Published in final edited form as:

Matern Child Health J. 2015 March ; 19(3): 548–556. doi:10.1007/s10995-014-1536-6.

Clinical Correlates of Prescription Opioid Analgesic Use in Pregnancy

Megan V. Smith, DrPH, MPH, Darce Costello, PhD, and Kimberly A. Yonkers, M.D.

Yale School of Medicine, Department of Psychiatry, New Haven, CT

Abstract

Objective—A 2012 committee opinion from the American College of Obstetricians and Gynecologists highlights the considerable increase in opioid addiction in recent years, yet little is known about clinical correlates of prescribed opioids among pregnant women. This study examines clinical and demographic factors associated with the use of opioid analgesics in pregnancy.

Methods—Data were derived from a prospective cohort study of pregnant women. Participants were administered the Composite International Diagnostic Interview to identify depressive and anxiety disorders and data on medication use were gathered at three assessment points and classified according to the Anatomical Therapeutic Chemical Code (ATC) classification system ATC group N02A. Participants included 2,748 English or Spanish speaking pregnant women.

Results—Six percent (n=165) of women used opioid analgesics at any point in pregnancy. More pregnant women using opioids met diagnostic criteria for major depressive disorder (16% vs. 8% for non users), generalized anxiety disorder (18% vs. 9% for non users), post-traumatic stress disorder (11% vs. 4% for non users) and panic disorder (6% vs. 4% for non users). Women who reported opioid use were also significantly more likely than non users to report using illicit drugs and almost three times as likely to report smoking cigarettes in the second or third trimester of pregnancy (4% and 23%, respectively) as compared to non-opioid users (0.5% and 8%).

Conclusion—The use of opioids in pregnancy was associated with higher levels of psychiatric comorbidity and use of other substances as compared to non-opioid users.

Introduction

The non-medical use of prescription opioids has increased dramatically over the past two decades to “epidemic” proportions with an estimated 10 million individuals (1–5, 6). Moreover, prescription opioids have been shown to surpass illicit drugs as the most commonly initiated drugs within the past year (7). Emergency department visits, admissions to substance abuse treatment facilities, and overdose deaths associated with non-medical use of prescription opioids have accompanied the growth in prescription use (7–9). Specific to

Corresponding Author: Megan Smith, 142 Temple Street, Suite #301, New Haven, CT 06510, (203) 764-8655, (203) 764-6766 (fax), megan.smith@yale.edu.

Conflict of Interest Statement: Dr. Yonkers has the following conflicts to disclose: she has received study medication from Pfizer for an NIMH trial and has received royalties from Up to Date. All other investigators do not have any conflicts of interest.

pregnant women in the United States, between 6 and 26% of women use a prescription opioid in pregnancy, with variation by state (10), although only a handful of studies have examined the topic. (10–12) Opioid concentrations in maternal blood, even in therapeutic doses, have been linked to fetal withdrawal and overdose, and risk for perinatal stroke (13–16). The impact of opiate use in pregnancy on infant outcome has been shown to last well into early childhood (17–19).

The co-occurrence of psychiatric disorders and opioid use and misuse in non-pregnant women has been well documented. Individual characteristics and psychosocial factors strongly predict prescriptions for opioid use and misuse (20–22). However, individuals with comorbid psychiatric conditions associated with opioid use and misuse are often excluded from studies of opioid use in pregnancy. The majority of studies to date have examined opioid use among pregnant women seeking treatment for substance abuse or diagnosed with a substance use disorder. To our knowledge, there has only been one study to examine the psychiatric correlates of opioid use in a general cohort of pregnant, non-substance abusing women (23). The co-morbidity of psychiatric diagnoses and opioid use in pregnant women is necessary for clinicians and maternal and child health professionals to understand in order to better design education, screening and intervention programs that may necessitate programming across multiple domains. Specific to the safety of opioids in pregnancy, researchers should aim to disentangle the effects of opioid use and psychiatric diagnoses in pregnancy that may differentially impact maternal and child health outcomes. Defining how commonly opioids are used in pregnancy, which opioids are used, and other co-occurring psychiatric disorders associated with opioid use in pregnancy are important in operationalizing research priorities in the field.

This study adds to the extant literature through an exploration of the correlates of opioid use obtained prospectively across pregnancy in a cohort of pregnant women not specifically recruited for either a substance use diagnosis or treatment. We examine rates of opioid use at any point in pregnancy and evaluate diagnostic and demographic determinants of opioid use. We hypothesized that pregnant women using prescription opioids would be more likely to meet clinical criteria for a psychiatric diagnosis and be more likely to use other licit and illicit substances in pregnancy as compared to their non-opioid using counterparts.

