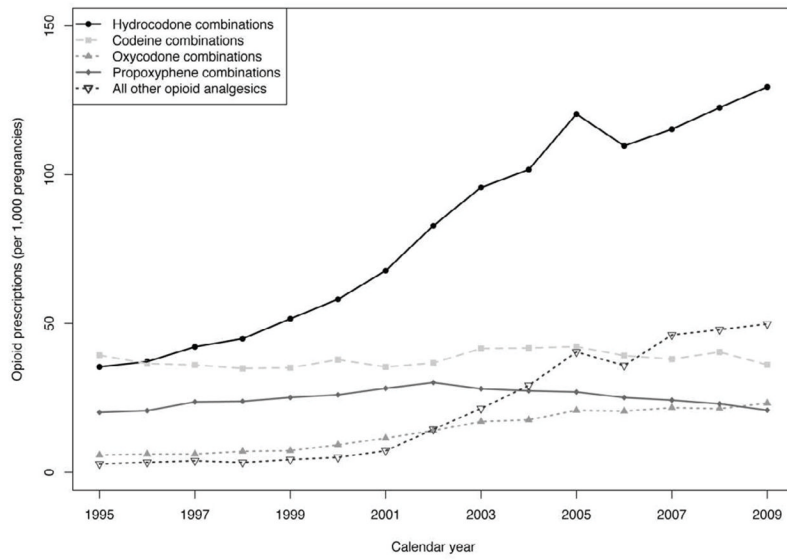


Figure 2. First trimester opioid use by individual medication: Tennessee Medicaid, 1995–2009

Table 1

Number of pregnancies and pregnancy characteristics, 1995–2009

Year	Number of pregnancies	% < 21 yrs old	% Black race	% Urban residence	% Enrolled disabled
All years	277,555	41.9	42.1	45.9	8.1
1995	14,448	45.7	47.6	52.1	8.1
1996	17,346	44.7	43.7	49.7	7.3
1997	17,090	44.1	43.7	48.6	7.6
1998	18,602	43.6	43.0	47.5	8.0
1999	19,421	42.2	41.2	46.1	7.7
2000	20,146	42.6	41.1	45.5	7.7
2001	20,839	41.3	39.8	44.7	7.4
2002	20,821	41.0	38.8	44.0	7.4
2003	18,308	41.1	39.8	43.5	8.9
2004	17,728	39.5	40.5	44.3	9.2
2005	18,367	39.1	41.1	44.3	9.0
2006	19,197	40.7	42.3	45.0	8.0
2007	19,100	41.2	43.6	45.0	8.1
2008	18,708	41.1	44.1	45.2	8.8
2009	17,434	42.2	43.9	45.3	8.5

Table 2

Characteristics of women that did and did not use any opioid analgesic during pregnancy, 1995–2009

Variable	Total Cohort (n = 277,555)	Non User (n = 196,947)	User (n = 80,608)
% Age < 21 yrs	41.9	43.9	37.1
% Black	42.1	45.8	33.2
% Hispanic	1.4	1.5	1.1
% Non prima gravid	25.0	27.1	19.9
% Urban	45.9	48.6	39.3
% Disabled	8.1	7.7	9.0

Table 3

Adjusted rate ratio (aRR) and 95% confidence interval (95% CI) for prescribing of opioid analgesics during pregnancy: Tennessee Medicaid, 1995–2009.

Variable	Any Use		First Trimester Use		Second or Third Trimester Use	
	aRR	95% CI	aRR	95% CI	aRR	95% CI
1995	1.00	Reference	1.00	Reference	1.00	Reference
2009	1.90	1.83, 1.98	2.27	2.14, 2.41	2.02	1.93, 2.12
Age less than 21 years	1.00	Reference	1.00	Reference	1.00	Reference
Age 21 years or more	1.11	1.09, 1.12	1.18	1.16, 1.21	1.13	1.11, 1.15
White race	1.00	Reference	1.00	Reference	1.00	Reference
Black	0.69	0.68, 0.70	0.61	0.59, 0.62	0.66	0.65, 0.67
Other	0.62	0.58, 0.67	0.63	0.56, 0.70	0.60	0.55, 0.66
Non-Hispanic	1.00	Reference	1.00	Reference	1.00	Reference
Hispanic	0.66	0.63, 0.70	0.63	0.58, 0.69	0.60	0.55, 0.66
Less than 12 years	1.00	Reference	1.00	Reference	1.00	Reference
12 years or more	0.95	0.93, 0.96	0.91	0.90, 0.93	0.94	0.93, 0.95
Not prima gravid	1.00	Reference	1.00	Reference	1.00	Reference
Prima gravid	1.30	1.28, 1.32	1.18	1.15, 1.22	1.08	1.06, 1.10
Urban residence	1.00	Reference	1.00	Reference	1.00	Reference
Suburban residence	1.11	1.09, 1.12	1.18	1.15, 1.22	1.08	1.06, 1.10
Rural residence	1.04	1.02, 1.05	1.12	1.09, 1.15	0.99	0.98, 1.01
Not disabled	1.00	Reference	1.00	Reference	1.00	Reference
Disabled	1.14	1.11, 1.16	1.29	1.25, 1.33	1.13	1.10, 1.16