MATERNAL

# Buprenorphine-naloxone use in pregnancy: a systematic review and metaanalysis



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**OBJECTIVE:** The goal of this systematic review and metaanalysis is to compare pregnancy outcomes between pregnant women undergoing treatment for opioid use disorder with buprenorphine-naloxone and those undergoing treatment for opioid use disorder with other forms of medication-assisted treatment.

**STUDY DESIGN:** PubMed, Embase, PsycINFO, Cochrane Clinical Trials, and Web of Science were searched to identify studies assessing the relationship between maternal buprenorphine-naloxone use and pregnancy outcomes. Outcomes assessed included neonatal abstinence syndrome diagnosis and treatment, neonatal intensive care unit admission, length of neonatal hospital stay, delivery complications, mode of delivery, labor analgesia, illicit drug use, medication-assisted treatment dosage, gestational age at delivery, breastfeeding status, miscarriage, congenital anomalies, intrauterine fetal demise, birthweight, head circumference, length, and Apgar scores.

**RESULTS:** Overall, 5 studies comprising 6 study groups met the inclusion criteria. Of the 1875 mother-baby dyads available for analysis, medications prescribed as part of the medication-assisted treatment included buprenorphine-naloxone, buprenorphine alone, methadone, or long-acting opioids. There were no serious adverse maternal or neonatal outcomes associated with maternal buprenorphine-naloxone use reported among any of the studies. Women prescribed with buprenorphine-naloxone for delivered neonates who were less likely to require treatment for neonatal abstinence syndrome were compared with pregnant women prescribed with other opioid agonist medications. Of the remaining outcomes assessed, metaanalysis did not detect any statistically significant differences when comparing the groups of women using buprenorphine-naloxone with the groups of women prescribed with other medications as part of the medication-assisted treatment.

**CONCLUSION:** Pregnant women undergoing treatment for opioid use disorder with buprenorphine-naloxone do not experience significantly different pregnancy outcomes than women undergoing treatment with other forms of opioid agonist medication-assisted therapy.

**Key words:** buprenorphine, buprenorphine-naloxone, medication-assisted treatment, methadone, neonatal abstinence syndrome, opioid use disorder, pregnancy

## Introduction

The United States is in the midst of an "opioid crisis" that has recently claimed the lives of more than 90 Americans per day.[1] In 2017, a nationwide public health emergency was declared, which led to an increased focus on strengthening treatment and recovery services, data collection, and research to combat this epidemic.[2] Recognizing the increasing rates of opioid use disorder (OUD) among pregnant women, the American College of Obstetricians and Gynecologists recommends that healthcare providers engage in universal screening and the provision of comprehensive services for OUD in pregnancy.[3–5]

These recommendations leverage the window of opportunity that pregnancy provides to affect health behavior changes and acknowledge the risks of untreated OUD in pregnancy. Medication-assisted treatment (MAT) is the mainstay of treatment for OUD during and outside of pregnancy.[6–8] However, fetal exposure to opioid agonist medications such as methadone or buprenorphine, like fetal exposure to all opioids, carries a risk of neonatal abstinence syndrome (NAS). NAS results from the abrupt discontinuation of in utero opioid exposure at birth and manifests clinically as a constellation of signs and symptoms that reflect dysregulation of the gastrointestinal, respiratory, central, and autonomic nervous systems.[9]

Methadone has been the cornerstone of MAT in pregnancy since the late 1960s.[10] Buprenorphine was approved in 2002 for treatment of OUD in the United States[11] and is, generally, a more favorable treatment option because of its superior safety profile and easier access (the medication is available from waivered providers and can be prescribed in a medical office).[7] A growing body of evidence has documented the use and relative safety of buprenorphine during pregnancy.[4,12,13] Treatment with buprenorphine in pregnancy is associated with a lower incidence of NAS and shorter duration of NAS treatment than MAT with methadone.[13] The initial studies examining the relative safety and maternal and neonatal treatment outcomes related to buprenorphine pharmacotherapy in pregnancy used the

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## AJOG MFM at a Glance

### Why was this study conducted?

Information regarding the use of buprenorphine-naloxone during pregnancy for medication-assisted treatment (MAT) of opioid use disorder (OUD) is limited. This systematic review and metaanalysis was conducted to review the available evidence and synthesize evidence-based recommendations for women using buprenorphine-naloxone in pregnancy.