Materials and Methods

Study Design

The methods of this study are presented in full elsewhere (24) but are described briefly herein. Data were derived from a large prospective cohort study of pregnant women who were enrolled between March of 2005 and May of 2009 in a Northeastern city in the United States with the primary aims of examining whether a diagnosis of major depressive disorder and/or use of a psychotropic medication were associated with adverse birth outcomes. Women were recruited from 137 obstetrical practices and hospital-based clinics throughout Connecticut and Western Massachusetts via informational letters and other printed methods of advertising. For this study, women were interviewed in-person prior to 16 completed weeks gestation and re-interviewed by phone at 28 ($\pm$ 2) weeks gestation and again at 8 ($\pm$ 4) weeks postpartum.

Inclusion/Exclusion Criteria

Women were eligible to participate if they were at least 18 years of age, had not yet completed their 16th week of pregnancy and were willing to provide written informed consent. Women were ineligible if they: 1) had a known multi-fetal pregnancy, 2) suffered from insulin-dependent diabetes, 3) did not speak English or Spanish, 4) did not have access to a telephone, 5) had plans to relocate or 6) intended to terminate their pregnancy at screening.

Study Recruitment

Figure I illustrates study recruitment. An initial 9525 women volunteered to be screened, of whom 1905 (20%) met entrance criteria and screened positive for a depressive episode within the last five years and/or experienced trauma with flashbacks and/or were undergoing antidepressant treatment. An additional group of 4533 (48%) met entrance criteria and screened negative for these clinical characteristics. We invited all women who screened positive and randomly selected 1612 (36%) who screened negative to participate. Of these 3517 potential participants, we interviewed 2793. All women completed written informed consent and the study received IRB approval from a University and affiliated hospitals. Women were included in the analytic cohort if they delivered a singleton, miscarried, or underwent a voluntary termination and provided complete data for opioid use (n=2748). Most missing data were due to women being out of contact for the second interview. Opioid users were no more likely than non-opioid users to fall out of contact ($p=0.9318$).

Exposure and Outcome Measures

At each assessment point information about psychiatric symptoms was obtained through administration of the depressive disorder, generalized anxiety disorder and panic disorder modules of the WMH-CIDI, (25) (see Yonkers 2012 (24) for complete list of instrumentation). A probable diagnosis of post-traumatic stress disorder was determined through administration of the Post-Traumatic Stress Disorder Symptom Scale (26).

Women who reported medication use were asked to provide the name of the medication and ideally, to show medication bottles to the interviewer. If the bottle was unavailable, respondents were asked to view pictures of various types of pills and capsules to aid their recall. Participants were asked again at subsequent interviews about the use of recent and current medication, amount and dates of cigarette smoking, alcohol use, and illicit drug use. Illicit drugs included marijuana, cocaine, heroin, LSD, PCP, methamphetamines, or any other illegal drug endorsed by women. The Anatomical Therapeutic Chemical Code (ATC) classification system was used to classify opioid analgesics in ATC group N02A and N07BC (methadone, and buprenorphine) (23, 27). These drugs were included because they are both used for treating pain in some patients and also for opioid maintenance therapy. Utilization of opioids in pregnancy was captured by month according to four categories: (1) no use; (2) used 1–7 days in a month; (3) used 8–14 days a month; (4) used 14 or more days (but not every day) and (5) used daily. Each participant endorsing opioid use was classified as using opioids at any point in pregnancy. Reasons for all prescription and nonprescription medication use were obtained by trained interviewers at all interviews and classified according to ICD-10 codes. A physician (KAY) with a specialization in addiction medicine,

psychiatry, and obstetrics, coded all opioid use as either “due to a medical condition that may be treated with an opioid” or a “medical condition not commonly treated with an opioid” as a proxy for nonmedical recreational use of opioids. In addition, we examined non-medical opioid use defined as women who took opioids during three separate months of pregnancy vs. women who took opioids in short intervals. A full list of medical conditions endorsed by participants and coded as likely to be treated with a prescription opioid is included in supplemental Table I. Trained medical record reviewers who were masked to a woman’s psychiatric and opioid status obtained data on pregnancy outcomes.

