Title
Buprenorphine versus Methadone for Opioid Use Disorder in Pregnancy.

Journal
The New England journal of medicine, 387(22)

ISSN
0028-4793

Authors
Suarez, Elizabeth A
Huybrechts, Krista F
Straub, Loreen
et al.

Publication Date
2022-12-01

DOI
10.1056/nejmoa2203318

Peer reviewed

HHS Public Access

Author manuscript

N Engl J Med. Author manuscript; available in PMC 2023 June 01.

Published in final edited form as:

N Engl J Med. 2022 December 01; 387(22): 2033–2044. doi:10.1056/NEJMoa2203318.

Buprenorphine versus Methadone for Opioid Use Disorder in Pregnancy

E.A. Suarez, Ph.D., M.P.H.,
Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Massachusetts

K.F. Huybrechts, Ph.D.,
Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Massachusetts

L. Straub, M.D.,
Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Massachusetts

S. Hernández-Díaz, M.D., Dr.P.H.,
Department of Epidemiology, Harvard T.H. Chan School of Public Health, Massachusetts

H.E. Jones, Ph.D.,
UNC Horizons and the Department of Obstetrics and Gynecology, University of North Carolina at Chapel Hill, Chapel Hill, Providence, RI

H.S. Connery, M.D., Ph.D.,
Department of Psychiatry, Harvard Medical School, Massachusetts; Division of Alcohol, Drugs, and Addiction, McLean Hospital, Belmont, Massachusetts

J.M. Davis, M.D.,
Department of Pediatrics, Tufts Medical Center and the Tufts Clinical and Translational Science Institute, Boston, Massachusetts

K.J. Gray, M.D., Ph.D.,
Division of Maternal–Fetal Medicine, Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Massachusetts

B. Lester, Ph.D.,
Center for the Study of Children at Risk, Departments of Psychiatry and Pediatrics, Warren Alpert Medical School of Brown University, and Women and Infants Hospital, Providence, RI

M. Terplan, M.D., M.P.H.,
Friends Research Institute, Baltimore

Dr. Suarez can be contacted at h4p@bwh.harvard.edu or at the Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School, 1620 Tremont St., Boston, MA 02120.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Seanna Vine for assistance in preparing the data for this analysis.

The authors' full names, academic degrees, and affiliations are listed in the Appendix.

H. Mogun, M.S.,
Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Massachusetts

B.T. Bateman, M.D.
Department of Anesthesiology, Perioperative, and Pain Medicine, Stanford University School of Medicine, Stanford, CA

Abstract

BACKGROUND—Opioid agonist therapy is strongly recommended for pregnant persons with opioid use disorder. Buprenorphine may be associated with more favorable neonatal and maternal outcomes than methadone, but existing data are limited.

METHODS—We conducted a cohort study involving pregnant persons who were enrolled in public insurance programs in the United States during the period from 2000 through 2018 in which we examined outcomes among those who received buprenorphine as compared with those who received methadone. Exposure to the two medications was assessed in early pregnancy (through gestational week 19), late pregnancy (gestational week 20 through the day before delivery), and the 30 days before delivery. Risk ratios for neonatal and maternal outcomes were adjusted for confounders with the use of propensity-score overlap weights.

RESULTS—The data source for the study consisted of 2,548,372 pregnancies that ended in live births. In early pregnancy, 10,704 pregnant persons were exposed to buprenorphine and 4387 to methadone. In late pregnancy, 11,272 were exposed to buprenorphine and 5056 to methadone (9976 and 4597, respectively, in the 30 days before delivery). Neonatal abstinence syndrome occurred in 52.0% of the infants who were exposed to buprenorphine in the 30 days before delivery as compared with 69.2% of those exposed to methadone (adjusted relative risk, 0.73; 95% confidence interval [CI], 0.71 to 0.75). Preterm birth occurred in 14.4% of infants exposed to buprenorphine in early pregnancy and in 24.9% of those exposed to methadone (adjusted relative risk, 0.58; 95% CI, 0.53 to 0.62); small size for gestational age in 12.1% and 15.3%, respectively (adjusted relative risk, 0.72; 95% CI, 0.66 to 0.80); and low birth weight in 8.3% and 14.9% (adjusted relative risk, 0.56; 95% CI, 0.50 to 0.63). Delivery by cesarean section occurred in 33.6% of pregnant persons exposed to buprenorphine in early pregnancy and 33.1% of those exposed to methadone (adjusted relative risk, 1.02; 95% CI, 0.97 to 1.08), and severe maternal complications developed in 3.3% and 3.5%, respectively (adjusted relative risk, 0.91; 95% CI, 0.74 to 1.13). Results of exposure in late pregnancy were consistent with results of exposure in early pregnancy.

CONCLUSIONS—The use of buprenorphine in pregnancy was associated with a lower risk of adverse neonatal outcomes than methadone use; however, the risk of adverse maternal outcomes was similar among persons who received buprenorphine and those who received methadone. (Funded by the National Institute on Drug Abuse.)

THE PREVALENCE OF OPIOID USE DISORder among pregnant persons has increased steadily in the United States since 2000.[1-3] As of 2017, approximately 8.2 per 1000 deliveries were estimated to be affected by opioid use disorder nationwide, with a particular burden in the population that was insured by Medicaid, in which an estimated 14.6 per 1000 deliveries

were affected.[2] The standard care for treating pregnant persons with opioid use disorder is opioid agonist therapy with buprenorphine or methadone,[4,5] which is associated with improved adherence to prenatal care, lower incidence of preterm birth, reduced return to opioid use, and fewer instances of opioid overdose and death from opioid overdose.[6,7] Buprenorphine and methadone have important differences.[8] Methadone is a full agonist with high intrinsic activity at mu-opioid receptors, whereas buprenorphine is a high-affinity partial agonist with low intrinsic activity. Methadone is administered during daily in-person visits to federally regulated opioid treatment programs. Buprenorphine can be prescribed by approved providers, which allows patients to administer the medication themselves.

