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Maternal treatment with opioid analgesics during pregnancy and risk for preterm birth or low birth weight

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2012

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By Stacey Peters

Introduction: Opioid analgesic medications are taken for pain management; their effects on infant gestational age and birth weight, when exposed in utero, are largely unknown. The purpose of this study was to describe the prevalence of opioid analgesic treatment during pregnancy and examine the relationship between maternal treatment and differences in infant gestational age and birth weight.

Methods: The National Birth Defects Prevention Study, an ongoing population-based case-control study for 1997 to 2007, was used for the analyses. The prevalence of opioid treatment was estimated for women from three months prior to pregnancy to delivery. Crude and adjusted linear and logistic regression models were used to examine the relationship between treatment during pregnancy (for three treatment lengths) and 1) birth weight among term births, 2) gestational age, and 3) preterm birth.

Results: The prevalence of opioid treatment just before or during pregnancy was found to be 5%. Of those, 54% were treated for ≤ 7 days. Treatment for any length of time or >7 days was statistically significantly associated with a decrease in gestational age among exposed infants, ¼ of a week decrease for any treatment length and ½ a week decrease for >7 days of treatment. Treatment for any length was not statistically significantly associated with a decrease in birth weight, but there was a borderline significant increase in the risk for preterm birth (aOR (95% CI): 1.4 (1.0, 2.1)).

Conclusion: Maternal treatment with opioid analgesics during pregnancy, particularly with longer treatment duration, has a possible relationship with decreased gestational age, but the decrease is not drastic. These data are not consistent with an association between opioid treatment and low birth weight among term births.

Maternal treatment with opioid analgesics during pregnancy and risk for preterm birth or low birth weight

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Chapter I: Background/Literature Review

Introduction

Opioid analgesics are prescription medications that are used for the treatment of severe, acute and chronic pain (1). The use of these therapeutic medications, sometimes referred to as prescription narcotics, in the United States, has been steadily increasing over the past 10 years (2, 3). When used correctly and under the direction of a physician, opioid pain relievers are beneficial to those who suffer acute or chronic pain, but if misused, opioid abuse, dependency, and addiction are possible (4).

Prevalence of opioid medication use

The prevalence of prescription analgesic use during pregnancy is relatively unknown, but was estimated to occur in 7.5% of pregnancies using the National Pregnancy and Health Survey in 1992 (4, 5). A study using the National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2002 estimated that 5.3% of all women used prescription pain medications (6). A retrospective cohort study, using prospectively collected hospital data, was utilized to assess all deliveries at the Mayo Clinic from 1998 to 2009, and an increase was seen in the prevalence of long term (≥1 month) opioid use during pregnancy (7). A recent study using a Norwegian population based cohort reported that 6% of pregnant women were prescribed opioids for pain before, during, or after their pregnancy, and 99% of these women were prescribed weak and short-acting forms (8). The study also found that codeine prescriptions given to pregnant women decreased at the beginning of pregnancy and increased again after birth (8).

Types of opioid analgesics

Opioid analgesics used for pain management include: hydrocodone, codeine, tramadol, hydromorphine, morphine, meperidine, pentazocine, oxycodone, methadone, and fentanyl (1). Hydrocodone is only available in combination with other drugs (acetaminophen, ibuprofen, or aspirin) and is a short acting drug that is used for moderate to severe pain management or coughing (1). Morphine is a long acting pain reliever for moderate to severe pain that can cause central nervous system problems if used with other opioids, alcohol or illegal drugs (9). Codeine is converted to morphine in the liver and is associated with nausea and vomiting more often compared to the other opioids (1). Tramadol is considered a weak opioid, but can still be addictive and has many side effects (1). Hydromorphone has two forms, regular and extended relief. The large dose, extended relief form (12mg pill) in conjunction with alcohol has been associated with fatal outcomes and is no longer available in the United States (10). Meperidine confers a short duration of relief and is associated with severe side effects, so it is not commonly prescribed (1). Pentazocine has very severe side effects, which include hallucinations, and is rarely used (1). Oxycodone is an extended release opioid that can come in combinations with ibuprofen, acetaminophen, or aspirin. Methadone is a synthetic opioid and can cause a wide range of side effects as well as accumulate in the body, which can lead to overdose (1, 10). Fentanyl is primarily used for breakthrough cancer pain that occurs suddenly even while medicating with other pain relievers (11).

Birth outcomes: prevalence of preterm birth and low birth weight

Preterm birth and low birth weight are major public health concerns as they have a high prevalence and are associated with many other health issues during infancy. In 2008, the rate of preterm birth (completed gestation less than 37 weeks) in the United States was 12.3%, which is about 1 in every 8 births, and is an increase from 9.5% in 1981 (12, 13). Preterm birth is associated with numerous negative infant outcomes, including death, respiratory distress at birth, prolonged hospitalization, and other morbidities including developmental challenges (14-18). Prematurity is estimated to be responsible for 75% of perinatal deaths (13). The rate of low birth weight (less than 2,500g at birth) in the United States was 8.2% in 2008 (17). Infants born with a low birth weight are 25 times as likely to die in infancy as those of a normal birth weight of 2,500 grams of more (18).

Risk factors for preterm birth and low birth weight

Research on the epidemiology of preterm birth has found that there are many risk factors for spontaneous preterm birth. A recent review by Shapiro-Mendoza and colleagues concluded that moderate and late spontaneous preterm birth is associated with maternal age and race/ethnicity, multiple gestations, and birth defects (19). Numerous other maternal and pregnancy characteristics have been connected with preterm birth as well. Known maternal risk factors for preterm birth are periodontal disease, low pre-pregnancy BMI, low socioeconomic status, low educational status, single marital status, stressful work environment, short interpregnancy interval, and maternal medical diseases such as diabetes, thyroid disease, hypertension, or asthma (13). Pregnancy-related risk factors for preterm birth are previous preterm birth (spontaneous or medically indicated), multiple gestations, vaginal bleeding as a result of placental abruption or placenta previa,

low or high amounts of amniotic fluid, smoking during pregnancy, heavy alcohol consumption during pregnancy, heroin use during pregnancy, intrauterine infection, and short cervix length (<25mm) (13).

Factors associated with low birth weight include race/ethnicity, previous pregnancy outcome, short interpregnancy interval, single marital status, no prenatal care or late entry into care, low or high maternal age, multiple gestations, inadequate weight gain during pregnancy, and maternal smoking (20, 21).

Associations between opioid use and preterm birth and/or low birth weight

The risk of preterm birth and low birth weight among infants whose mothers were exposed to opioid analgesics during pregnancy is unclear. Very few studies have looked at different opioids other than methadone. A large study (exposed n= 2,666 and unexposed n= 65,316) conducted on codeine use during pregnancy showed no increased odds for low birth weight (adjusted OR (95% CI): 1.1 (0.9, 1.3) or preterm birth (adjusted OR (95% CI): 1.1 (0.9, 1.3) among the exposed (22). Animal studies have also been conducted to examine the potential association between opioid exposure and adverse offspring outcomes. A study conducted on mice and hamsters found that there was a significant, dose-response, decrease in fetal body weight for mice and hamsters exposed in utero to codeine (23). Two studies showed no difference in the mean fetal weight for rats exposed in utero to morphine or fentanyl (24, 25).

An earlier analysis of National Birth Defects Prevention Study from 1997 to 2003 found that mothers treated with opioid analgesics, for any length of time, had an increased odds of delivering preterm compared to the unexposed mothers (adjusted OR

(95% CI): 1.66 (1.03, 2.68)). In that study (only published in abstract form), there was no significant difference in birth weight when comparing the exposed to the unexposed, and treatment was associated with a 1/3 week decrease in gestational age for any length of treatment time ($p<0.05$). Longer treatment time (>7 days) was associated with an even greater decrease in gestational age ($p<0.05$). Although the results for short treatment time (<7 days) were insignificant at a 5% level, the data hinted at a potential dose-response as the length of opioid analgesic treatment length increased (26).