Interviewers and Quality Control

Interviewer training on the CIDI and other instruments included a minimum of four days of didactics, review of training tapes that illustrated interview techniques and administration of the interview, completion of at least six practice interviews and a minimum of four supervised interviews before becoming eligible to conduct independent interviews. (see Yonkers et al. (28) for full description of methods) We audiotaped interviews with permission of participants and randomly selected a subset of tapes for quality control assessment.

Statistical Procedures

Opioid analgesic use versus no use of opioids at any time during pregnancy was the outcome variable of interest. Clinical predictors included psychiatric diagnosis (structured as any Axis I disorder and including major depressive disorder, post-traumatic stress disorder, generalized anxiety and panic disorders), SSRI use, any amount of substance use (smoking, illicit drugs, alcohol) during pregnancy and current or lifetime history of any medical condition likely to be treated with prescription opioids (list provided in Appendix A and determined in consultation with psychiatrist (KAY)). Alcohol use was coded as a binary variable (Y/N) defined as “heavy alcohol use” and included having four or more drinks per week or three or more drinks in one sitting.

To examine the association between opioid use in pregnancy and clinical and demographic characteristics, we fit a multivariable logistic regression model that contained variables determined a priori based on the relevant literature and included race/ethnicity, education, psychiatric disorder, SSRI use, substance use, and any medical condition likely to be treated with prescription opioids as predictors. Odds ratios and 95% confidence intervals were estimated for this model.

Results

Table I presents the means and percentages of the demographic and clinical characteristics of the analytic cohort. Mean years of education was 15.28 ($\pm$ 2.79) and the majority of mothers self-reported as white (73.81%). Of the 2,748 pregnant women included in our analytic cohort, 2,654 (96.58%) were singleton live births, 75 (2.73%) miscarriages, 12 (0.44%) abortions, and 7 (0.25%) still births.

Six percent of women in our sample ($n=165$) endorsed taking some kind of prescription opioid in pregnancy. As shown in Table II, acetaminophen with oxycodone was the most

commonly used opioid in pregnancy (39%), followed by acetaminophen with codeine (27.5%) and hydrocodone with acetaminophen (10.2%). Among the opioid users, we determined 20% (n=33) to have used a prescription opioid for a current or lifetime medical condition that may require treatment with opioids, whereas about eight percent (7.8%, n=203) of the non opioid users also had such a condition ($p<0.001$). Women who used opioids in pregnancy were more likely to have a small for gestational age birth (11.5%, n=19) as compared to women who did not report opioid use in pregnancy (7.7%, n=201) ($p=0.02$).

Associations between opioid use and demographic and clinical characteristics

The results of the logistic regression analysis are summarized in Table III. Demographic differences between opioid users and non-users did not exist when we controlled for the effects of women's clinical characteristics. However, with the exception of alcohol use and preterm birth, all of the clinical characteristics were positively associated with opioid use. The odds of opioid use during pregnancy among women reporting any Axis 1 depressive or anxiety disorder or SSRI use were nearly double the odds for women with no Axis 1 depressive or anxiety disorder or no SSRI use. Illicit drug use during the second or third trimester was significantly associated with opioid use (OR=2.88; 95% CI: 1.02–8.19; $p<.05$), but illicit drug use during the first trimester was not (OR=0.95; 95% CI: 0.52–1.75; $p=.87$). Compared with women who did not smoke cigarettes during pregnancy, women who smoked during the first trimester (OR=1.88; 95% CI: 1.07–3.32; $p<.03$) or second or third trimester (OR=2.66; 95% CI: 1.66–4.28; $p<.0001$) had greater odds of using opioids during pregnancy. The estimated odds for women who reported current or lifetime history of medical conditions that were likely to be treated with prescription opioids were nearly three times the odds for women who did not report such medical conditions (OR=2.77; 95% CI: 1.81–4.22; $p<.0001$).

Discussion

This study documents the considerable psychiatric comorbidity associated with prescription opioid use in a pregnant cohort of primarily Caucasian, educated women. Current knowledge about the psychiatric comorbidity of prescription opioid use in pregnancy is scarce, with extant research based primarily on populations of opioid maintained pregnant women (29–31), or on larger community samples and registry-based investigations which lack detailed information on psychopathology (10, 23, 32–34) or specific drug classification. (35–38) Thus, the findings presented herein are unique in their examination of prescription opioid use among a pregnant population of women with well characterized information on psychiatric comorbidity.