The randomized, controlled Maternal Opioid Treatment: Human Experimental Research (MOTHER) trial showed that infants who were exposed to buprenorphine in utero received less morphine for treatment of neonatal abstinence syndrome,[9] received treatment and were hospitalized for less time,[9] and had significantly fewer signs of neonatal abstinence syndrome than infants exposed to methadone.[10,11] However, the MOTHER trial was subject to differential loss to follow-up; treatment was discontinued by a higher percentage of participants in the buprenorphine group (33%) than in the methadone group (18%).[9] This difference could have resulted in a lower percentage of persons with severe opioid use disorder in the buprenorphine group, leading to better outcomes in that group. Some observational studies and randomized trials also suggested a lower prevalence of preterm birth and greater birth weight among infants who were exposed to buprenorphine than among those who were exposed to methadone,[12-14] but these studies were generally small, limited to a single center, or were not fully controlled for potential confounders.[12,15,16]

Data on maternal outcomes are even more limited. In the MOTHER trial, cesarean sections comprised a smaller proportion of all deliveries among pregnant persons who had received buprenorphine than among those who had received methadone, but the differences were not significant.[9] Observational studies have also shown a lower proportion of deliveries by cesarean section among patients who received buprenorphine than among those who received methadone, but those studies were not adjusted for potential confounders.[11,17-20] The goal of the current study was to assess the risks of adverse neonatal and maternal outcomes associated with the use of buprenorphine as compared with methadone in pregnancy in a large U.S. cohort in which there was careful control for confounders.

METHODS

DATA SOURCE AND STUDY COHORT

We defined a pregnancy cohort nested in nationwide Medicaid data (2000 through 2018) that included beneficiaries from 47 states and Washington, D.C. The process for developing the cohort that linked pregnancies to infants has been described previously,[21] and additional details are provided in Table S1 and the text in the Supplementary Appendix (available with the full text of this article at NEJM.org). Medicaid data include the demographic characteristics of the patients; diagnoses and procedures received during inpatient, outpatient, or emergency department visits; and prescription medications dispensed to outpatients. Pregnancies resulting in live births to persons 12 to 55 years of age who had Medicaid coverage from 3 months before the date of the last menstrual period to

1 month after delivery were eligible for inclusion in the study. Infants who had Medicaid coverage through 3 months after delivery (or until death, if death occurred before 3 months of age) were eligible for inclusion. Most pregnant persons with opioid use disorder in the United States are insured by Medicaid[1,3]; therefore, our study cohort is highly representative of this population (Table S2).

EXPOSURE

Buprenorphine exposure was assessed with the use of records of medication dispensing for buprenorphine monotherapy (restricted to formulations approved for opioid agonist therapy; i.e., films or sublingual tablets) or buprenorphine–naloxone combination therapy. Methadone exposure was defined as receipt of the medication according to Healthcare Common Procedure Coding System codes S0109 and H0020 for methadone administration.

For the analysis of neonatal abstinence syndrome, exposure was defined as having occurred in the 30 days before delivery. For the analyses of all other outcomes, exposure was defined as having occurred in early pregnancy (from the last menstrual period through gestational week 19) or late pregnancy (gestational week 20 through the day before delivery). For the analysis of preterm birth, exposure during late pregnancy was assessed through 36 weeks. Pregnancies in which the person was receiving one of the medications and received a dispensing of or code for the comparator medication from 90 days before the last menstrual period through the end of the exposure window were excluded (Fig. S1).

OUTCOMES

Neonatal outcomes included neonatal abstinence syndrome, preterm birth, small size for gestational age, and low birth weight and were defined with the use of validated algorithms with high positive predictive values (Table S3). Maternal outcomes included cesarean section and severe maternal complications, which was defined as a composite of potentially life-threatening conditions caused or aggravated by pregnancy (Table S3). All the outcomes were ascertained at delivery or in the 30 days afterward.

COVARIATES

We considered a broad range of potential confounders, including markers of a history of opioid use disorder and severity (e.g., opioid-related emergency department and inpatient visits and treatment with opioid agonists before pregnancy), nonopioid substance use or dependence, medical conditions associated with opioid use disorder (e.g., hepatitis C, hepatitis B, sexually transmitted diseases, and human immunodeficiency virus infection), mental health conditions, chronic coexisting conditions, other medication use, health care utilization metrics (e.g., number of visits, number of distinct medications, score on the Adequacy of Prenatal Care Utilization Index[22]), proxies for social issues (including homelessness and domestic violence as documented with diagnosis codes), and demographic characteristics of the pregnant persons. County-level indicators of education, poverty, and unemployment were used as proxies for socioeconomic status. Covariates and assessment periods are summarized in Table S4.

STATISTICAL ANALYSIS

Baseline covariates were compared between the exposure groups with the use of standardized mean differences (a difference of <10% was considered to be balanced). Propensity scores for each exposure window were calculated with the use of logistic regression, with exposure to buprenorphine as the dependent variable and with all the covariates as independent predictors.[23] In addition, we used a high-dimensional propensity-score algorithm to empirically select variables from all available diagnosis codes, procedure codes, and medication dispensings, with the goal of capturing confounders beyond the prespecified list.[24] All the prespecified covariates were forced into the high-dimensional propensity-score model, and 200 additional covariates were included on the basis of the strength of their relationship to the exposure status.

Overlap weights were calculated. This method upweighted persons in the overlapping portion of the propensity-score distribution by assigning each person a weight reflective of the propensity to receive the alternative treatment and created perfect balance between the exposure groups with regard to all the covariates included in the propensity score.[25] Crude and adjusted risk ratios for buprenorphine as compared with methadone were estimated with the use of log-binomial regression, and two-sided 95% confidence intervals were calculated with the use of a robust variance estimator to account for weighting. Absolute risk differences were estimated with the use of weighted binomial regression. No adjustment was made for multiple testing, so the widths of the confidence intervals should not be used in place of hypothesis testing.

Multiple sensitivity analyses were conducted to test the robustness of the findings. Exposure misclassification is possible for buprenorphine because we had records of dispensings, not of consumption, whereas methadone was administered under supervision in a clinic. To address this potential misclassification, buprenorphine exposure was redefined as two or more dispensings during the exposure window on the assumption that if the medication was refilled, it was probably taken as prescribed.