### Key findings

Pregnant women receiving MAT for OUD with buprenorphine-naloxone have similar pregnancy outcomes when compared with women undergoing treatment with other forms of MAT.

### What does this add to what is known?

Healthcare providers can use these results to both reassure patients regarding pregnancy outcomes and be thoughtful about any consideration for adjustment of MAT. For women restricted in their access to MAT, these results can be utilized to further support the use of buprenorphine-naloxone.

buprenorphine monoproduct as it was the only product available at the time the studies were initiated.[13–16] Since then, buprenorphine was also approved as a combination product with naloxone to decrease the risk of diversion and misuse.[17] Although there is no strong reason to believe that buprenorphine-naloxone will result in different clinical outcomes, the current robust and high-quality evidence regarding the safety and efficacy of buprenorphine in pregnancy exists for buprenorphine alone. Information regarding the use of buprenorphine-naloxone during pregnancy is limited to smaller cohorts and case series.[18–24] Although clinical guidance has historically recommended switching women from buprenorphine-naloxone to buprenorphine alone because of the lack of relative safety data on the combination produced, switching can result in unintended problems for women (eg, lack of buprenorphine availability, vulnerability of relapse because of switching medications, etc.).[4,25,26] Currently, a systematic review and metaanalysis of the collected evidence regarding the relative safety and efficacy of OUD treatment with buprenorphine-naloxone during pregnancy is needed to provide an evidence base for recommendations regarding the use of this medication and whether or not women should be urged to switch to buprenorphine alone if they are newly pregnant or considering pregnancy.

## Objective

The goal of this systematic review and metaanalysis is to compare pregnancy outcomes between pregnant women undergoing treatment for OUD with buprenorphine-naloxone and those undergoing treatment for OUD with other forms of MAT.

## Methods

### Search strategy and eligibility criteria

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (2009) framework guidelines. We conducted systematic manual searches on PubMed, Embase, PsycINFO, Cochrane Clinical Trials, and Web of Science through October 2019 to identify all published observational and retrospective cohort studies and randomized controlled trials assessing the relationship between maternal buprenorphine-naloxone use and pregnancy outcomes. The following key words, in different combinations and Medical Subject Headings, were used to identify relevant studies: "pregnant," "opioids," "neonatal abstinence syndrome," "buprenorphine," "naloxone," and "methadone." Additional search terms included generic names, brand names, and synonyms for all the listed pharmaceuticals. The search was restricted to full-text English-language references. Conference abstracts were excluded as it was not always possible to determine from the abstract whether buprenorphine or buprenorphine-naloxone were included in the data presented. We excluded cross-sectional studies, guidelines, expert opinion, editorials, letters to the editors, and comments (Supplemental Table).

### Study selection

Data were screened and extracted by a single investigator (H.L.). Outcomes that were assessed included NAS diagnosis and treatment, neonatal intensive care unit (NICU) admission, length of neonatal hospital stay, delivery complications, mode of delivery, labor analgesia, illicit drug use, MAT dosage, gestational age at delivery, breastfeeding status, miscarriage, congenital anomalies, intrauterine fetal demise, birthweight, head circumference, length, and Apgar scores.

### Data synthesis

Assessment of bias was performed using an approach similar to that described by the Cochrane nonrandomized study group.[27] With this approach, differences in baseline characteristics are compared to evaluate for selection bias because the factors determining to which group a woman is allocated are often unknown. The study design and similarity of treatment and control groups for the following 8 characteristics were evaluated to estimate the risk of bias: preterm birth, breastfeeding, active psychiatric disease, use of psychiatric medications (benzodiazepines and/or selective serotonin reactive inhibitors), smoking, delivery dose of MAT, multimodal treatment for NAS, and ongoing illicit drug use. These characteristics were identified by the authors as potential sources for confounding when evaluating neonatal outcomes after exposure to MAT. If a study reported a statistically significant ($P<.05$) difference between the buprenorphine-naloxone group and the control group in a given characteristic or did not assess for differences in a characteristic between the 2 groups, the potential for treatment bias was

considered to be high for that characteristic. If sufficient details (eg, mean and standard deviation [SD]) about a particular baseline characteristic was not reported in the article, the potential for treatment bias associated with that characteristic was defined as unable to be determined. Quality assessment was used for descriptive purposes only.