The prevalence of prescription opioid use in our sample (6%) agrees with the prevalence of prescription opioid use in a population of perinatal women in a large cohort of insurance beneficiaries in the third trimester of pregnancy not in treatment for substance abuse (10) and aligns with the state-level prescription prevalence in the State in which the study occurred. Our results support findings from large population-based studies that indicate short-acting codeine and hydrocodone are the most frequently prescribed opioid analgesics

in pregnancy both in Europe (23) and the United States (10, 39). Although common in medications such as prescription cough syrups and in general found to be safe for use in pregnancy (40), neonatal codeine withdrawal has been observed in infants of mothers not addicted to other substances (13). Clinical implications for our findings include the importance of obtaining a detailed history of maternal medication intake in pregnancy. Pregnant women may be under the mistaken impression that because opioids are prescribed by physicians and used to treat medical conditions they are “safer” than other illicit drugs in pregnancy (3). Mothers may not consider a prescribed cough medication to be a “drug” and thus questions which probe both prescription and illicit drugs use should be utilized.

Our proposed hypothesis was supported by our data. All psychiatric and substance use variables were associated with opioid use in pregnancy, with the exception of alcohol use. Women who met criteria for a psychiatric disorder in pregnancy, women who smoked, and women who took an SSRI in pregnancy all independently, had double the odds of using opioids in pregnancy as compared to their counterparts without a diagnosis and who did not endorse licit and illicit substance use. In pregnant populations of women on opioid maintenance treatment, rates of co-occurring disorders are high, especially for depression (35–73%) (29, 30), however, we have little extant information on comorbidity in pregnant women not in treatment for substance abuse and non-opioid maintained women.

Women who used prescription opioids in pregnancy represent a group of women with other adverse health behaviors. For example, women who continued to use illicit substances in their second or third trimester of pregnancy, a population at high risk for poor maternal and fetal outcomes, were also almost three times as likely to use a prescription opioid. This finding suggests either (1) women using illicit substances in pregnancy may also be abusing prescription opioids in pregnancy, (2) pregnant women substance abusers are more likely to have a medical condition which requires the use of a prescription opioid, for example, methadone, (3) prescription opioid use may independently predict psychopathology; or (4) psychopathology may independently predict prescription opioid use. Although our study was a secondary data analysis and was not designed to answer these questions, findings from large epidemiological cohorts of non-pregnant women indicate non-medical use of prescription medication is a risk factor for the onset of psychopathology, is a stronger risk factor than other illicit drug use, (41) and also increases reoccurrence of alcohol and substance use disorders (42). Additionally, studies that have found associations between depression and antidepressant use and birth outcomes (43, 44) may not have controlled for other prescription drug use, which we have found in this sample, can be close to 6%, and thus important to consider. Our study, which may underreport opioid use, suggests that adverse birth outcomes found among women with depressive and other psychiatric symptoms may be confounded by opioid use.

In addition to the limitations already noted, our results should be interpreted with consideration of the following. First, while accuracy of self-report for medications taken for chronic conditions (e.g., antihypertensive medications) has been reported to range from “moderate to substantial” accuracy of maternal self-report for medications taken episodically or for a short period of time (e.g., opioid analgesics) often is much lower (45). Our reliance on self-report data for medication use may add substantial bias to our findings

as we collapsed prescription opioid use into one single category in pregnancy. Although women were asked to report use over a period of 3–4 months, we did not examine use by trimester, thus women only needed to recall use of prescription medications in small time intervals. Finally, this study was not designed to examine prescription drug misuse, and thus we can only draw preliminary conclusions regarding the appropriateness of use of opioids through our proxy variable on general medical conditions. With a larger sample recruited specifically to examine prescription opioid use in pregnancy, we may have been able to sort out subtypes of nonmedical opioid users (e.g. polysubstance users and nonmedical opioid users with health-related problems) (20, 21, 46), but we are unable to draw conclusions on categories of prescription opioid use given the design of our study. In general, what constitutes prescription medication misuse is still heavily debated (47, 48).

Several guidelines on the management of opioid dependent pregnant women exist (49–51) with the most recent published by the American College of Obstetricians and Gynecologists in 2012. Critically important to these guidelines is the recommendation for obstetric providers to screen pregnant women for substance abuse as part of complete obstetric care. Based on 2007 questionnaire data from surveys with obstetrician-gynecologists in the United States, 98% of providers asked women about prescription drugs, but far fewer asked about illegal drugs or whether prescription medication was taken in a medically inappropriate manner (51%) (52). ACOG recommends all pregnant women should be routinely asked about their use of alcohol and drugs, including prescription opioids and other medications used for nonmedical reasons. The guidelines also suggest monitoring infants of women who use opioids during pregnancy for neonatal abstinence syndrome, which is characterized by hyperactivity of the central and autonomic nervous system (53). Early identification of women who abuse and more generally use prescription opioids in pregnancy may benefit maternal and infant outcomes given our findings on the link between maternal psychopathology, illicit substance use and prescription opioid use. Future research should examine the relationship between maternal psychopathology, patterns and subtypes of prescription opioid use and misuse, and course of use in the perinatal period.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