We did not require a diagnosis code for opioid use disorder in order for a person to be included in the study population because we limited exposure to formulations and procedure codes that were indicated only for opioid agonist therapy. To test the robustness of the underlying assumption that all the patients treated with these formulations had opioid use disorder, the cohort was restricted to pregnant persons with a diagnosis code for opioid use disorder from 90 days before the last menstrual period to 1 day before delivery.

Buprenorphine and methadone treatment were not covered by Medicaid in all states or for all years of our study period. This factor could have introduced confounding if the risk of the outcomes varied between states or changed over time. Therefore, we identified the start of Medicaid coverage for buprenorphine and methadone treatment in each state[26] and limited the analysis to pregnancies in which the date of the last menstrual period occurred when both medications were covered by Medicaid.

Persons who received buprenorphine may have received more comprehensive care in an office-based care setting than persons who received methadone in an opioid treatment

program,[16,27] which could have resulted in the underdiagnosis of health conditions in persons who received methadone; therefore, we performed an analysis in each group that included only pregnant persons who received the highest level of prenatal care according to the Adequacy of Prenatal Care Utilization Index (which measures the adequacy of the timing of initiation of prenatal care and number of received prenatal care visits).[22] Pregnant persons who received timely prenatal care were assumed to have similar quality of care across all health care domains and therefore to be less susceptible to residual confounding. Finally, in order to quantify potential bias owing to unmeasured confounding and outcome misclassification, we conducted an E-value assessment[28] and quantitative bias analyses.[29]

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION

Among 2,548,372 pregnancies that ended in live births, we identified 10,704 pregnant persons who had been exposed to buprenorphine in early pregnancy and 4387 who had been exposed to methadone (Fig. 1). The relative sizes of the groups were similar in late pregnancy (11,272 persons who had been exposed to buprenorphine and 5056 to methadone). Among the pregnant persons who had exposure in early pregnancy, 85% of those who had received buprenorphine and 89% who had received methadone had exposure to the same medication in late pregnancy (Table S5), reflecting a high degree of treatment persistence during pregnancy. Most of the pregnant persons who had exposure in late pregnancy had evidence of exposure in the 30 days before delivery (9976 persons in the buprenorphine group and 4597 in the methadone group).

Pregnant persons who received buprenorphine were more likely to be White than those who received methadone, and they were more likely to be from the Northeast or Midwest and to live in nonmetropolitan or rural areas. Characteristics of the persons in the study population are shown in Table 1 and Tables S6 through S8. Persons in the buprenorphine group were more likely than those in the methadone group to have received diagnoses of depression and anxiety and have documented nonopioid substance use disorders. The use of antidepressants and other psychotropic medication was also more common among persons who received buprenorphine than among those who received methadone. In contrast, the use of prescription opioid agents was more common in the methadone group. The groups were similar with regard to the prevalence of coexisting conditions, the quality of prenatal care, and most complications of opioid use disorders that occurred. When measured covariates were analyzed according to the different exposure windows (i.e., early pregnancy, late pregnancy, and the 30 days before delivery), findings in the study populations were similar.

OUTCOMES

Neonatal abstinence syndrome occurred in 69% of the infants exposed to methadone as compared with 52% of those exposed to buprenorphine in the 30 days before delivery (adjusted relative risk, 0.73; 95% confidence interval [CI], 0.71 to 0.75) (Table 2 and Fig. 2); corresponding risk differences are shown in Table S9. An inverse association was also observed between buprenorphine exposure (as compared with methadone exposure) and preterm birth regardless of whether exposure occurred in early or late pregnancy in both

the unadjusted and adjusted analyses (adjusted relative risk in early pregnancy, 0.58 [95% CI, 0.53 to 0.62]; in late pregnancy, 0.57 [95% CI, 0.53 to 0.62]). Inverse associations were also observed between buprenorphine exposure (as compared with methadone exposure) and small size for gestational age (adjusted relative risk in early pregnancy, 0.72 [95% CI, 0.66 to 0.80]; in late pregnancy, 0.75 [95% CI, 0.69 to 0.82]) and low birth weight (adjusted relative risk in early pregnancy, 0.56 [95% CI, 0.50 to 0.63]; in late pregnancy, 0.56 [95% CI, 0.50 to 0.62]). Risks of adverse maternal outcomes (cesarean section and severe maternal complications) were similar among persons who received buprenorphine and those who received methadone (Table 2 and Fig. 2). Analyses that used high-dimensional propensity scores resulted in similar estimates for all neonatal and maternal outcomes; however, confidence intervals were wider.

Results were largely unchanged across sensitivity analyses (Fig. 3 and Table S10). Restricting analyses to pregnancies in which there was the highest level of prenatal care slightly attenuated the associations for all neonatal outcomes except neonatal abstinence syndrome. The E-value assessment and bias analyses for outcome misclassification suggested that the results were robust to potential biases (Tables S11 and S12).

DISCUSSION

In this cohort study that drew from a large database of Medicaid beneficiaries, we observed strong inverse associations between buprenorphine use in pregnancy (as compared with methadone use) and neonatal abstinence syndrome, preterm birth, small size for gestational age, and low birth weight. Adjustment for an extensive list of measured confounders did not meaningfully change the estimates. No association was found between the use of buprenorphine or methadone and cesarean section and severe maternal complications. Sensitivity analyses that targeted exposure and outcome misclassification as well as unmeasured confounding did not change the interpretation of the findings.