A similar study researching opioids and preterm birth, from the Norwegian Institute of Public Health, compared pregnant women who were not exposed to opioids to three different opioid exposure categories (women who were given at least one prescription of opioids during pregnancy, women who were given more than 17 defined daily doses while pregnant, and women who were given at least one prescription for opioids in all three trimesters) (27). The researchers found a dose-response relationship between increasing amounts of opioid exposure and preterm birth. Consistent with previous findings on the use of opioids during pregnancy, the study found that a very small proportion of pregnant women use opioids for longer periods of time; therefore, the dose-response seen in this study is likely not applicable to the majority of women who are exposed to opioids during pregnancy (8, 27).

Heroin addiction and methadone treatment

A close structural relative of opioids is the illegal drug heroin. Heroin use during pregnancy is a known risk factor for premature delivery and intrauterine growth restriction (28, 13). Methadone is a medication commonly administered to pregnant

heroin addicts because it is believed to be safer than heroin withdrawal and heroin itself, for the infant (29). The relationship between methadone treatment for addiction during pregnancy and the risk for adverse infant outcomes is unclear and often confounded by the continued use of heroin. One study found a dose-response relationship between maternal methadone use during pregnancy for opioid dependency and a decrease in gestational age, birth weight and head circumference, and an increase in length of hospital stay, compared to non-opioid dependent women (30). Another study found that women who used methadone during pregnancy had an increased risk for delivering very preterm and small for gestational age infants, compared to women who did not take methadone during pregnancy (31).

Two other studies conducted on methadone treatment for opiate addiction and infant outcomes showed improved results (better infant care post-delivery, earlier antenatal care, and decreased likelihood for preterm delivery) for the methadone treatment exposed infants compared to methadone unexposed infants/heroin exposed infants (32, 33); however, rarely are these comparisons also made to unexposed, drug-free infants. One study that used a completely unexposed control group compared methadone treatment exposed infants to untreated, heroin exposed infants and also to drug-free infants and reported that the infants of both exposure groups (methadone and heroin without methadone) were smaller at birth compared to the drug-free infants (32).

It has been suggested that methadone does not cross the placenta as easily as heroin, although infants exposed to methadone in utero have a high risk of going through neonatal withdrawal syndrome (29). Most of the methadone studies have focused on neonatal withdrawal syndrome rather than preterm birth, gestational age and/or low birth

weight. In one study, the mean birth weights of the infants exposed to methadone were not discernible from the general population of the study hospital, but the infants born addicted to methadone had a mean birth weight in the tenth percentile (34). A problem with these studies is that heroin use is a known cause of prematurity and intrauterine growth restriction; therefore, heroin could be confounding the association attributed to methadone exposure, due to continued use of heroin during pregnancy regardless of treatment, or other confounders associated with opiate use (28, 35, 36).

A study on infants born in New Zealand attempted to control for the confounding factors that are associated with opioid dependence and found that methadone exposed infants still had an increased risk for adverse outcomes, such as low birth weight, decreased gestational age, decreased length and head circumference and increased hospital stay (30). In another study, pregnant women who took methadone for pain treatment compared to pregnant women who took methadone as part of an opiate addiction maintenance program had a higher rate of prematurity and infant morbidities, but the sample size was small (19 exposed mothers and 24 control mothers) (37).

Currently, published studies regarding methadone use during pregnancy mostly focus on it as a treatment for heroin addiction, rather than as a pain medication. Not many studies focus on this use of methadone during pregnancy and its effects on the infant, compared to drug-free infants.

Current study objectives

The first objective of this study was to determine the prevalence and demographic distribution of opioid analgesic treatment (and treatment length) from three months

before pregnancy to the end of pregnancy among the control mothers in the National Birth Defects Prevention Study (NBDPS). The second objective was to examine the potential relationship between maternal treatment with opioid analgesics (for three treatment lengths) at any time during pregnancy and 1) birth weight among term births, 2) gestational age, and 3) preterm birth, among liveborn singleton infants born without any major birth defect.

Chapter II: Manuscript

Maternal treatment with opioid analgesics during pregnancy and risk for preterm birth or low birth weight

S. Peters, C. Broussard, and C. Hogue

Introduction: Opioid analgesic medications are taken for pain management; their effects on infant gestational age and birth weight, when exposed in utero, are largely unknown. The purpose of this study was to describe the prevalence of opioid analgesic treatment during pregnancy and examine the relationship between maternal treatment and differences in infant gestational age and birth weight.

Methods: The National Birth Defects Prevention Study, an ongoing population-based case-control study for 1997 to 2007, was used for the analyses. The prevalence of opioid treatment was estimated for women from three months prior to pregnancy to delivery. Crude and adjusted linear and logistic regression models were used to examine the relationship between treatment during pregnancy (for three treatment lengths) and 1) birth weight among term births, 2) gestational age, and 3) preterm birth.

Results: The prevalence of opioid treatment just before or during pregnancy was found to be 5%. Of those, 54% were treated for ≤ 7 days. Treatment for any length of time or >7 days was statistically significantly associated with a decrease in gestational age among

exposed infants, ¼ of a week decrease for any treatment length and ½ a week decrease for >7 days of treatment. Treatment for any length was not statistically significantly associated with a decrease in birth weight, but there was a borderline significant increase in the risk for preterm birth (aOR (95% CI): 1.4 (1.0, 2.1)).

Conclusion: Maternal treatment with opioid analgesics during pregnancy, particularly with longer treatment duration, has a possible relationship with decreased gestational age, but the decrease is not drastic. These data are not consistent with an association between opioid treatment and low birth weight among term births.

Introduction

Opioid analgesics are prescription medications that are used for the treatment of severe, acute and chronic pain (1). The prevalence of opioid analgesic use during pregnancy is estimated to occur in 7.5% of pregnancies, and the prevalence appears to be increasing (4, 5, 7). In the United States, the annual rate of preterm birth is 12.3%, and the annual rate of low birth weight is 8.2% (12, 17). Preterm birth and low birth weight are both associated with numerous negative infant outcomes, most significant being neonatal death (14-18).

A major issue in the current literature relating to opioid use during pregnancy is that most studies focus on methadone treatment for heroin dependence during pregnancy rather than for pain management. Only a handful of studies have been conducted on the impact of prescription opioid use, for pain management, during pregnancy on the developing fetus. A study from the Norwegian Institute of Public Health found a dose-

response relationship between preterm birth and increasing exposure to opioid analgesics during pregnancy (27). The National Birth Defects Prevention Study (NBDPS) data for the years 1997 to 2003 was previously used to examine risks for opioid treatment during pregnancy (published only in abstract form); this previous analysis found that infants exposed to maternal opioid treatment during pregnancy had an increased risk for preterm birth, a ⅓ of a week decrease in gestational age, and no significantly different change in birth weight (26).

This study adds 4 years of additional data (3563 more mother/infant pairs to the previous analysis of the NBDPS). The first objective was to determine the prevalence and demographic distribution of opioid analgesic treatment (and treatment length) from three months before pregnancy to the end of pregnancy among the control mothers. The second objective was to examine the potential relationship between maternal treatment with all opioid analgesics (for three treatment lengths) and of two specific opioid analgesics at any time during pregnancy and 1) birth weight among term births, 2) gestational age, and 3) preterm birth, among liveborn singleton infants born without any major birth defect.

Methods

Data source

NBDPS is an ongoing population-based case-control study that randomly selects infants, with and without major structural birth defects, from ten sites across the United States (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah). Data from controls (those without a major birth defect)

in the NBDPS from October 1, 1997 through December 31, 2007 were utilized. Controls without birth defects are randomly selected using birth certificates or hospital data, depending on the study site (38).

Mothers of cases and controls are mailed a packet at least six weeks after their estimated due date (EDD) with a letter that explains the NBDPS and also contains a $20 money order. Ten days after the packet is mailed, an interviewer calls the mother for the interview or sets up another time to call back. The interview lasts approximately one hour and is available in English or Spanish. The interviewers use a computer-assisted telephone interview (CATI) system. Before the interview begins, the interviewer asks for verbal consent for participation from the mother. The interview gathers information on many types of exposures (environmental, infectious, occupational, and pharmacological) for the time period of three months prior to pregnancy to the end of pregnancy. The time period for interview completion is between six weeks and 24 months after EDD, with the target interview completion time being before 6 months after EDD (38). For the current study, the participation rate among controls was 65%, and the mean time to interview for controls was 9.5 months.

For each section of the interview, all reported medications are compiled and coded using the Slone Drug Dictionary, which links the medication products to their active ingredients (licensed by NBDPS from Boston University's Slone Epidemiology Center) (39).