### Statistical analysis

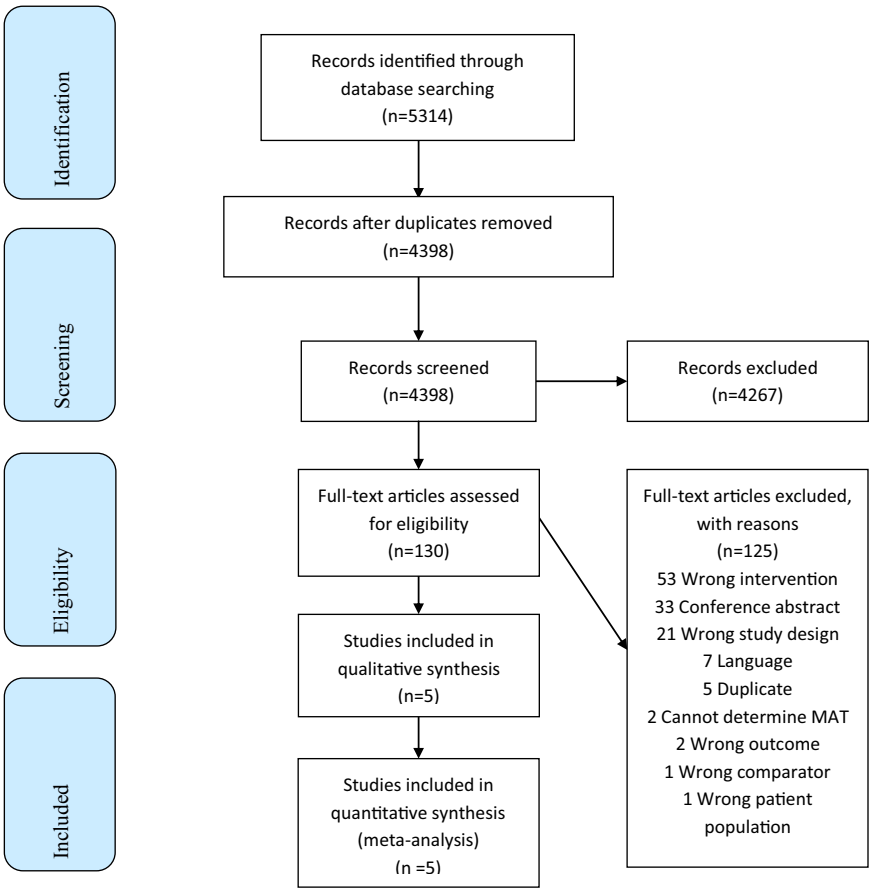
The Review Manager software (version 5.3, Cochrane, London, United Kingdom) was used for statistical analyses. Metaanalyses were performed, and the studies were weighted on the basis of the number of participants. Study results that were reported as median and range were converted to estimated mean and variance using established methodology.[28,29] Statistical heterogeneity of the studies was assessed using the Cochrane Q statistic and Higgins $I^2$ statistics. In the absence of statistically significant heterogeneity, a fixed effects model was planned. The summary measures were reported as odds ratios or mean difference with 95% confidence intervals (CIs).

## Results

### Study selection

The initial search yielded 5314 citations. Preliminary screening excluded 916 duplicates, and the remaining 4398 studies were reviewed by title and abstract. A total of 4267 studies were excluded according to the inclusion criteria, leaving 130 records for full-text review. Full review excluded 125 additional citations, leaving 5 records for full analysis. The search flow process is illustrated in Figure 1.

**FIGURE 1**
**Search flow process for study selection**




*MAT*, medication-assisted treatment.

*Link. Buprenorphine-naloxone use in pregnancy: a systematic review and metaanalysis. AJOG MFM 2020.*

### Study characteristics

Study characteristics are summarized in Table 1. The 2018 paper by Nechanska et al[24] compared neonatal outcomes after prenatal exposure to methadone and buprenorphine of 2 European countries—Czech Republic and Denmark. For the purposes of analysis, these 2 study samples were treated separately and identified as Nechanska (Czech Republic) or Nechanska (Norway).