Previous studies have suggested that buprenorphine may be associated with more favorable neonatal outcomes than methadone, but estimates were imprecise or potentially confounded.[9,12-16] The relatively small sample size in the MOTHER trial (58 persons in the buprenorphine group and 73 in the methadone group) did not permit definitive conclusions with regard to some of the primary and secondary outcomes. For example, the trial showed 30% lower odds of pharmacologic treatment for neonatal abstinence syndrome among infants exposed to buprenorphine (47% for buprenorphine vs. 57% for methadone)[9] but with very wide confidence intervals (odds ratio, 0.7; 99% CI, 0.2 to 1.8). We found a similar point estimate for the lower risk of neonatal abstinence syndrome with exposure to buprenorphine than with methadone, but our large sample size resulted in narrow confidence intervals around this estimate (adjusted relative risk, 0.73; 95% CI, 0.71 to 0.75). Similarly, in the MOTHER trial, between-group differences in birth weight and in the risk of preterm birth favored buprenorphine (birth weight was on average 215 g greater with buprenorphine, and the odds ratio for preterm birth was 0.3 [99.7% CI, 0.1 to 2.0]), but differences were not significant. We found marked reductions in the risk of preterm delivery, small size for gestational age, and low birth weight associated with exposure to buprenorphine as compared with methadone after adjustment for numerous potential confounders.

Our results support the findings of the MOTHER trial that buprenorphine exposure in utero results in more favorable outcomes for neonates than methadone exposure.[9] Although the biologic mechanism for these observed differences remains uncertain,[9] differences in the pharmacologic mechanism of action between buprenorphine (partial agonist) and methadone (full agonist) may support the plausibility of these findings.

It has been suggested that the observation of more favorable outcomes among infants exposed to buprenorphine may be explained by the use of buprenorphine in pregnant persons with less severe opioid use disorder and fewer complications.[4,15,16,30] However, results of our study do not support this possibility. Pregnant persons who received buprenorphine had more documented mental health conditions and more dispensings of nearly all medications except opioids; in addition, proxies for the severity of opioid use disorder suggest similar severity in the two groups (Table 1). Adjustment for an extensive list of measured potential confounders and use of a high-dimensional propensity-score algorithm to capture proxies for confounders did not materially affect the results. Moreover, the lack of an association between buprenorphine use (as compared with methadone use) and maternal outcomes also suggests that confounding by health status and opioid use disorder severity is an unlikely explanation for the benefits observed in infants who were exposed to buprenorphine.

It has also been hypothesized that persons who receive buprenorphine may receive higher quality care and thus have more accurate documentation of health conditions than those who receive methadone.[16,27] When the population in our study was restricted to persons who were assumed to have received high-quality care, potentially inverse associations remained the same or were only slightly attenuated, which suggests that differential capture of health conditions is unlikely to explain our findings.

Our study has some limitations. Outcomes that were defined with the use of health care utilization data may be subject to nondifferential misclassification. Bias analyses reassuringly indicated that correction for such misclassification would result in even stronger associations and would not change the interpretation of the results. Residual confounding is possible, given the lack of information on lifestyle and behavioral factors. The E-value assessment suggested that any such confounder would need to be associated with exposure and the outcomes by a relative risk of greater than 2 to explain the results. Our cohort was restricted to live births to enable linkage of pregnancies to infants and assessment of neonatal outcomes. However, it is unlikely that our results for preterm birth, low birth weight, and small size for gestational age are explained by selection bias related to this restriction. Although there is limited evidence that methadone use may be associated with a greater risk of still-birth than buprenorphine use,[13,31] this association would result in an underestimation of the protective association for buprenorphine.

Inclusion in the analysis cohort required that payment for opioid agonist therapy was made through a state Medicaid program, which is affected by state coverage policies, variable acceptance of Medicaid,[32] and funding through alternative mechanisms. Limiting the study population to states that covered both therapies and to the years in which both therapies were covered did not change the results.

We also do not expect that potential unobserved opioid agonist therapy resulted in exposure misclassification that could have had a meaningful effect on the results. Our data suggest that switching therapy during pregnancy was uncommon; furthermore, switching would have been expected to be from buprenorphine to methadone, given the treatment guidelines for pregnant persons.[532] If pregnant persons who had been classified as exposed to buprenorphine were also exposed to methadone, we would expect this factor to result in bias toward the null. Finally, we were unable to compare dose amounts of buprenorphine and methadone or adjustment of doses of the medications because dose information for methadone was not available in our data.

Any opioid agonist therapy is recommended over untreated opioid use disorder during pregnancy, because untreated persons have greater incidence of adverse outcomes owing to withdrawal, return to opioid use, overdose, intravenous drug use, and inadequacy of prenatal care.[6] Results of our study using a large, national database of Medicaid beneficiaries showed that buprenorphine treatment for opioid use disorder during pregnancy was associated with more favorable neonatal outcomes than methadone treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported by a grant (R01DA049822) from the National Institute on Drug Abuse.

APPENDIX

The authors' full names and academic degrees are as follows: Elizabeth A. Suarez, Ph.D., M.P.H., Krista F. Huybrechts, Ph.D., Loreen Straub, M.D., Sonia Hernández-Díaz, M.D., Dr.P.H., Hendrée E. Jones, Ph.D., Hilary S. Connery, M.D., Ph.D., Jonathan M. Davis, M.D., Kathryn J. Gray, M.D., Ph.D., Barry Lester, Ph.D., Mishka Terplan, M.D., M.P.H., Helen Mogun, M.S., and Brian T. Bateman, M.D.

The authors' affiliations are as follows: the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine (E.A.S., K.F.H., L.S., H.M.), and the Division of Maternal–Fetal Medicine, Department of Obstetrics and Gynecology (K.J.G.), Brigham and Women's Hospital, the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine (E.A.S., K.F.H., L.S., H.M.), and the Department of Psychiatry (H.S.C.), Harvard Medical School, the Department of Epidemiology, Harvard T.H. Chan School of Public Health (S.H.-D.), and the Department of Pediatrics, Tufts Medical Center and the Tufts Clinical and Translational Science Institute (J.M.D.), Boston, and the Division of Alcohol, Drugs, and Addiction, McLean Hospital, Belmont (H.S.C.) — all in Massachusetts; UNC Horizons and the Department of Obstetrics and Gynecology, University of North Carolina at Chapel Hill, Chapel Hill (H.E.J.); the Center for the Study of Children at Risk, Departments of Psychiatry and Pediatrics, Warren Alpert Medical School of Brown University, and Women and Infants Hospital — both in Providence, RI (B.L.); Friends Research Institute, Baltimore (M.T.); and the Department of Anesthesiology,

Perioperative, and Pain Medicine, Stanford University School of Medicine, Stanford, CA (B.T.B.).