Inclusion/exclusion criteria

Data were obtained from the NBDPS CATI database using the NBDPS Tools Dataset Version 8. The initial total number of control subjects was 8,494 mother/infant pairs. Women who were treated with an opioid analgesic during the three months before pregnancy and throughout pregnancy were defined as exposed for the purposes of the prevalence analysis. Infants were excluded if they were not liveborn (n=9), weighed less than 500 grams at birth (n=9), or were delivered at <8 weeks or >45 completed weeks' gestation (n=4); mothers were excluded if they reported using heroin just before or during pregnancy (or either refused to answer the heroin question or were unsure about their heroin exposure) (n=5), reported having preexisting diabetes (type 1 or 2) (n=50), reported an uncertain opioid treatment duration [i.e., indicated taking opioids "as needed" and were documented as having the longest duration of exposure (360 or 270 days)] (n=2), were carrying multiples (n=232), or had missing exposure data (n=59). After exclusions 8,124 infant/mother pairs were analyzed (Figure 1).

For the pregnancy outcome analyses (examining risks for low birth weight and gestational age/preterm birth), only mothers who were exposed during pregnancy (from conception to birth) were included. The same exclusion criteria as for the descriptive analysis were applied, and one additional subject was excluded due to missing exposure data in the pregnancy time period, leaving a study population of 8,123 infant/mother pairs for these analyses (Figure 1).

Exposure and outcomes definitions

Opioid exposure was defined as oral consumption of any of the following medications for any medical reason and in any dose (codeine, fentanyl, hydrocodone,

hydromorphone, meperidine, methadone, morphine, oxycodone, pentazocine, propoxyphene or tramadol). Exposure during pregnancy was categorized into three groups: any treatment length, ≤ 7 days of treatment, and >7 days of treatment. Each treatment group was compared to non-opioid users between conception and delivery. The outcome variables for birth weight (grams) and gestational age (weeks) were analyzed as continuous variables. A dichotomous outcome variable for gestational age (preterm birth: delivery <37 or 37-44 completed weeks' gestation) was also examined.

Covariates

The potential confounders considered in the analyses were maternal race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian/Pacific Islander, Native American/Alaska Native, and other), maternal age (years), maternal education (0-8 years, 9-11 years, 12 years, 13-15 years, and 16 or more years), maternal pre-pregnancy BMI (<18.5, 18.5-24, 25-29, and 30 or more), maternal periconceptional smoking (reported smoking or not smoking), maternal periconceptional alcohol consumption (reported drinking alcohol or reported not drinking alcohol), infant gender (male or female), and total household income (<10,000 dollars/year, 10,000-50,000 dollars/year, and >50,000 dollars/year).

Statistical analysis

Univariate analyses were performed for both exposure subsets (three months before conception to delivery, and conception to delivery) to obtain the mean values and the corresponding standard deviations, as well as the unadjusted betas and 95% confidence intervals, for the following continuous variables: maternal age at delivery

(yrs), maternal height (cm), pre-pregnancy weight (kg), opioid exposure (days), gestational age (wks), and birth weight (gm). Bivariate analyses were also conducted using the categorical potential confounders, for both exposure subsets, to obtain descriptive statistics.

Multivariable linear regression was performed to compare the mean gestational ages and the mean birth weights among term births (gestational age 37-44 weeks). Logistic regression was used to obtain the crude and adjusted odds ratios and 95% confidence intervals for preterm birth for each treatment group. Interaction was assessed for, using Likelihood Ratio tests and backwards elimination, and found not to be an issue; multicollinearity was also not found. The potential confounders included in the final model were initially selected based on the exploratory analysis and assessed for final inclusion using the all possible subsets method. The final models adjusted for maternal age, maternal race, maternal education, maternal pre-pregnancy BMI, maternal smoking, maternal alcohol consumption, infant gender, and total household income. Sub-analyses were performed for the two opioid medications with the most exposures (codeine and hydrocodone). The sub-analyses consisted of the previously mentioned linear and logistic regression methods for gestational age, preterm birth and birth weight.

The reason for taking the opioid medications was not collected explicitly in the maternal interviews, but when a medication is reported, it is documented in the questionnaire section under which it was reported. These interview sections correspond with disease categories (infection, pregnancy complication prevention, procedure, and injury), which were used to get the best available information about the indication for medication treatment.

Opioid treatment during delivery only could bias the association between opioid treatment and gestational age or birth weight because the infants would only have been exposed in the last hours of pregnancy rather than during the developmental stages. In a sensitivity analysis, infants presumed to have been exposed only during delivery, were excluded. These included mothers treated for ≤7 days during the third trimester and reported their opioid use in either the procedure or pregnancy complication prevention section of the interview. The sensitivity analysis was performed by repeating each of the main analyses for any treatment length, ≤ 7 days, and >7 days of treatment.

All analyses were performed using SAS 9.3 Cary, North Carolina. The study protocol was submitted to the Emory Institutional Review Board (IRB) for review and was determined to not require IRB approval.

Results

A total of 404 control mothers were treated with opioid analgesics starting three months before pregnancy to delivery, or 5% of the study population (n=8,124). The prevalence of opioid use was lowest during the three months prior to pregnancy and the first trimester, with a treatment prevalence of approximately 1.5% during each period. The highest prevalence of use occurred during the second trimester (2.5%). In the third trimester, prevalence of opioid treatment was 1.9%. The distribution of opioid use by exposure time period can be seen in Figure 2.

The majority of exposed women were treated with codeine (37%) or hydrocodone (33%), while none of the women were exposed to pentazocine (Table 1). A small

percentage of the preterm births were exposed to the individual opioids (Table 1). About 2% of preterm infants were exposed to codeine and 2.5% were exposed to hydrocodone. No preterm infants were exposed to fentanyl, hydromorphone, methadone, pentazocine, or tramadol. A large number of women (19%) were treated with more than one opioid for the time period three months before pregnancy to delivery, most of whom were exposed to two opioid medications (n=66).

Among exposed women, 54% were treated for ≤7 days and 46% reported using opioids for >7 days (Table 2). During pregnancy, the prevalence of opioid treatment was 4% (n=327). Half of these women reported use for ≤7 days (n=165) and the other half reported opioid use for >7 days during pregnancy (n=162) (Table 3). The prevalence of treatment with more than one opioid analgesic during pregnancy was 21%. The reason for opioid treatment was widespread among the women, with 37% reporting medication use for procedures, 29% for infections, 18% for injuries, and 16% for other diseases/disorders.

The mean days of opioid exposure overall was 1.7 days. For the specific treatment groups -- any treatment length, ≤7 days, and >7 days -- the mean days of exposure were 42.1 days, 3.1 days, and 81.8 days, respectively. The mean gestational age and birth weight for the any treatment length group were 38.5 weeks gestation and 3355.0 grams. The mean gestational age and birth weight for ≤7 days treatment were slightly higher than the >7 days treatment means (38.7 weeks for ≤7 days compared to 38.3 weeks for >7 days treatment and 3368.0 grams for ≤7 days compared to 3342.0 grams for >7 days treatment) (Table 3). Women who used opioids were more likely to be White, have 12 years of education compared to women with less or more than 16 years of education, be

obese (BMI ≥30), smoke periconceptionally, drink alcohol periconceptionally, have a total household income between 10,000 dollars and 50,000 dollars, and have a male infant. Similar relationships were seen for ≤7 days of treatment and >7 days of treatment (Table 4).

Gestational age was significantly associated with any treatment length and >7 days of treatment but not with ≤7 days of treatment. Birth weight was not significantly associated with any of the three opioid treatment lengths (Table 4). Maternal height and pre-pregnancy weight were both significantly associated with opioid treatment (Table 4). The unadjusted ORs for smoking and opioid treatment were significant for all treatment lengths, but alcohol consumption was not significantly associated with opioid treatment.

Among term births, any treatment length and >7 days of treatment showed mean birth weight values that were slightly lower compared to the unexposed mean birth weight, with >7 days of treatment having the lowest mean birth weight (3418.3 grams) (Table 5). The treatment length of ≤7 days had a slightly higher mean birth weight compared to the unexposed (3450.4 grams compared to 3441.5 grams for the unexposed).