K12 DA031050 (Smith) & R01 HD045735

References Cited

1. National Center on Addiction and Substance Use. Controlled prescription drug abuse at epidemic level. *J Pain Palliat Care Pharmacother*. 2006; 20:61–4.
2. Becker W, Sullivan L, Tetrault J, Desai R, Fiellin D. Non-medical use, abuse and dependence on prescription opioids among U.S. adults: Psychiatric, medical and substance use correlates. *Drug Alcohol Depend*. 2008; 94(1–3):38–47. [PubMed: 18063321]
3. Compton W, Volkow N. Major increases in opioid analgesic abuse in the United States: concerns and strategies. *Drug Alcohol Depend*. 2006; 81:103–7. [PubMed: 16023304]

4. Compton W, Volkow N. Abuse of prescription drugs and the risk of addiction. *Drug Alcohol Depend.* 2006; 83S:S4–S7. [PubMed: 16563663]
5. Kuehn B. Opioid prescriptions soar: Increase in legitimate use as well as abuse. *JAMA.* 2007; 297(3):249–51. [PubMed: 17227967]
6. Blanco C, Alderson D, Ogburn E, Grant BF, Nunes EV, Hatzenbuehler ML, et al. Changes in the prevalence of non-medical prescription drug use and drug use disorders in the United States: 1991–1992 and 2001–2002. *Drug Alcohol Depend.* 2007; 90(2–3):252. [PubMed: 17513069]
7. SAMHSA SAaMHSA. Results from the 2007 National Survey on Drug Use and Health: National Findings. Rockville, MD: Office of Applied Studies; 2007. p. 1-290.
8. Manchikanti L, Singh A. Therapeutic opioids: a ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. *Pain physician.* 2008; 9(4):287–321. [PubMed: 17066115] 11:S63–88.
9. Hall A, Logan J, Toblin R, Kaplan J, Kraner J, Bixler D. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA.* 2008; 300(22):2613–20. [PubMed: 19066381]
10. Bateman B, Hernandez-Diaz S, Rathmell J, Seeger J, Doherty M, Fischer M, et al. Patterns of opioid utilization in pregnancy in a large cohort of commercial insurance beneficiaries in the United States. *Anesthesiology.* 2014 On line first February, 2014.
11. Andrade S, Gurtwitz J, Davis R. Prescription drug use in pregnancy. *Am J Obstet Gynecol.* 2004; 191:398–407. [PubMed: 15343213]
12. Mitchell A, Gilboa S, Werler M, Kelley K, Louik C, Hernandez-Diaz S. National Birth Defects Prevention Study: Medication use during pregnancy, with particular focus on prescription drugs: 1976–2008. *A, J Obstet Gynecol.* 2011; 205(51):e1–8.
13. Reynolds E, Riel-Romero R, Bada H. Neonatal abstinence syndrome and cerebral infarction following maternal codeine use during pregnancy. *Clin Pediatr.* 2007; 46
14. Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med.* 2010; 363(24):2320–31. [PubMed: 21142534]
15. Finnegan LP. Treatment issues for opioid-dependent women during the perinatal period. *J Psychoactive Drugs.* 1991; 23(2):191–201. [PubMed: 1765892]
16. Creanga AA. Maternal Drug Use and Its Effect on Neonates: A Population-Based Study in Washington State. *Obstet Gynecol.* 2012; 119(5):924. [PubMed: 22525903]
17. Minnes S. Prenatal tobacco, marijuana, stimulant, and opiate exposure: Outcomes and practice implications. *Addiction science & clinical practice.* 2011; 6(1):57. [PubMed: 22003423]
18. Quesada O, Gotman N, Howell HB, Funai EF, Rounsaville BJ, Yonkers KA. Prenatal hazardous substance use and adverse birth outcomes. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet.* 2012 Aug; 25(8):1222–7.
19. Stanhope T, Gill L, Rose C. Chronic Opioid Use During Pregnancy: maternal and fetal implications. *Clin Perinatol.* 2013; 40:337–50. [PubMed: 23972743]
20. Wu L, Woody G, Yang C, Blazer D. Subtypes of nonmedical opioid users: Results from the national epidemiologic survey on alcohol and related conditions. *Drug Alcohol Depend.* 2010; 112:69–80. [PubMed: 20580168]
21. Cicero T, Lynskey M, Todorov A, Inciardi J, Surratt H. Co-morbid pain and psychopathology in males and females admitted to treatment for opioid and analgesic abuse. *Pain.* 2008; 39:127–35. [PubMed: 18455314]
22. Back S, Payne R, Simpson A, Brady K. Gender and prescription opioids: Findings from the National Survey on Drug Use and Health. *Addictive Behaviors.* 2010; 35:1001–7. [PubMed: 20598809]
23. Handal M, Engeland A, Ronning M, Skurtveit S, Furu K. Use of prescribed opioid analgesics and co-medication with benzodiazepines in women before, during, and after pregnancy: a population-based cohort study. *Eur J Clin Pharmacol.* 2011; 67:953–60. [PubMed: 21484468]