The 6 groups were each part of a retrospective cohort study. They included a total of 291 mother-baby dyads exposed to buprenorphine-naloxone during pregnancy, 361 to buprenorphine alone (occurring in 3 groups in 2 of the studies), 382 to methadone (in 4 groups in 3 of the studies), 159 to illicit opioids or long-acting agonist medication other than buprenorphine-naloxone (in 1 group) during pregnancy, and 682 with no prenatal exposure to opioids (in 1 group).

In the study by Jumah et al,[19] women exposed to buprenorphine-naloxone during pregnancy were compared with 2 control groups, the first group with 682 women without exposure to any opioids during pregnancy and the second group with 159 women with opioid exposure other than buprenorphine-naloxone. Within the geographically isolated treatment region of this study, it is common to treat OUD in pregnancy with long-acting opioids; however, the second control group included a mixture of pregnant women receiving long-acting opioids as pharmacotherapy for OUD as well as women who continued to use illicit opioids throughout their pregnancy. Notably, for the purposes of our systematic review, the data included in the study by Jumah et al[19] were extracted; however, the data could not be included in the metaanalysis owing to the lack of control groups that were composed solely of MAT.

Most of the patient cohorts came from single tertiary care centers; however, 2 patient cohorts were identified through national health registries. More than 81% of the buprenorphine-naloxone patient data came from these single tertiary care

**TABLE 1**
**Characteristics of included studies**

| Study | Study design, location, time | Sample | Study groups (n) | Primary outcomes | Secondary outcomes | Results |
|---|---|---|---|---|---|---|
| Gawronski et al[21] | Retrospective cohort, US academic, 2010–2011 | Cohort delivered from single labor and delivery unit | B-N (58)<br>Methadone (92) | NAS treatment (yes vs no) | Duration of NAS treatment, total cumulative dose of treatment medication, and duration | Primary: the B-N group had a significantly lower rate (or frequency) of NAS treatment than the methadone group |
| Jumah et al[19] | Retrospective cohort, rural Canada, 2013–2015 | Cohort received care at the district hospital in Northwestern Ontario | B-N (62)<br>No prenatal opioid exposure (618)<br>Prenatal opioid exposure (illicit opioid use or long-acting agonist medication other than B-N) (159) | Birthweight, preterm delivery, congenital anomalies, stillbirth | Gestational age at delivery<br>Apgar score at 1 and 5 min<br>NAS score<br>NAS treatment (yes vs no)<br>Maternal outcome data (CD rate, LOS, hemorrhage, out of hospital delivery) | Primary: no significant differences in the primary outcomes among the 3 groups<br>Secondary: longer neonatal LOS when comparing B-N with no opioid exposure; no other significant differences among the 3 groups |
| Nechanska et al,[24] 2018 (Czech Republic) | Retrospective cohort, Czech Republic, 2000–2014 | Linked national registry data | B-N (22)<br>Buprenorphine (154)<br>Methadone (158) | Neonatal outcomes | — | No significant differences in neonatal outcomes among the 3 groups in both studies<br>Most B-N patients were switched to buprenorphine alone before delivery |
| Nechanska et al,[24] 2018 (Norway) | Retrospective cohort, Norway, 2004–2013 | Linked national registry data | B-N (33)<br>Buprenorphine (99)<br>Methadone (101) | Neonatal outcomes | — | |
| Wiegand et al[20] | Retrospective cohort, US academic center, 2011–2013 | Cohort delivered from single labor and delivery unit | B-N (31)<br>Methadone (31) | NAS treatment (yes vs no), peak NAS score, total morphine treatment, duration of NAS treatment | Neonatal outcomes<br>Maternal outcome data (mode of delivery, analgesia, weight gain, prenatal care visits, MAT dosage) | The B-N group had a significantly lower rate of NAS treatment, lower peak NAS scores, and a shorter duration of hospitalization than the methadone group |
| Mullins et al[23] | Retrospective cohort, United States, 2014–2018 | Cohort obtained care from a community-based perinatal substance program and from a local delivery unit | B-N (85)<br>Buprenorphine (108) | NAS treatment (yes vs no) | Maternal outcome data (prenatal care, pregnancy comorbidities, mode of delivery, LOS, breastfeeding)<br>Neonatal outcome data (gestational age at delivery, sex, birthweight, length, head circumference, 5-min Apgar score, NICU admission, congenital anomalies) | Similar maternal and neonatal outcomes for neonates exposed to B-N vs buprenorphine monoproducts. No evidence of adverse pregnancy outcomes with B-N |

NAS score was determined by a modified Finnegan scale taken by a bedside nurse in Jumah et al[19] and by a 13-item modified Finnegan opioid weaning scale taken by a clinical nurse in Wiegand et al.[20] The study of Nechanska et al was a single study reporting outcomes of 2 separate populations.