Although there appears to be a slight decrease in the mean infant birth weight associated with maternal opioid treatment, the crude and adjusted betas for each treatment group are not significantly different than the unexposed group. Even though the difference is not statistically significant, after adjusting for maternal race, age, education, smoking status, alcohol use, pre-pregnancy BMI, total household income and infant gender, there appears to be a decrease in birth weight of about 33 grams for the infants whose mothers were exposed to opioids for >7 days during pregnancy. The decrease for

women exposed to opioids for ≤7 days was much smaller (5 grams) and nonsignificant as well.

Gestational age also decreased for all three treatment duration groups (Table 5). Any opioid treatment length was associated with a ¼ of a week decrease in gestational age compared to the unexposed. This association was seen in the crude analysis as well as after controlling for confounding in the adjusted analysis, both of which were statistically significant. The women exposed for ≤7 days did not have a decrease in the gestational age at birth of their infants, but the mothers treated for >7 days had a ½ week shorter gestation. This decrease remained after controlling for confounders and was statistically significant. Even though there were significant decreases in the gestational age for any treatment length and >7 days treatment, the mean gestational ages for each group were in the full term range.

The prevalence of preterm birth among the infants exposed to any treatment length of opioid analgesics was 10.7% compared to a preterm prevalence of 7.9% for the unexposed infants. When the treatment lengths were stratified, the preterm birth prevalence for infants exposed for ≤7 days was 10.3% and 11.1% for the infants exposed for >7 days (Table 5). Women who were exposed to opioids for any length of time had an increased odds for preterm birth of about 1.4, but the increase was of borderline statistical significance with an adjusted 95% confidence interval of 1.0 to 2.1. Women exposed for ≤7 days had a smaller increased odds for preterm birth, which was not statistically significant (aOR (95% CI): 1.4 (0.8, 2.3)). The magnitude of the OR for exposure >7 days was highest at 1.5 but was also not statistically significant, with a 95% confidence interval of 0.9 to 2.5.

For the women treated with codeine, there were 13 total exposed preterm cases (6 for ≤ 7 days of treatment and 7 for >7 days). The crude associations between codeine exposure (any treatment length, ≤7 days, and >7 days) were all nonsignificant, but after controlling for confounding, >7 days treatment was significantly associated with a ½ week decrease in birth weight (Table 6). The crude and adjusted results for codeine treatment and preterm birth were all nonsignificant. Women treated with hydrocodone had a total of 13 exposed cases as well (5 for ≤ 7 days of treatment and 8 for >7 days). For gestational age, the adjusted associations between any treatment length and >7 days of treatment were both significantly associated with a decrease in gestational age (just under a ½ week decrease and about a ¾ week decrease respectively) (Table 7).

The results for preterm birth and hydrocodone treatment were borderline significant for >7 days (aOR (95% CI): any treatment: 1.7 (0.9, 3.1), ≤7 days: 1.3 (0.5, 3.3) and >7 days: 2.1 (1.0, 4.5)). The prevalence of preterm birth among the codeine treated compared to the hydrocodone treated was different. The prevalence of preterm birth in the hydrocodone treated infants was consistently higher, for all treatment lengths, than the corresponding prevalence in the codeine treated groups (12.9 vs. 9.7 for any treatment length, 10.0 vs. 8.5 for ≤7 days, and 15.7 vs. 11.1 for >7 days). The results for codeine and hydrocodone exposure individually on birth weight were nonsignificant (results not shown).

Fourteen mothers reported treatment with opioids for ≤ 7 days during the third trimester due to procedures (none reported use for pregnancy complication prevention). The results of the sensitivity analysis, without these presumed delivery-related opioid treatments, can be seen in Table 8. As expected, the increase of ~9 grams in birth weight

seen among the infants exposed for ≤7 days changed to a decrease of ~11 grams, excluding those infants. The decreases in the birth weights for the exposed infants remained statistically nonsignificant. As for gestational age and preterm birth, excluding the potential delivery-related treatments resulted in very small differences from the original numbers, but the confidence intervals shifted slightly to indicate nonsignificant changes instead of borderline significance. Only gestational age was significantly affected by opioid treatment for >7 days, showing almost ½ a week decrease in gestational age (the same without exclusion). But, as seen in the original analyses, the risk for preterm birth was not significantly increased.

Discussion

The results suggest that treatment with opioid analgesics during pregnancy may affect gestational length and put infants at higher risk for preterm birth. Fetal growth (measured as birth weight among term births), however, does not appear to be affected by therapeutic use of opioids during pregnancy. Maternal treatment with opioid analgesics during pregnancy, particularly with longer treatment duration, has a possible relationship with decreased gestational age, but the decrease is not drastic. Gestational age appears to be affected by longer durations of treatment with codeine or hydrocodone.

The current study, an update of an earlier study (published only in abstract form) conducted with NBDPS data for the years 1997 to 2003 (26) did not substantially alter the estimated prevalence of opioid treatment during pregnancy in the study population (~4%). Effect estimates for each of the three outcomes examined were consistent between

the two studies; however, the elevated odds previously found for preterm birth with maternal opioid treatment were no longer observed to be statistically significant in the larger data set, although still of borderline significance (26). The updated results verify the previous conclusions that the use of opioid analgesics during pregnancy might affect gestation, either by direct influence by the medication or the medication serving as a proxy for the underlying conditions.

A Norwegian study conducted by Handal et al., using 2004 to 2008 population-based, linked data from the Medical Birth Registry of Norway and the Norwegian Prescription Database, categorized maternal exposure to opioids during pregnancy by the number of prescriptions written and the defined daily dose dispensed during pregnancy (27). The authors found an increase in the adjusted ORs for spontaneous preterm birth that was dose dependent and statistically significant. The magnitude of the association in the Handal study was much greater than the current study (and statistically significant), but the exposure categorizations were different (Handal used ≥1 prescription dispensed throughout pregnancy, ≥17 defined daily doses of opioids during pregnancy, and ≥1 prescription or more in every trimester) compared to the current study (use of any treatment length, ≤7 days of treatment, and >7 days of treatment) (27). These differences in exposure measurement could account for the discrepancy in the actual values of the ORs and the statistical significance, but the same general pattern was seen in both studies; as the maternal exposure to opioids increased, the odds for preterm birth increased accordingly.

Population-based data from the Norwegian Mother and Child Cohort Study (1999 to 2006) was used to conduct a prospective study on the effects of codeine on pregnancy

outcomes in Norway (22). The authors found an increased risk for having a planned Caesarean delivery among the codeine exposed women, but not an increased risk for low birth weight (aOR(95% CI): 1.1 (0.9, 1.3)) or preterm birth (aOR(95% CI): 1.1 (0.9, 1.3)) after adjusting for multiple confounders. The birth weight results of this study correspond to the current analysis in that there was not a discernible difference between the birth weight of the codeine treated women and untreated, or between opioid treatment in general and the unexposed. The mean gestational age was not provided in the study, so it is unclear if there was a decrease related to codeine, as seen in the current analysis (22).

A very small retrospective case study from Canada (total n=13) that focused on the effects of opioid analgesics during pregnancy for chronic nonmalignant pain found that the mean gestational age and birth weight for the infants exposed to opioids throughout pregnancy was 37 weeks and 2,739 grams (40). The 13 live births were exposed to at least one of the following opioids: oxycodone, codeine, meperidine, fentanyl, hydromorphone, morphine, and/or methadone. Similar to the current study, the mean gestational age and birth weight were both lower but still within normal gestational age and birth weight ranges. Actual dosage information or treatment length was not collected to know how much of the medication the infants were actually exposed to in utero. Due to the nature of the study design (case study), the sample size was small and there was no control group, and no statistical tests were conducted (only mean values for gestational age, birth weight, head circumference, and body length were calculated).