REFERENCES

1. Hirai AH, Ko JY, Owens PL, Stocks C, Patrick SW. Neonatal abstinence syndrome and maternal opioid-related diagnoses in the US, 2010–2017. JAMA 2021;325:146–55. [PubMed: 33433576]
2. Haight SC, Ko JY, Tong VT, Bohm MK, Callaghan WM. Opioid use disorder documented at delivery hospitalization — United States, 1999–2014. MMWR Morb Mortal Wkly Rep 2018;67:845–9. [PubMed: 30091969]
3. Maeda A, Bateman BT, Clancy CR, Creanga AA, Leffert LR. Opioid abuse and dependence during pregnancy: temporal trends and obstetrical outcomes. Anesthesiology 2014;121:1158–65. [PubMed: 25405293]
4. Committee opinion no. 711: opioid use and opioid use disorder in pregnancy. Obstet Gynecol 2017;130(2):e81–e94. [PubMed: 28742676]
5. ACOG Committee on Obstetric Practice; American Society of Addiction Medicine. ACOG committee opinion no. 711: opioid use and opioid use disorder in pregnancy. 2012 (https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2017/08/opioid-use-and-opioid-use-disorder-in-pregnancy).
6. Jones HE, Martin PR, Heil SH, et al. Treatment of opioid-dependent pregnant women: clinical and research issues. J Subst Abuse Treat 2008;35:245–59. [PubMed: 18248941]
7. 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;103:1429–40. [PubMed: 18783498]
8. Jones HE, Heil SH, Baewert A, et al. Buprenorphine treatment of opioid-dependent pregnant women: a comprehensive review. Addiction 2012;107:Suppl 1:5–27. [PubMed: 23106923]
9. Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med 2010;363:2320–31. [PubMed: 21142534]
10. Holbrook AM, Baxter JK, Jones HE, et al. Infections and obstetric outcomes in opioid-dependent pregnant women maintained on methadone or buprenorphine. Addiction 2012;107:Suppl 1:83–90. [PubMed: 23106930]
11. Gaalema DE, Scott TL, Heil SH, et al. Differences in the profile of neonatal abstinence syndrome signs in methadone- versus buprenorphine-exposed neonates. Addiction 2012;107:Suppl 1:53–62.
12. Brogly SB, Saia KA, Walley AY, Du HM, Sebastiani P. Prenatal buprenorphine versus methadone exposure and neonatal outcomes: systematic review and meta-analysis. Am J Epidemiol 2014;180:673–86. [PubMed: 25150272]
13. Zedler BK, Mann AL, Kim MM, et al. Buprenorphine compared with methadone to treat pregnant women with opioid use disorder: a systematic review and meta-analysis of safety in the mother, fetus and child. Addiction 2016;111:2115–28. [PubMed: 27223595]
14. Piske M, Homayra F, Min JE, et al. Opioid use disorder and perinatal outcomes. Pediatrics 2021;148(4):e2021050279. [PubMed: 34479983]
15. Lemon LS, Caritis SN, Venkataramanan R, Platt RW, Bodnar LM. Methadone versus buprenorphine for opioid use dependence and risk of neonatal abstinence syndrome. Epidemiology 2018;29:261–8. [PubMed: 29112519]
16. Brogly SB, Hernández-Diaz S, Regan E, Fadli E, Hahn KA, Werler MM. Neonatal outcomes in a Medicaid population with opioid dependence. Am J Epidemiol 2018;187:1153–61. [PubMed: 29155919]
17. Coulson CC, Lorencz E, Rittenhouse K, Ramage M, Lorenz K, Galvin SL. Association of maternal buprenorphine or methadone dose with fetal growth indices and neonatal abstinence syndrome. Am J Perinatol 2021;38:28–36. [PubMed: 31421639]
18. Kakko J, Heilig M, Sarman I. Buprenorphine and methadone treatment of opiate dependence during pregnancy: comparison of fetal growth and neonatal outcomes in two consecutive case series. Drug Alcohol Depend 2008;96:69–78. [PubMed: 18355989]

19. Welle-Strand GK, Skurtveit S, Jones HE, et al. Neonatal outcomes following in utero exposure to methadone or buprenorphine: a National Cohort Study of opioid-agonist treatment of pregnant women in Norway from 1996 to 2009. Drug Alcohol Depend 2013;127:200–6. [PubMed: 22841456]
20. Wiegand SL, Stringer EM, Stuebe AM, Jones H, Seashore C, Thorp J. Buprenorphine and naloxone compared with methadone treatment in pregnancy. Obstet Gynecol 2015;125:363–8. [PubMed: 25569005]
21. Palmsten K, Huybrechts KF, Mogun H, et al. Harnessing the Medicaid Analytic eXtract (MAX) to evaluate medications in pregnancy: design considerations. PLoS One 2013;8(6):e67405. [PubMed: 23840692]
22. Kotelchuck M An evaluation of the Kessner Adequacy of Prenatal Care Index and a proposed Adequacy of Prenatal Care Utilization Index. Am J Public Health 1994;84:1414–20. [PubMed: 8092364]
23. Stürmer T, Wyss R, Glynn RJ, Brookhart MA. Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. J Intern Med 2014;275:570–80. [PubMed: 24520806]
24. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. Epidemiology 2009;20:512–22. [PubMed: 19487948]
25. Li F, Thomas LE, Li F. Addressing extreme propensity scores via the overlap weights. Am J Epidemiol 2019;188:250–7. [PubMed: 30189042]
26. Burns RM, Pacula RL, Bauhoff S, et al. Policies related to opioid agonist therapy for opioid use disorders: the evolution of state policies from 2004 to 2013. Subst Abus 2016;37:63–9. [PubMed: 26566761]
27. Brogly SB, Turner S, Lajkosz K, et al. Infants born to opioid-dependent women in Ontario, 2002–2014. J Obstet Gynaecol Can 2017;39:157–65. [PubMed: 28343557]
28. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med 2017;167:268–74. [PubMed: 28693043]
29. Lash TL, Fox MP, Fink AK. Applying quantitative bias analysis to epidemiologic data. New York: Springer, 2009.
30. Lemon LS. Invited commentary: a novel strategy for addressing unmeasured confounding when comparing opioid agonist therapies in pregnancy. Am J Epidemiol 2018;187:1162–4. [PubMed: 29155916]
31. Kinsella M, Halliday LOE, Shaw M, Capel Y, Nelson SM, Kearns RJ. Buprenorphine compared with methadone in pregnancy: a systematic review and meta-analysis. Subst Use Misuse 2022;57:1400–16. [PubMed: 35758300]
32. Patrick SW, Richards MR, Dupont WD, et al. Association of pregnancy and insurance status with treatment access for opioid use disorder. JAMA Netw Open 2020;3(8):e2013456. [PubMed: 32797175]