*B-N*, buprenorphine-naloxone combination product; *CD*, cesarean delivery; *LOS*, length of stay; *MAT*, medication-assisted treatment; *NAS*, neonatal abstinence syndrome; *NICU*, neonatal intensive care unit.

*Link. Buprenorphine-naloxone use in pregnancy: a systematic review and metaanalysis. AJOG MFM 2020.*

centers. In contrast, more than 67% of the buprenorphine monoproduct patient data and more than 70% of the methadone patient data came from the 2 national health registries.

All studies attempted to evaluate neonatal outcomes after maternal exposure to buprenorphine-naloxone during pregnancy. The most common primary outcome was need for NAS treatment. Studies varied in reporting adherence to MAT. Ongoing nonprescribed psychoactive substance use was mainly assessed using periodic urine drug screening. However, results of urine screening were not reported in the registry-based studies.

### Risk of bias of included studies

The risk of bias within studies is shown in Table 2. All studies demonstrated enough information to assess for bias in most of the predefined categories. Two studies demonstrated a low risk of bias across all categories. The registry data from Nechanksa et al examining populations in the Czech Republic and Norway were subject to the limitations of population registries and hence limited in its ability to assess for some of the characteristics. In addition, most of the women in the Norway cohort who conceived while being prescribed buprenorphine-naloxone switched to buprenorphine monoproducts, but information about the timing of that transition is not provided. The study by Jumah et al[19] was identified as being at high risk for bias across all categories because the control group included both patients taking long-acting opioids for MAT and those with ongoing illicit opioid use. Wiegand et al[20] and Mullins et al[23] were the only studies that performed a multivariate analysis to adjust for confounders.

### Results of individual studies

All 5 studies (6 groups) included an assessment of neonatal outcomes (Table 1), although not every study necessarily assessed the same neonatal outcomes. Wiegand et al[20] reported a significantly increased gestational age at delivery in the buprenorphine-naloxone group when compared with methadone-exposed neonates (mean [SD], 39.7±1.8 vs 38.1±2.9).

Four study groups found no significant difference in the prevalence of preterm birth (PTB) between the buprenorphine-naloxone–exposed groups and those groups exposed to other treatments for OUD.[19–21] The prevalence of PTB among neonates exposed to buprenorphine-naloxone ranged from 3% to 20% with most of the studies reporting a prematurity rate of ~17% to 20%. The range of reported PTB rates among neonates exposed to other forms of MAT ranged from 4% to 25%.[19–21,23,24] Notably, the study by Jumah et al[19] reported PTB rates of only of 3% and 4% within their entire delivery cohorts, which included women without any opioid exposure likely skewing their reported rates.

Three study groups included stillbirth as a neonatal outcome and did not find a difference in prevalence between buprenorphine-exposed neonates and groups of neonates using other forms of MAT including buprenorphine alone, methadone, or other long-acting or illicit opiods.[19,24] Jumah et al[19] and Mullins et al[23] were the only studies that included an assessment for congenital anomalies as an outcome. The authors did not find a significant difference in the prevalence when comparing neonates exposed to buprenorphine-naloxone with the study control groups.

NICU admission rates were evaluated in 3 studies. Among buprenorphine-naloxone–exposed neonates, the NICU admission rate ranged from 19% to 41%. The NICU admission rates of neonates exposed to other forms of MAT ranged from 20% to 39%, which, on a study-by-study basis, were not significantly different.[20,21,23] Four study groups compared the need for treatment of neonatal abstinence syndrome after maternal treatment with buprenorphine-naloxone vs other forms of MAT. Of the buprenorphine-naloxone–exposed neonates, the need for NAS treatment ranged from 25% to 64%, whereas neonates exposed to other forms of MAT ranged from 51% to 80%.[20,21,23,24] Gawronski et al[21] and Wiegand et al[20] reported a significantly decreased need for NAS treatment when buprenorphine-naloxone–exposed neonates were compared with those exposed to methadone. Mullins et al[23] reported that significantly fewer buprenorphine-naloxone–exposed neonates required treatment for NAS than those exposed to buprenorphine alone; however, this finding did not persist after adjustment for confounders.