A small, methadone focused retrospective study by Sharpe and Kuschel used the Pain Service at the National Women's Hospital in New Zealand to identify mothers who reported using methadone during pregnancy for pain management. For the years 1997 to

2000, 19 methadone exposed mothers were included in the study and 24 mothers who also used methadone during pregnancy as an opiate addiction maintenance therapy were selected to form a control comparison group. The authors reported that infants exposed to methadone for pain management compared to infants exposed to methadone for maintenance of opiate addiction had a higher rate of slight prematurity (delivery between 36 and 37 weeks) with a median gestational age of 36 weeks (37). These results are not directly comparable to the current study as the control group was composed of mothers exposed to methadone for opiate addiction treatment rather than using non-opioid exposed infants, and the exposed group was only exposed to methadone. That being said, the higher rate of slight prematurity among the opioid exposed infants for pain management was also seen in the current study. The prevalence of prematurity among the exposed to any treatment length was 10.7% compared to 7.9% in the opioid unexposed group.

The current study has some limitations. First, power was insufficient to look at all the opioid medications separately, except for codeine and hydrocodone. They are all in the same class of medication, but that does not mean that all the compounds will affect the fetus in the same way. Second, as the overarching study aim of the NBDPS was to collect information on birth defects some instrumental information was unavailable for consideration in the analysis, such as previous preterm birth, periodontal disease, cervical length, raised cervical-vaginal fetal fibronectin concentrations (all of which have been associated with preterm birth in other studies (13)). There is also not a way to distinguish between preterm births that occurred spontaneously or were induced. Because opioid use was collected retrospectively and by self-report, exposure misclassification and recall

bias are of some concern; however, the mothers are given a pregnancy calendar during the interview to help aid their recall of exposures and specific exposure information.

Opioid treatment during delivery only was a potential source of bias in the analysis. Information about treatments or exposures specifically during delivery was not directly ascertained in the maternal interview. For this reason, the presumed delivery-related exposures were excluded from the sensitivity analysis and not excluded from the main analyses. The sensitivity analysis results indicate that exposure during delivery and possibly delivery type (Caesarean or vaginal) should be considered in future studies because it may affect the associations.

The study also has several strengths. The study population was obtained from a large population-based study that collects detailed information on medication use before and during pregnancy. The medications are classified and linked to their active ingredients using the Slone Drug Dictionary (39). Many of the previous studies related to opioid exposure during pregnancy focus on methadone treatment for opiate addiction and neonatal withdrawal syndrome, while this study focused on therapeutic use of opioids and risk for preterm birth or low birth weight. Also, many studies only research methadone or codeine exposure, whereas this study included all opioid analgesic medication types to which study subjects were exposed. It was also possible to conduct sub-analyses with codeine and hydrocodone individually.

Understanding how medications affect the fetus can help health care providers when attempting to manage pain safely for pregnant patients and those planning or contemplating a pregnancy. Because 49% of all pregnancies in the United States are

unintended (41), determining prevalence patterns in the months preceding pregnancy is important as well, since these patterns will likely continue into early pregnancy before pregnancy is detected.

A major issue when researching the effect of a medication on a fetus is whether or not the outcome is a result of the medication itself or the underlying condition being treated with the medication. This study indicates that there might be a relationship between opioid analgesic use during pregnancy or the underlying condition on the developing fetus, specifically on gestational length. Understanding why this relationship exists may be helpful in developing new medications or when a health care provider is trying to determine how best to treat pregnant patients for pain, while taking into consideration all the risk factors.

This study indicates that there is a decrease in the gestational age of opioid exposed infants, but the decrease does not result in an increased risk for preterm birth. This indicates that the decrease in gestational age from opioid treatment during pregnancy may not be clinically significant, but other exposures or risk factors along with opioid treatment could potentially increase the risk for preterm birth. Further research is needed to determine if opioid use is in fact related to a decrease in gestational age, if the association is actually due to the underlying condition, and/or if there is interaction with other exposures that could be associated with the underlying condition or opioid use.

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Tables

Table 1. Number of mothers treated with opioid analgesic medications and the percent of exposure by preterm status for three months prior to pregnancy to delivery

Generic Name	Exposures from 1997-2007+	Preterm exposed n (%)	Non-preterm exposed n (%)
Codeine	150	14 (2.15)	136 (1.82)
Fentanyl	1	0	1 (0.01)
Hydrocodone	135	16 (2.46)	119 (1.59)
Hydromorphone	3	0	3 (0.04)
Meperidine	56	12 (1.85)	44 (0.59)
Methadone	3	0	3 (0.04)
Morphine	43	7 (1.08)	36 (0.48)
Oxycodone	62	2 (0.31)	60 (0.80)
Pentazocine	0	0	0
Propoxyphene	34	2 (0.31)	32 (0.43)
Tramadol	3	0	3 (0.04)

+Exposures for individual medications do not add to the total opioid analgesic exposed count of 404 because 75 women (19%) were treated with more than one opioid analgesic medication (2 opioids: 66, 3 opioids: 7, and 4 opioids: 2) from three months before pregnancy to delivery.

Table 2. Demographic distribution for opioid analgesic use, three months before pregnancy to delivery.

Mean (SD)	Total (n=8124)	Any Opioid Treatment (n=404)	≤ 7 days Opioid Treatment (n=220)	> 7 days Opioid Treatment (n=184)	No Opioid Treatment (n=7719)
Age at Delivery (yr)	27.5 (6.1)	27.2 (5.6)	27.5 (5.6)	26.9 (5.6)	27.5 (6.1)
Maternal Height (cm)	164.2 (7.5)	165.4 (7.2)	165.7 (7.6)	165.0 (6.8)	164.1 (7.5)
Pre-Pregnancy Weight (kg)	67.3 (16.2)	70.8 (18.2)	70.4 (18.0)	71.2 (18.6)	67.1 (16.0)
Opioid Exposure (days)	2.1 (20.5)	42.8 (81.9)	3.1 (2.1)	90.4 (103.0)	0
Gestational Age (wk)	38.7 (1.9)	38.6 (2.0)	38.8 (1.8)	38.3 (2.2)	38.7 (1.9)
Birth weight (gm)	3377.8 (522.7)	3356.8 (571.3)	3376.6 (567.8)	3333.5 (576.0)	3378.9 (520.1)
N (%)					
Maternal Race					
Non-Hispanic White	4769	309 (6.5)	168 (3.5)	140 (2.9)	4461 (93.5)
Non-Hispanic Black	908	41 (4.5)	21 (2.3)	20 (2.2)	867 (95.5)
Hispanic	1914	31 (1.6)	16 (0.8)	15 (0.8)	1883 (98.4)
Asian/Pacific Islander	238	3 (1.3)	2 (0.8)	1 (0.4)	235 (98.7)
Native American/Alaskan Native	41	3 (7.3)	2 (4.9)	1 (2.4)	38 (92.7)
Other	250	18 (7.2)	11 (4.4)	7 (2.8)	232 (92.8)
Maternal Education Level					
0-8 years	433	4 (0.9)	1 (0.2)	3 (0.7)	429 (99.1)
9-11 years	957	32 (3.3)	17 (1.8)	15 (1.6)	925 (96.7)
12 years	1958	115 (5.9)	67 (3.4)	48 (2.5)	1843 (94.1)
13-15 years	2174	134 (6.2)	58 (2.7)	76 (3.5)	2040 (93.8)
16 years or more	2505	112 (4.5)	73 (2.9)	39 (1.6)	2393 (95.5)
Maternal BMI					
Underweight (<18.5)	425	21 (4.9)	14 (3.3)	7 (1.6)	404 (95.1)
Normal Weight (18.5 - 24)	4294	195 (4.5)	106 (2.5)	89 (2.1)	4099 (95.5)
Overweight (25-29)	1768	105 (5.9)	53 (3.0)	52 (2.9)	1663 (94.1)
Obese (≥30)	1297	82 (6.3)	46 (3.5)	36 (2.8)	1215 (93.7)
Preterm Birth					
Infants born before 37 weeks	650	39 (6.0)	20 (3.1)	19 (2.9)	611 (94.0)
Term infants (37-44 weeks)	7473	365 (4.9)	201 (2.7)	165 (2.2)	7108 (95.1)
Low Birth Weight among Term Births					
Birth weight less than 2500g	119	4 (3.4)	1 (0.8)	3 (2.5)	115 (96.6)
Birth weight greater than 2500g	7355	361 (4.9)	200 (2.7)	162 (2.2)	6993 (95.1)
Smoking					
Mother reported smoking	1486	141 (9.5)	68 (4.6)	73 (4.9)	1345 (90.5)
Mother reported no smoking	6566	256 (3.9)	148 (2.3)	108 (1.6)	6310 (96.1)
Alcohol					
Mother reported drinking	2967	170 (5.7)	93 (3.1)	77 (2.6)	2797 (94.3)
Mother reported no drinking	5054	226 (4.5)	122 (2.4)	104 (2.1)	4828 (95.5)
Total Household Income					
< 10,000 dollars	1429	59 (4.1)	32 (2.2)	27 (1.9)	1370 (95.9)
10,000 to 50,000 dollars	3395	197 (5.8)	99 (2.9)	98 (2.9)	3198 (94.2)
>50,000 dollars	2539	125 (4.9)	79 (3.1)	46 (1.8)	2414 (95.1)
Infant Gender					
Male	4126	234 (5.7)	121 (2.9)	113 (2.7)	3892 (94.3)
Female	3989	170 (4.3)	99 (2.5)	71 (1.8)	3819 (95.7)