24. Yonkers KA, Norwitz ER, Smith MV, Lockwood CJ, Gotman N, Luchansky E, et al. Depression and serotonin reuptake inhibitor treatment as risk factors for preterm birth. *Epidemiology*. 2012 Sep; 23(5):677–85. [PubMed: 22627901]
25. Kessler R, TBU. The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *The International Journal of Methods in Psychiatric Research* 2004. 2004; 13(2):93–121.
26. Falsetti S, Resnick H, Pesick P, Kilpatrick D. The modified PTSD symptom scale: A brief self-report measure of posttraumatic stress disorder. *Behavior Therapist*. 1993; 16:161–2.
27. WHO Collaborating Center for Drug Statistics Methodology. ATC Classification Index with DDDs 2010. 2010
28. Yonkers KANE, Smith MV, Lockwood CJ, Gotman N, Luchansky E, Lin H, Belanger K. Depression and Serotonin Reuptake Inhibitor Treatment as Risk Factors for Preterm Birth. *Epidemiology*. 2012; 23(5):677–85. [PubMed: 22627901]
29. Tuten M, Heil SH, O'Grady KE, Fitzsimons H, Chisolm MS, Jones HE. The impact of mood disorders on the delivery and neonatal outcomes of methadone-maintained pregnant patients. [Erratum appears in *Am J Drug Alcohol Abuse* 2010 Sep;36(5):304]. *American Journal of Drug & Alcohol Abuse*. 2009; 35(5):358–63. [PubMed: 20180664]
30. Lund I, Skurtveit S, Sarfi M, Bakstad B, Welle-Strand G, Ravndal E. A two-year prospective study of psychological distress among a national cohort of pregnant women in opioid maintenance treatment and their partners. *J Subst Use*. 2011:10.
31. Lund IO, Skurtveit S, Engeland A, Furu K, Ravndal E, Handal M. Prescription drug use among pregnant women in opioid Maintenance Treatment. *Addiction*. 2013 Feb; 108(2):367–76. [PubMed: 22882166]
32. Daw JR, Hanley GE, Greyson DL, Morgan SG. Prescription drug use during pregnancy in developed countries: a systematic review. *Pharmacoepidemiol Drug Saf*. 2011 Sep; 20(9):895–902. [PubMed: 21774029]
33. Donati S, Baglio G, Spinelli A, Grandolfo ME. Drug use in pregnancy among Italian women. *Eur J Clin Pharmacol*. 2000 Jul; 56(4):323–8. [PubMed: 10954347]
34. Headley J, Northstone K, Simmons H, Golding J, Team AS. Medication use during pregnancy: data from the Avon Longitudinal Study of Parents and Children. *European Journal of Clinical Pharmacology*. 2004 Jul; 60(5):355–61. [PubMed: 15168103]
35. Colvin L, Slack-Smith L, Stanley FJ, Bower C. Pharmacovigilance in pregnancy using population-based linked datasets. *Pharmacoepidemiol Drug Saf*. 2009 Mar; 18(3):211–25. [PubMed: 19173342]
36. Gagne J, Maio V, Berghella V, Louis D, Gonnella J. Prescription drug use during pregnancy: a population-based study in Regione Emilia-Romagna, Italy. *European Journal of Clinical Pharmacology*. 2008 Nov 01; 64(11):1125–32. [PubMed: 18685836]
37. Lacroix I, Hurault C, Sarramon MF, Guitard C, Berrebi A, Grau M, et al. Prescription of drugs during pregnancy: a study using EFEMERIS, the new French database. *Eur J Clin Pharmacol*. 2009 Aug; 65(8):839–46. [PubMed: 19365629]
38. Riley E, Fuentes-Afflick E, Jackson R. Correlated of prescription drug use during pregnancy. *J Womens Health*. 2005; 14:401–9.
39. Broussard CS, Rasmussen SA, Reefhuis J, Friedman JM, Jann MW, Riehle-Colarusso T, et al. Maternal treatment with opioid analgesics and risk for birth defects. *American journal of obstetrics and gynecology*. 2011; 204(4):314, e1–e11. [PubMed: 21345403]
40. Nezvalova-Henriksen K, Spigset O, Nordeng H. Effects of codeine on pregnancy outcome: results from a large population-based cohort study. *Eur J Clin Pharmacol*. 2011 Dec; 67(12):1253–61. [PubMed: 21656212]
41. Martin S, Keyes K, Storr C, Zhu H, Chilcoat H. Pathways between nonmedical opioid use/dependence and psychiatric disorders: results from the National Epidemiologic Survey on alcohol and related conditions. *Drug Alcohol Depend*. 2009; 103:16–24. [PubMed: 19414225]
42. Schepis T, Hakes J. Non-medical prescription use increases the risk for the onset and recurrence of psychopathology: results from the National Epidemiological Survey on Alcohol and Related Conditions. *Addiction*. 2011; 106:2146–55. [PubMed: 21631624]

43. Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. *Arch Gen Psychiatry*. 2010 Oct; 67(10):1012–24. [PubMed: 20921117]
44. Wisner K, Sit D, Hanusa B, Moses-Kolko E, Bogen D, Hunker D, et al. Major Depression and Antidepressant Treatment: Impact on Pregnancy and Neonatal Outcomes. *Am J Psychiatry*. 2009; 166:557–66. [PubMed: 19289451]
45. Sarangarm P, Young B, Rayburn W, Jaiswal P, Dodd M, Phelan S, et al. Agreement between self-report and prescription data in medical records for pregnant women. *Birth Defects Research (Part A)*. 2012; 94:153–61.
46. McCabe S, Boyd C, Teter C. Subtypes of nonmedical prescription drug misuse. *Drug Alcohol Depend*. 2009; 102:63–70. [PubMed: 19278795]
47. Barrett S, Meisner J, Stewart S. What constitutes prescription drug misuse? Problems and pitfalls of current conceptualizations. *Current Drug Abuse Reviews*. 2008; 1:255–62. [PubMed: 19630724]
48. Catalano R, White H, Fleming C, Haggerty K. Is nonmedical prescription opiate use a unique form or illicit drug use? *Addictive Behaviors*. 2011; 36:79–86. [PubMed: 20864261]
49. Winklbaur B, Kopf N, Ebner N, Jung E, Thau K, Fischer G. Treating pregnant women dependent on opioids is not the same as treating pregnancy and opioid dependence: a knowledge synthesis for better treatment for women and neonates. *Addiction*. 2008; 103(9):1429–40. [PubMed: 18783498]
50. American College of Obstetricians & Gynecologists. Opioid abuse, dependence, and addiction in pregnancy. 2012
51. Jones H. Treating opioid use disorders during pregnancy: historical, current, and future directions. *Substance Abuse*. 2013; 34(2):89–91. [PubMed: 23577898]
52. Morgan M, Cragan J, Goldenberg R, Rasmussen S, Schulkin J. Management of prescription and nonprescription drug use during pregnancy. *The Journal of Maternal-Fetal and Neonatal Medicine*. 2010; 23(8):813–9. [PubMed: 19883263]
53. Jansson LMV. Neonatal abstinence syndrome. *Curr Opin Pediatr*. 2012

Figure 1.
Recruitment and Selection of the Analytic Sample

Table I

Frequencies (means) and percentages¹ (standard deviations) of sample demographic and clinical characteristics