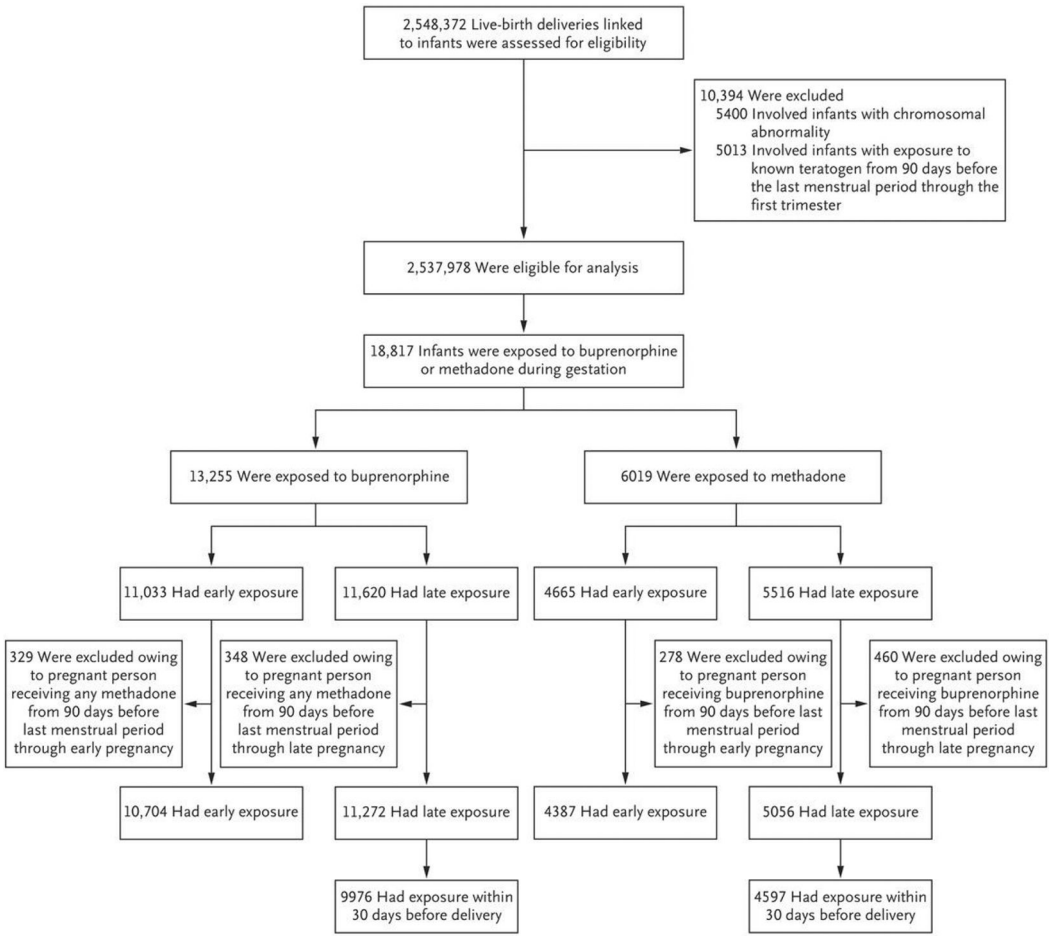

Figure 1. Characteristics of Pregnant Persons and Infants Included in the Study Population.

Receipt of any methadone as an exclusion criterion for persons in the buprenorphine exposure group was defined according to procedure codes for methadone administration and methadone dispensings for indications unrelated to opioid use disorder. Receipt of any buprenorphine as an exclusion criterion for persons in the methadone group was defined as dispensings of buprenorphine of any formulation (not limited to formulations indicated for opioid use disorder). Adjusted analyses were further restricted to pregnant persons with complete ZIP Code data to enable calculation of the socioeconomic status proxies (missing for <1%). This restriction resulted in 10,635 persons in the buprenorphine group and 4332 in the methadone group being included in the analysis during early exposure (from the last menstrual period to gestational week 19), 11,200 in the buprenorphine group and 5001 in the methadone group being included in the analysis during late exposure (gestational week 20 through the day before delivery), and 9908 in the buprenorphine group and 4545 in the methadone group being included in the analysis for exposure in the 30 days before delivery.