Table 3. Demographic distribution for opioid analgesic use during the pregnancy (conception to delivery)

Mean (SD)	Total (n=8123)	Any Opioid Treatment (n=327)	≤ 7 days Opioid Treatment (n=165)	> 7 days Opioid Treatment (n=162)	No Opioid Treatment (n=7796)
Age at Delivery (yr)	27.5 (6.1)	27.1 (5.6)	27.2 (5.6)	28.0 (5.6)	27.5 (6.1)
Maternal Height (cm)	164.2 (7.5)	165.7 (7.2)	166.1 (7.7)	165.2 (6.7)	164.1 (7.5)
Pre-Pregnancy Weight (kg)	67.3 (16.2)	71.4 (18.5)	71.5 (18.5)	71.4 (18.5)	67.1 (16.1)
Opioid Exposure (days)	1.7 (16.4)	42.1 (70.8)	3.1 (2.0)	81.8 (83.6)	0
Gestational Age (wk)	38.7 (1.9)	38.5 (2.0)	38.7 (1.6)	38.3 (2.3)	38.7 (1.9)
Birth weight (gm)	3377.8 (522.7)	3355.0 (576.3)	3368.0 (569.7)	2242.0 (584.2)	3378.7 (520.4)
N (%)					
Maternal Race					
Non-Hispanic White	4769	250 (5.2)	126 (2.6)	124 (2.6)	4519 (94.8)
Non-Hispanic Black	908	35 (3.9)	16 (1.8)	19 (2.1)	873 (96.8)
Hispanic	1914	26 (1.4)	14 (0.7)	12 (0.6)	1888 (98.6)
Asian/Pacific Islander	238	1 (0.4)	1 (0.4)	0 (0.0)	237 (99.6)
Native American/Alaskan Native	41	2 (4.9)	1 (2.4)	1 (2.4)	39 (95.1)
Other	250	13 (5.4)	7 (2.8)	6 (2.4)	237 (94.8)
Maternal Education Level					
0-8 years	433	3 (0.7)	1 (0.2)	2 (0.5)	430 (99.3)
9-11 years	957	25 (2.6)	11 (1.1)	14 (1.5)	932 (97.4)
12 years	1558	99 (6.4)	54 (3.5)	45 (2.9)	1459 (93.6)
13-15 years	2174	107 (4.9)	45 (2.1)	62 (2.9)	2067 (95.1)
16 years or more	2505	87 (3.5)	51 (2.0)	36 (1.4)	2418 (96.5)
Maternal BMI					
Underweight (<18.5)	425	14 (3.3)	8 (1.9)	6 (1.4)	411 (96.7)
Normal Weight (18.5 - 24)	4294	160 (3.7)	81 (1.9)	79 (1.8)	4134 (96.3)
Overweight (25-29)	1768	84 (4.8)	40 (2.3)	44 (2.5)	1684 (95.2)
Obese (≥30)	1297	68 (5.2)	35 (2.7)	33 (2.5)	1229 (94.8)
Preterm Birth					
Infants born before 37 weeks	650	35 (5.4)	17 (2.6)	18 (2.8)	615 (94.6)
Term infants (37-44 weeks)	7473	292 (3.9)	148 (2.0)	144 (1.9)	7181 (96.1)
Low Birth Weight among Term Births					
Birth weight less than 2500g	119	4 (3.4)	1 (0.8)	3 (2.5)	115 (96.6)
Birth weight greater than 2500g	7354	288 (3.9)	147 (2.0)	141 (1.9)	7066 (96.1)
Smoking					
Mother reported smoking	1486	123 (8.3)	58 (3.9)	65 (4.4)	1363 (91.7)
Mother reported no smoking	6566	198 (3.0)	104 (1.6)	94 (1.8)	6368 (97.0)
Alcohol					
Mother reported drinking	2967	134 (4.5)	66 (2.2)	68 (2.3)	2833 (95.5)
Mother reported no drinking	5054	187 (3.7)	96 (1.9)	91 (1.8)	4867 (96.3)
Total Household Income					
< 10,000 dollars	1429	49 (3.4)	23 (1.6)	26 (1.8)	1380 (96.6)
10,000 to 50,000 dollars	3395	162 (4.8)	79 (2.3)	83 (2.4)	3233 (95.2)
>50,000 dollars	2539	98 (3.9)	56 (2.2)	42 (1.7)	2441 (96.1)
Infant Gender					
Male	4126	201 (4.9)	95 (2.3)	106 (2.6)	3925 (95.1)
Female	3989	126 (3.2)	70 (1.8)	56 (1.4)	3863 (96.8)

Table 4. Unadjusted continuous and categorical covariate associations with opioid treatment (conception to delivery)

Continuous Unadjusted Associations	**F statistic for Any treatment vs. none (p-value)**	**F statistic for ≤ 7 days vs. none (p-value)**	**F statistic for >7 days vs. none (p-value)**
Age at Delivery (yr)	1.47 (0.23)	0.38 (0.54)	1.24 (0.26)
Maternal Height (cm)	13.13 (<0.01)	11.34 (<0.01)	3.24 (0.07)
Pre-Pregnancy Weight (kg)	22.28 <0.01)	11.70 (<0.01)	11.18 (<0.01)
Gestational Age (yr)	4.65 (0.03)	0.04 (0.85)	8.37 (<0.01)
Birth weight (gm)	0.64 (0.42)	0.07 (0.80)	0.79 (0.38)
Categorical Unadjusted Associations	**OR for Any treatment vs. none (95% CI)**	**OR for ≤ 7 days vs. none (95% CI)**	**OR for > 7 days vs. none (95% CI)**
Maternal Race			
Non-Hispanic White	(referent)	(referent)	(referent)
Non-Hispanic Black	0.73 (0.51, 1.04)	0.66 (0.39, 1.11)	0.79 (0.49, 1.29)
Hispanic	0.25 (0.17, 0.37)	0.27 (0.15, 0.46)	0.23 (0.13, 0.42)
Asian/Pacific Islander	0.08 (0.01, 0.55)	0.15 (0.02, 1.09)	-
Native American/Alaskan Native	0.93 (0.22, 3.86)	0.92 (0.13, 6.75)	0.93 (0.13, 6.86)
Other	0.99 (0.56, 1.76)	1.06 (0.49, 2.29)	0.92 (0.40, 2.12)
Maternal Education Level			
0-8 years	0.13 (0.04, 0.42)	0.08 (0.01, 0.58)	0.19 (0.05, 0.80)
9-11 years	0.50 (0.32, 0.79)	0.41 (0.21, 0.78)	0.62 (0.34, 1.14)
12 years	(referent)	(referent)	(referent)
13-15 years	0.97 (0.73, 1.29)	0.75 (0.50, 1.12)	1.24 (0.84, 1.83)
16 years or more	0.68 (0.50, 0.91)	0.73 (0.49, 1.07)	0.62 (0.40,0.96)
Maternal BMI			
Underweight (<18.5)	0.88 (0.51, 1.53)	0.99 (0.48, 2.07)	0.99 (0.48, 2.07)
Normal Weight (18.5 - 24)	(referent)	(referent)	(referent)
Overweight (25-29)	1.29 (0.98, 1.69)	1.21 (0.83,1.78)	1.12 (0.83, 1.78)
Obese (≥30)	1.43 (1.07, 1.91)	1.45 (0.97, 2.17)	1.45 (0.97, 2.17)
Preterm Birth			
Infants born before 37 weeks	1.4 (0.98, 2.00)	1.34 (0.81, 2.23)	1.46 (0.89, 2.40)
Term infants (37-44 weeks)	(referent)	(referent)	(referent)
Low Birth Weight among Term Births			
Birth weight less than 2500g	0.85 (0.31, 2.33)	0.42 (0.06, 3.01)	1.31 (0.41, 4.16)
Birth weight greater than 2500g	(referent)	(referent)	(referent)
Smoking			
Mother reported smoking	2.90 (2.30, 3.66)	2.61 (1.88, 3.61)	3.23 (2.34, 4.46)
Mother reported no smoking	(referent)	(referent)	(referent)
Alcohol			
Mother reported drinking	1.23 (0.98, 1.54)	1.18 (0.86, 1.62)	1.28 (0.94, 1.76)
Mother reported no drinking	(referent)	(referent)	(referent)
Total Household Income			
< 10,000 dollars	0.71 (0.51, 0.98)	0.68 (0.43, 1.09)	0.73 (0.47, 1.15)
10,000 to 50,000 dollars	(referent)	(referent)	(referent)
>50,000 dollars	0.80 (0.62, 1.04)	0.94 (0.66, 1.33)	0.67 (0.46, 0.98)
Infant Gender			
Male	1.57 (1.25, 1.97)	1.34 (0.98, 1.83)	1.86 (1.34, 2.58)
Female	(referent)	(referent)	(referent)