	All N=2748	No Opioid Use N=2583 (94.00)	Opioid Use N=165 (6.00)	p value
Education				
Grade School	18 (0.66)	17 (0.66)	1 (0.61)	.0484
High School	562 (20.45)	520 (20.13)	42 (25.45)	
College/Vocational	1344 (48.91)	1257 (48.66)	87 (52.73)	
Professional/Graduate	824 (29.99)	789 (30.55)	35 (21.21)	
Race/Ethnicity				.2385
White	2027 (73.76)	1897 (73.44)	130 (78.79)	
Black	209 (7.61)	196 (7.59)	13 (7.88)	
Hispanic	390 (14.19)	371 (14.36)	19 (11.52)	
Other	122 (4.44)	119 (4.61)	3 (1.82)	
Psychiatric disorders				
Major depressive disorder	224 (8.15)	198 (7.67)	26 (15.76)	.0002
Generalized anxiety disorder	261 (9.50)	231 (8.94)	30 (18.18)	<.0001
Panic disorder	101 (3.68)	92 (3.56)	9 (5.45)	.2103
Post traumatic stress disorder	132 (4.80)	113 (4.37)	19 (11.52)	<.0001
Any Axis 1 disorder	497 (18.09)	441 (17.07)	56 (33.94)	<.0001
SSRI use	302 (10.99)	264 (10.22)	38 (23.03)	<.0001
Illegal drug use ²				<.0001
None	2553(92.90)	2409 (93.26)	144 (87.27)	
First trimester only	174 (6.33)	160 (6.19)	14 (8.48)	
Second or third trimester	21 (0.76)	14 (0.54)	7 (4.24)	
Smoking				<.0001
First trimester only	180 (6.55)	163 (6.31)	17 (10.30)	
Second or third trimester	233 (8.48)	195 (7.55)	38 (23.03)	
Heavy alcohol use ³	25 (0.91)	22 (0.85)	3 (1.82)	.1867
Current or lifetime history of medical conditions that may be treated with opioids ⁴	236 (8.59)	203 (7.86)	33 (20.00)	<.0001
Pregnancy outcome				.0876
Live birth	2654 (96.58)	2490 (96.40)	164 (99.39)	
Miscarriage	75 (2.73)	75 (2.90)	0 (0.00)	
Abortion	12 (0.44)	12 (0.46)	0 (0.00)	
Still birth	7 (0.25)	6 (0.23)	1 (0.61)	
Birth outcome				
Small for gestational age	220 (8.01)	201 (7.78)	19 (11.52)	.0299
Preterm birth	317 (11.54)	298 (11.54)	19 (11.52).	.9932

¹Column percentages

²Illegal drugs included marijuana, cocaine, heroin, LSD, PCP, methamphetamines, or any other illegal drug not listed in the interview question.

³ Heavy alcohol use was defined as having four or more drinks per week or three or more drinks in one sitting.

⁴ Coded positively if the participant endorsed general medical conditions listed in Supplemental Table 1.

Table IIFrequencies (percentages) of type of opioid drug used during pregnancy (N=165) ^I

Drug	Subjects who used^I
Acetaminophen/Oxycodone	78 (39.80)
Acetaminophen/Codeine	54 (27.55)
Acetaminophen/hydroxydocone	20 (10.20)
Morphine	15 (7.65)
Methadone	12 (6.12)
Hydromorphone	7 (3.57)
Tramadol	5 (2.55)
Fentanyl	3 (1.53)
Demerol	2 (1.02)

^I Total exceeds 165 because 34 women reported using more than one drug (29 used 2 drugs; 4 used 3 drugs; 1 used 4 drugs).

Table III

Estimated odds ratios and 95% confidence intervals from a series of logistic regression models examining predictors of any opioid use during pregnancy

	Adjusted Odds Ratio	95% CI
Education		
Grade School	0.73	0.07, 7.46
High School	1.22	0.72, 2.09
College/Vocational	1.28	0.84, 1.95
Professional/Graduate	1.00	Reference
Race/Ethnicity		
Hispanic	1.00	Reference
Black	0.94	0.44, 2.01
Other	0.67	0.19, 2.37
White	1.40	0.82, 2.38
Psychiatric disorders [†]		
No Axis 1 disorder	1.00	Reference
Any Axis 1 disorder	1.83	1.27, 2.65
SSRI use [†]		
No SSRI use	1.00	Reference
SSRI use	1.92	1.28, 2.89
Illegal drug use		
No illegal drugs	1.00	Reference
Illegal drugs in trimester 1 only	0.99	0.53, 1.80
Illegal drugs in trimester 2 or 3	3.10	1.08, 8.88
Smoking [‡]		
No smoking	1.00	Reference
Smoking in trimester 1 only	1.97	1.12, 3.46
Smoking in trimester 2 or 3	2.87	1.80, 4.57
Alcohol		
No heavy alcohol use	1.00	Reference
Heavy alcohol use	1.36	0.37, 4.99
Medication [‡]		
No general medical conditions treated with opioids	1.00	Reference
Any general medical condition treated with opioids	2.76	1.80, 4.21

[†] p < 0.01

[‡] p < 0.0001