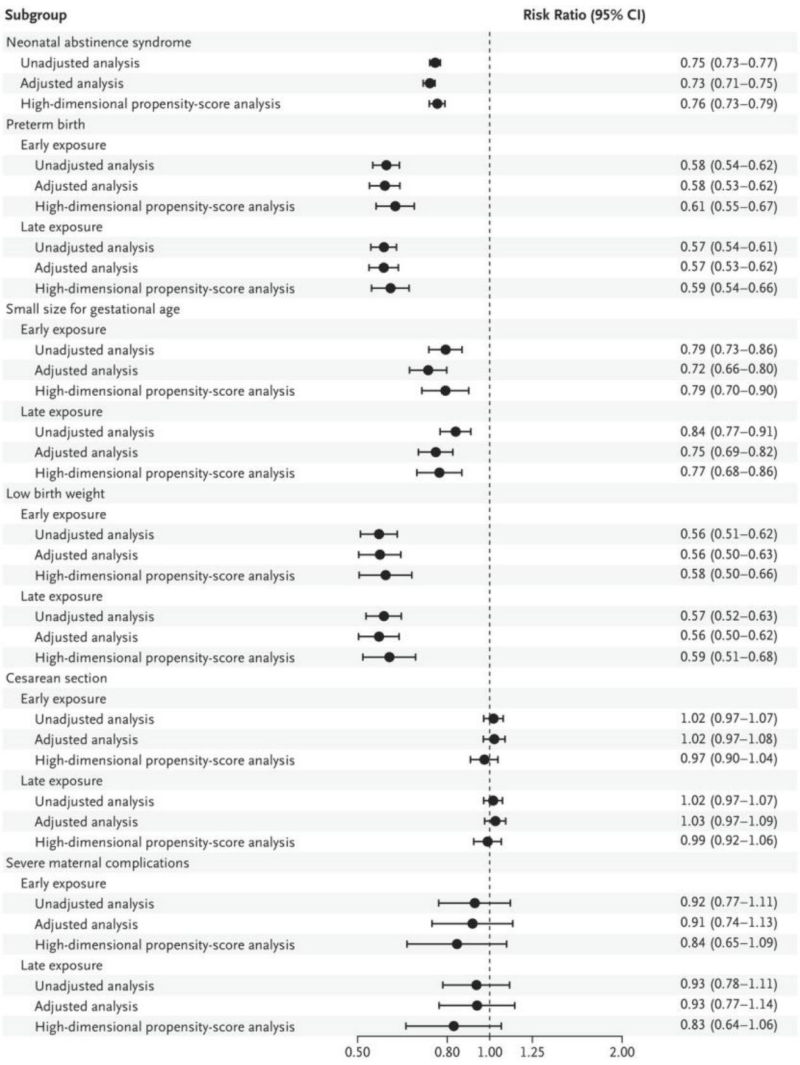

Figure 2. Adverse Outcomes at Birth with Buprenorphine as Compared with Methadone in Pregnancy.

The adjusted analysis was adjusted for all defined covariates, including markers of a history of opioid use disorder and severity, nonopioid substance use or dependence, medical conditions associated with opioid use disorder, mental health conditions, chronic coexisting conditions, other medication use, health care utilization metrics, proxies for social issues, demographic characteristics, and proxies for socioeconomic status. The high-dimensional propensity-score analysis empirically selected 200 variables from all available diagnosis codes, procedure codes, and medication dispensings on the basis of the strength of their relationship to the exposure status for inclusion in the propensity score along with all prespecified covariates. Confidence intervals have not been adjusted for multiple testing and therefore should not be used in place of a hypothesis test.

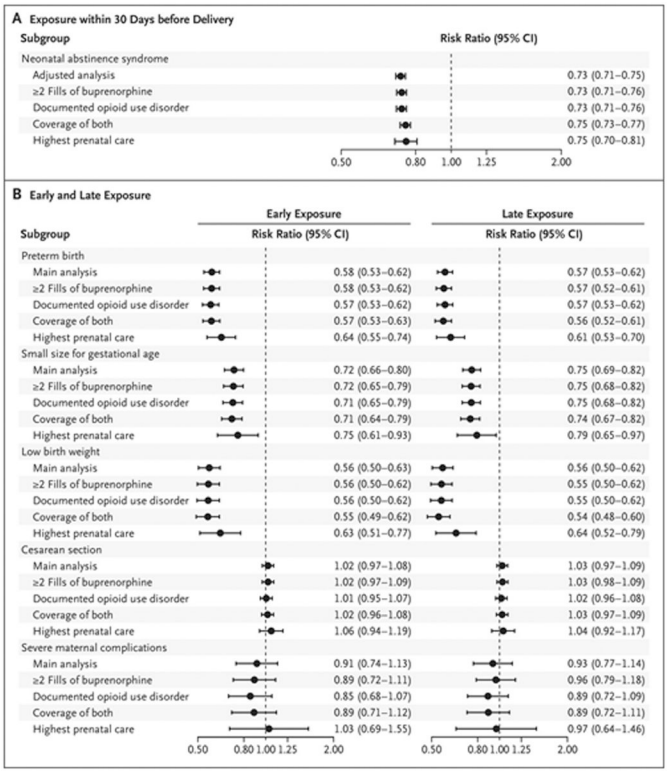

Figure 3. Sensitivity Analyses of Adverse Outcomes at Birth with Exposure to Buprenorphine as Compared with Methadone during Pregnancy.

For the early and late exposure, the definition of two or more fills of buprenorphine was two or more dispensings during the exposure windows. For the exposure window of 30 days before delivery, the definition of two or more fills of buprenorphine was two or more dispensings during the 30-day window or at least one dispensing in the 30-day window and one dispensing that was filled before the 30-day window but overlapped with the 30-day window based on the number of days supplied by that dispensing (e.g. a 30-day supply). The subgroup regarding documented opioid use disorder was restricted to persons with a diagnosis code for opioid use disorder from 90 days before the last menstrual period to 1 day before delivery. Coverage of both medications was an analysis cohort restricted to persons who received buprenorphine or methadone when both were covered by the state Medicaid program. The subgroup regarding highest prenatal care was restricted to persons with the highest level of prenatal care as measured with the Adequacy of Prenatal Care Utilization Index (consisting of four categories ranging from inadequate [the lowest rating] to adequate plus [the highest] that rank the adequacy of when prenatal care began and the number of prenatal care visits received). Confidence intervals have not been adjusted for multiple testing and therefore should not be used in place of a hypothesis test.

Table 1.