Table 5. Adjusted effect estimates for maternal opioid treatment and infant birth weight among term births, gestational age, and preterm birth

Gestational Age

Treatment length	Mean in unexposed (weeks)	Mean in exposed (weeks)	Crude β	Crude 95% CI	Adjusted β*	Adjusted 95% CI*
Any treatment	38.74	38.51	-0.23	-0.45, -0.02	-0.25	-0.46, -0.03
≤ 7 days	38.74	38.72	-0.03	-0.32, 0.27	-0.02	-0.31, 0.28
> 7 days	38.74	38.3	-0.44	-0.74, -0.14	-0.48	-0.79, -0.18

Preterm Birth

Treatment length	Prevalence in unexposed (%)	Prevalence in exposed (%)	Crude OR	Crude 95% CI	Adjusted OR*	Adjusted 95% CI*
Any treatment	7.9	10.7	1.40	0.98, 2.00	1.43	0.99, 2.07
≤ 7 days	7.9	10.3	1.34	0.81, 2.23	1.37	0.82, 2.29
> 7 days	7.9	11.1	1.46	0.89, 2.40	1.51	0.91, 2.50

Birth Weight among Term Births

Treatment length	Mean in unexposed (grams)	Mean in exposed (grams)	Crude β	Crude 95% CI	Adjusted β*	Adjusted 95% CI*
Any treatment	3441.52	3434.40	-7.12	-60.71, 46.48	-19.52	-73.17, 34.14
≤ 7 days	3441.52	3450.44	8.92	-65.95, 83.79	-5.32	-79.53, 68.88
> 7 days	3441.52	3418.25	-23.27	-98.29, 51.76	-33.58	-108.84, 41.69

*Adjusted for maternal age, race, education, smoking, alcohol use, BMI, total household income, and infant gender.

Table 6. Crude and adjusted effect estimates for maternal codeine treatment and gestational age, and preterm birth

Gestational Age

Treatment length	Mean in unexposed (weeks)	Mean in exposed (weeks)	Crude β	Crude 95% CI	Adjusted β*	Adjusted 95% CI*
Any treatment	38.74	38.62	-0.12	-0.45, 0.21	-0.15	-0.48, 0.19
≤ 7 days	38.74	38.89	0.15	-0.30, 0.60	0.17	-0.28, 0.61
> 7 days	38.74	38.32	-0.42	-0.90, 0.06	-0.52	-1.01, -0.03

Preterm Birth

Treatment length	Prevalence in unexposed (%)	Prevalence in exposed (%)	Crude OR	Crude 95% CI	Adjusted OR*	Adjusted 95% CI*
Any treatment	8.0	9.7	1.24	0.70, 2.21	1.29	0.72, 2.31
≤ 7 days	8.0	8.5	1.07	0.46, 2.47	1.06	0.46, 2.48
> 7 days	8.0	11.1	1.44	0.66, 3.18	1.58	0.71, 3.50

*Adjusted for maternal age, race, education, smoking, alcohol use, BMI, total household income, and infant gender.

Table 7. Crude and adjusted effect estimates for maternal hydrocodone treatment and gestational age and preterm birth

Gestational Age

Treatment length	Mean in unexposed (weeks)	Mean in exposed (weeks)	Crude β	Crude 95% CI	Adjusted β*	Adjusted 95% CI*
Any treatment	38.74	38.30	-0.44	-0.82, -0.07	-0.41	-0.79, -0.04
≤ 7 days	38.74	38.66	-0.08	-0.61, 0.45	-0.03	-0.56, 0.50
> 7 days	38.74	37.94	-0.80	-1.33, -0.27	-0.79	-1.31, -0.26

Preterm Birth

Treatment length	Prevalence in unexposed	Prevalence in exposed	Crude OR	Crude 95% CI	Adjusted OR*	Adjusted 95% CI*
Any treatment	8.0	12.9	1.71	0.95, 3.08	1.69	0.93, 3.05
≤ 7 days	8.0	10.0	1.29	0.51, 3.26	1.30	0.51, 3.30
> 7 days	8.0	15.7	2.16	1.01, 4.60	2.08	0.97, 4.47

*Adjusted for maternal age, race, education, smoking, alcohol use, BMI, total household income, and infant gender.

Table 8. Sensitivity analysis excluding presumed delivery-related exposures (treatment reported in procedure section of maternal interview, during the third trimester, for ≤7 days of treatment (n=14))

Gestational Age

Treatment length	Mean in unexposed (weeks)	Mean in exposed (weeks)	Crude β	Crude 95% CI	Adjusted β*	Adjusted 95% CI*
Any treatment	38.74	38.54	-0.20	-0.42, 0.01	-0.22	-0.44, 0.00
≤ 7 days	38.74	38.73	-0.01	-0.32, 0.29	-0.00	-0.31, 0.31
> 7 days	38.74	38.36	-0.38	-0.68, -0.08	-0.42	-0.73, -0.12

Preterm Birth

Treatment length	Prevalence in unexposed (%)	Prevalence in exposed (%)	Crude OR	Crude 95% CI	Adjusted OR*	Adjusted 95% CI*
Any treatment	7.9	10.5	1.38	0.95, 1.99	1.41	0.97, 2.06
≤ 7 days	7.9	10.5	1.38	0.81, 2.32	1.41	0.83, 2.39
> 7 days	7.9	10.6	1.38	0.83, 2.30	1.42	0.85, 2.39