Length of hospital stay was evaluated in 3 studies and ranged from 5.6 to 9 days for buprenorphine-naloxone–exposed neonates, compared with 6 to 10 days for neonates exposed to other forms of MAT.[20,21,23] Wiegand et al[20] reported a significant decrease in length of hospitalization, as well as peak NAS scores, among buprenorphine-naloxone–exposed neonates when compared with methadone-exposed neonates. Gawronski and colleagues[21] reported a trend toward a decreased treatment duration for NAS and lower cumulative treatment medication dose required among buprenorphine-naloxone–exposed neonates as compared with methadone-exposed neonates.[20]

There were no serious adverse maternal or neonatal outcomes associated with maternal buprenorphine-naloxone use for MAT reported among any of the studies. Gawronski et al[21] reported that the number of urine tests in pregnancy positive for illicit substances was significantly higher among women using buprenorphine-naloxone for MAT as compared with those women using methadone (47% vs 22%, respectively, $P$=.01).

### Synthesis of results

Metaanalysis results are shown in Table 3 and in the forest plots in Figure 2. For the outcome of need for NAS treatment, 4 studies provided data sufficient to compare the need for NAS treatment for neonates exposed to buprenorphine-naloxone vs other forms of MAT.[20,21,24] Women prescribed buprenorphine-naloxone for MAT delivered neonates who were less likely to require treatment for NAS compared with those utilizing other forms of MAT. Odds of need for NAS treatment was 0.52 times lower

**TABLE 2**
**Risk of bias in the cohort studies under review**

| | Baseline characteristics | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Study** | **Preterm** | **Breastfeeding** | **Active psychiatric history** | **Use of psychiatric medications** | **Smoking** | **Delivery dose of agonist medication** | **Multimodal treatment for NAS** | **Ongoing illicit drug use** |
| Gawronski et al[21] | Low risk | High risk | Low risk | High risk | High risk | Low risk | Unable to determine | High risk |
| Jumah et al[19] | High risk | High risk | High risk | High risk | High risk | High risk | High risk | High risk |
| Nechanska et al,[24] 2018 (Czech Republic) | Low risk | High risk | High risk | High risk | Low risk | High risk | High risk | Low risk |
| Nechanska et al,[24] 2018 (Norway) | Unable to determine | High risk | High risk | High risk | Low risk | High risk | High risk | High risk |
| Wiegand et al[20] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Mullins et al[23] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |

How determination was made. Unable to determine: methods indicate characteristic was identified. High risk: variable was included in the results without identification or was not assessed. Low risk: variable was identified and accounted for clearly in the results.

Individual application of determination was made for the respective characteristics as follows:

Preterm:

Unable to determine: methods indicate whether preterm patients were included; however, there were no statistics (eg, mean or SD) in the results.

High risk: included in the results without identification.

Low risk: population identified and accounted for clearly in the results.

Breastfeeding:

Unable to determine: methods indicate breastfeeding was identified; however, there were no statistics (eg, mean or SD) in the results.

High risk: included in the results without identification.

Low risk: population identified and accounted for clearly in the results.

Active psychiatric history:

Unable to determine: methods indicate active psych history was identified; however, there were no statistics (eg, mean or SD) in the results.

High risk: included in the results without identification (not assessed).

Low risk: population identified and accounted for clearly in the results.

Use of psychiatric medications:

Unable to determine: methods indicate active psych history was identified; however, there were no statistics (eg, mean or SD) in the results or only reported on benzodiazepines alone or SSRI alone, not both.

High risk: included in the results without identification (not assessed).

Low risk: benzodiazepines+SSRI use identified and accounted for clearly in the results.

Smoking:

Unable to determine: methods indicate smoking was identified; however, there were no statistics (eg, mean or SD) in the results.

High risk: included in the results without identification (not assessed).

Low risk: population identified and accounted for clearly in the results.

Delivery dose of agonist medication:

Unable to determine: methods indicate final dose was identified; however, there were no statistics (eg, mean or SD) in the results.