Characteristics of Persons with Exposure to Buprenorphine or Methadone in Early Pregnancy.*

Characteristic	Unweighted Population			Weighted Population†	
	Buprenorphine Population (N=10,704)	Methadone Population (N = 4387)	Standardized Difference‡	Buprenorphine Population (N = 2477)	Methadone Population (N = 2477)
			%		
Age — yr	28.4±4.6	28.7±4.7	−6.2	28.6±2.2	28.6±3.5
Race or ethnic group — no. (%)§					
Black	265 (2.5)	294 (6.7)	−20.3	116 (4.7)	116 (4.7)
Hispanic	372 (3.5)	332 (7.6)	−18.0	148 (6.0)	148 (6.0)
Other	239 (2.2)	193 (4.4)	−12.1	90 (3.6)	90 (3.6)
White	9462 (88.4)	3390 (77.3)	29.8	2044 (82.5)	2044 (82.5)
Unknown	366 (3.4)	178 (4.1)	−3.4	79 (3.2)	79 (3.2)
Substance use or abuse — no. (%)					
Any opioid agonist use before pregnancy	7528 (70.3)	3123 (71.2)	−1.9	1745 (70.4)	1745 (70.4)
Alcohol abuse	848 (7.9)	189 (4.3)	15.1	131 (5.3)	131 (5.3)
Cocaine abuse	660 (6.2)	220 (5.0)	5.0	138 (5.6)	138 (5.6)
Psychostimulant abuse	375 (3.5)	149 (3.4)	0.6	81 (3.3)	81 (3.3)
Sedative or hypnotic agent abuse	520 (4.9)	161 (3.7)	5.9	102 (4.1)	102 (4.1)
Tobacco use	5242 (49.0)	1792 (40.8)	16.4	1105 (44.6)	1105 (44.6)
Mental health conditions — no. (%)					
Anxiety	3686 (34.4)	1182 (26.9)	16.3	741 (29.9)	741 (29.9)
Bipolar disorder	1221 (11.4)	441 (10.1)	4.4	270 (10.9)	270 (10.9)
Depression	3386 (31.6)	1027 (23.4)	18.5	657 (26.5)	657 (26.5)
Medication use — no. (%)					
Antidepressant	4715 (44.0)	1324 (30.2)	29.0	864 (34.9)	864 (34.9)
Antipsychotic agent	1124 (10.5)	322 (7.3)	11.1	207 (8.4)	207 (8.4)
Benzodiazepine	2164 (20.2)	767 (17.5)	7.0	460 (18.6)	460 (18.6)
Other hypnotic agent	2177 (20.3)	680 (15.5)	12.6	420 (17.0)	420 (17.0)
Prescription opioid	3027 (28.3)	1544 (35.2)	−14.9	810 (32.7)	810 (32.7)
Health care utilization					
Opioid-related emergency department visit — no. (%)	563 (5.3)	295 (6.7)	−6.2	161 (6.5)	161 (6.5)
Opioid-related inpatient visit — no. (%)	770 (7.2)	258 (5.9)	5.3	162 (6.5)	162 (6.5)
No. of emergency department visits	1.6±2.5	1.7±3.2	−5.5	1.7±1.4	1.7±1.7
No. of hospitalizations	0.1±0.5	0.1±0.6	2.0	0.1±0.3	0.1±0.5
No. of outpatient visits	23.5±18.7	24.5±25.6	−4.5	23.3±9.3	23.3±17.2
Adequacy of Prenatal Care Utilization Index classification — no. (%)¶					
Inadequate	4535 (42.4)	1969 (44.9)	−5.1	1094 (44.2)	1094 (44.2)
Intermediate	1809 (16.9)	772 (17.6)	−1.8	424 (17.1)	424 (17.1)
Adequate	1739 (16.2)	619 (14.1)	6.0	363 (14.7)	363 (14.7)

Characteristic	Unweighted Population			Weighted Population[†]	
	Buprenorphine Population (N=10,704)	Methadone Population (N = 4387)	Standardized Difference[‡]	Buprenorphine Population (N = 2477)	Methadone Population (N = 2477)
			%		
Adequate plus	2621 (24.5)	1027 (23.4)	2.5	597 (24.1)	597 (24.1)

[*] Plus-minus values are means ±SD. Percentages may not total 100 because of rounding.

[†] Overlap weights create a perfect balance of mean values of covariates included in the propensity score; therefore, the exposure groups are identical after weighting.

[‡] A standardized difference of less than 10% was considered to be balanced.

[§] Race and ethnic group were determined on the basis of information that was derived from data that had been collected and coded from Medicaid applications and submitted to the Centers for Medicare and Medicaid Services by individual states.

[¶] The Adequacy of Prenatal Care Utilization Index consists of four categories ranging from inadequate (the lowest rating) to adequate plus (the highest) that rank the adequacy of when prenatal care began and the number of prenatal care visits received.

Table 2.

Absolute Risk Estimates of Neonatal and Maternal Outcomes.

Exposure and Outcome	Buprenorphine Population		Methadone Population		Adjusted Relative Risk (95% CI)
		Absolute Risk (95% CI)		Absolute Risk (95% CI)	
	no.	*percent*	*no.*	*percent*	
Exposure 30 days before delivery					
Neonatal abstinence syndrome	5188	52.0 (51.0–53.0)	3182	69.2 (67.9–70.6)	0.73 (0.71–0.75)
Exposure in early pregnancy					
Preterm birth	1541	14.4 (13.7–15.1)	1086	24.9 (23.6–26.2)	0.58 (0.53–0.62)
Small size for gestational age	1294	12.1 (11.5–12.7)	669	15.3 (14.2–16.4)	0.72 (0.66–0.80)
Low birth weight	886	8.3 (7.8–8.8)	649	14.9 (13.8–15.9)	0.56 (0.50–0.63)
Cesarean section	3597	33.6 (32.7–34.5)	1446	33.1 (31.7–34.6)	1.02 (0.97–1.08)
Severe maternal complications	347	3.3 (2.9–3.6)	154	3.5 (2.9–4.0)	0.91 (0.74–1.13)
Exposure in late pregnancy					
Preterm birth	1599	14.3 (13.6–14.9)	1238	25.0 (23.8–26.2)	0.57 (0.53–0.62)
Small size for gestational age	1467	13.0 (12.4–13.6)	787	15.6 (14.6–16.6)	0.75 (0.69–0.82)
Low birth weight	925	8.2 (7.7–8.7)	723	14.4 (13.4–15.3)	0.56 (0.50–0.62)
Cesarean section	3733	33.1 (32.2–34.0)	1646	32.7 (31.4–34.0)	1.03 (0.97–1.09)
Severe maternal complications	376	3.4 (3.0–3.7)	181	3.6 (3.0–4.1)	0.93 (0.77–1.14)