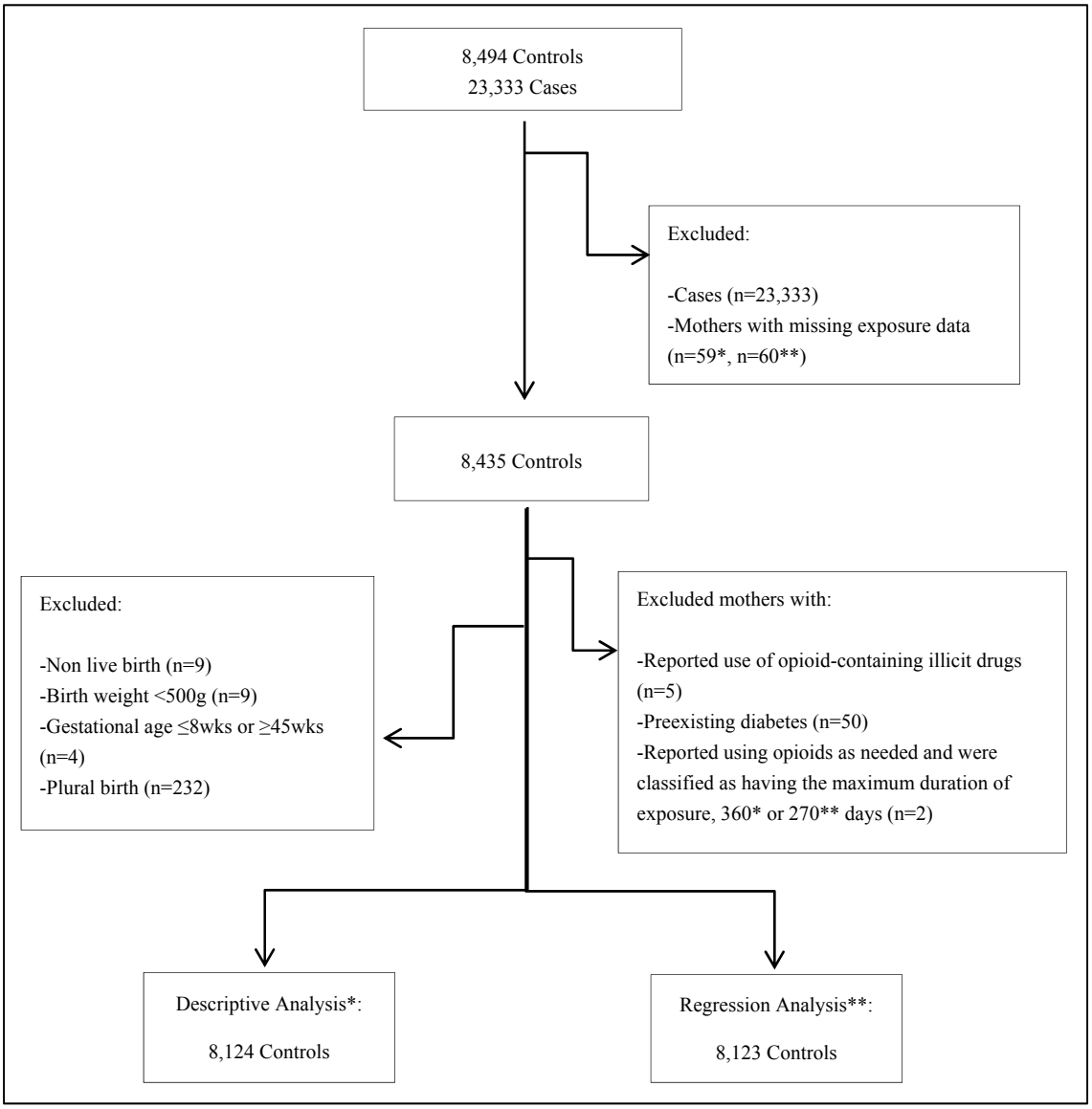
Birth Weight among Term Births

Treatment length	Mean in unexposed (grams)	Mean in exposed (grams)	Crude β	Crude 95% CI	Adjusted β*	Adjusted 95% CI*
Any treatment	3441.52	3424.19	-17.33	-71.87, 37.22	-27.92	-82.57, 26.73
≤ 7 days	3441.52	3430.57	-10.94	-88.68, 66.80	-21.70	-98.85, 55.44
> 7 days	3441.52	3418.25	-23.27	-98.29, 51.76	-33.58	-108.84, 41.69

*Adjusted for maternal age, race, education, smoking, alcohol use, BMI, total household income, and infant gender.

Figures

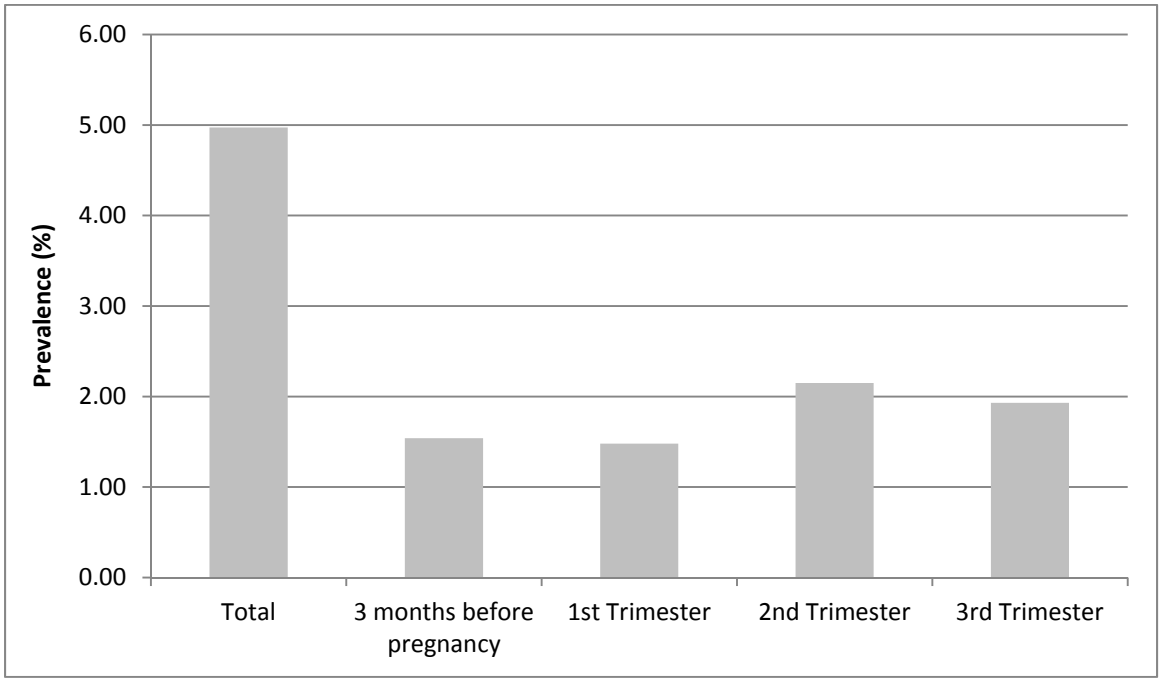
Figure 1. Flow chart of included participants for descriptive and regression analyses



*Descriptive analysis was performed for the time period of three months prior to pregnancy to delivery

**Linear and logistic regression analyses were performed for the time period of conception to delivery

Figure 2. Distribution of prevalence of opioid analgesic treatment among control mothers in the National Birth Defects Prevention Study, 1997–2007



Note. The denominator used to calculate the prevalence by trimester decreases by trimester because as the women give birth they are no longer eligible to be exposed. This affects the prevalence of exposure estimates, especially for the third trimester when most deliveries occur.

Chapter III: Summary/Public Health Implications/Possible Future Directions

Assuming that the NBDPS control mothers are representative of the 4.1 million live births that occur in the United States every year, then using the opioid exposure prevalence found in this study (5%), about 205,000 live births were exposed to an opioid analgesic(s) between three months before pregnancy and delivery (42). Furthermore, 20,000 of those exposed births would have been preterm. Although there does appear to be a small decrease in the gestational age of opioid exposed infants, for longer durations of treatment, the decrease does not confer a statistically significant increased risk for preterm birth. The mean gestational lengths for the exposed groups, although they were shorter than the unexposed mean gestational age, were still within normal gestational age values. Exposure to opioid analgesics during pregnancy does appear to either reduce gestational age itself, or possibly serves as a proxy for the underlying condition, but the decrease might not be clinically relevant. According to similar studies, opioid exposure during pregnancy does appear to be a potential risk factor for preterm birth, and further research is needed in order to deduce what the actual relationship is and the magnitude of effect.

There was only sufficient power to analyze codeine and hydrocodone separately in this study. Although hydrocodone was more prevalent and was associated with a larger decrease in gestational age compare to codeine, the total number of mothers treated with hydrocodone or codeine were small, and recommendations for which opioid is safer to take during pregnancy cannot be made. More large-scale studies that analyze all the opioids separately are needed in order to determine if one or more opioid analgesics are safer to take during pregnancy compared to others.

This study only looked into the potential relationship between opioid analgesic treatment and gestational age/preterm birth and birth weight, but there are many other concerns regarding the infant when medications are taken during pregnancy, such as birth defects. A recent study by Broussard et al. 2011 found a significant association between early pregnancy exposure to opioid analgesics and the risk for conoventricular septal defects, atrioventricular septal defects, hypoplastic left heart syndrome, spina bifida, and gastroschisis (43). The importance of understanding the full effect of exposure to opioid analgesics in utero is not limited to one or two infant outcomes; all outcomes should be considered by physicians when weighing the risks versus benefits of treating a pregnant patient for pain management.