High risk: final dose not assessed in the results.

Low risk: final dose identified and accounted for clearly in the results.

Multimodal treatment for NAS:

Unable to determine: methods indicate multiple treatment modalities employed in the cohort; however, there were no statistics (eg, mean or SD) in the results.

High risk: included in the results without identification (not assessed).

Low risk: treatment method of population identified and accounted for clearly in the results; however, only 1 treatment method was used for the entire cohort.

Ongoing illicit drug use:

Unable to determine: methods indicate active illicit drug use was identified in the cohort; however, there were no statistics (eg, mean or SD) in the results.

High risk: included in the results without identification (not assessed).

Low risk: population identified and accounted for clearly in the results.

*NAS*, neonatal abstinence syndrome; *SD*, standard deviation; *SSRI*, selective serotonin reuptake inhibitors.

*Link. Buprenorphine-naloxone use in pregnancy: a systematic review and metaanalysis. Am J Obstet Gynecol MFM 2020.*

with buprenorphine-naloxone when compared with other forms of MAT (risk ratio [RR], 0.52; 95% CI, 0.36–0.75; $I^2$, 22%) (Figure 2; Table 3).

Of the remaining neonatal and pregnancy outcomes, metaanalysis did not detect any statistically significant differences when comparing the groups of women using buprenorphine-naloxone for MAT vs other forms of MAT (Table 3). The Jumah et al[19] study results could not be incorporated in

the metaanalysis owing to the limitations in its definition of the control groups.

## Comment

Our findings suggest that pregnant women receiving MAT for OUD with buprenorphine-naloxone have similar pregnancy outcomes when compared with women undergoing treatment with other forms of MAT. The articles included in this analysis underscore the current dearth of evidence published regarding the use of buprenorphine-naloxone in pregnancy.

### Comparison with existing literature

The results of our metaanalysis are consistent with both the conclusions of the included studies and evidence from case series.[18,22,30] The first published report documenting the outcomes of MAT with buprenorphine-naloxone during pregnancy was a case series of 10 women by Debelak et al[18] in 2013. Of the 10 women, 8 had been maintained on buprenorphine-naloxone before pregnancy, and the remaining 2 women initiated treatment in the first trimester. No untoward neonatal outcomes were noted in this small series.

Lund and colleagues[30] expanded on this case series with the addition of a comparison group of women receiving buprenorphine monotherapy and methadone (both maintenance and detoxification). They reported that maternal and neonatal outcomes for the 10 women using buprenorphine-naloxone were similar to the comparison cohorts with the following exceptions: methadone was associated with a smaller head circumference, whereas buprenorphine monotherapy was associated with increased neonatal length and higher 5-minute Apgar score compared with those for buprenorphine-naloxone–exposed neonates.[30] Although there were statistically significant differences, all birth parameters in the buprenorphine-naloxone group were within the normal range, and differences were not clinically significant. Our analysis did not demonstrate a significant difference comparing head circumference or length between groups of neonates exposed to buprenorphine-naloxone and those exposed to other forms of MAT.

**TABLE 3**
**Primary and secondary outcomes**

| Outcome | Number of studies | Total number of participants | Buprenorphine/naloxone (n/N [%]) | Other MAT[a] | Effect estimate (OR [95% CI]) |
|---|---|---|---|---|---|
| NICU admission | 3 | 405 | 56/174 (32.2) | 71/231 (30.7) | 1.04 (0.68–1.60) |
| Full-term delivery | 3 | 729 | 164/194 (84.5) | 446/535 (83.4) | 1.04 (0.64–1.70) |
| Vaginal delivery | 3 | 405 | 120/174 (69.0) | 166/231 (71.9) | 0.87 (0.56–1.34) |
| NAS treatment | 4[b] | 634[b] | 92/207 (44.4)[b] | 252/427 (59.0)[b] | 0.52 (0.36–0.75)[b] |
| | | | Mean (SD) | Mean (SD) | Mean difference (95% CI) |
| Neonatal LOS, d | 4 | 403 | 5.6–9.0 | 6.0–10.0 | −1.64 (−3.90 to 0.61) |
| GA at delivery, wk | 5 | 958 | 38.0–39.7 | 38.0–39.0 | 0.28 (−0.06 to 0.62) |
| Neonatal length, cm | 3 | 404 | 49.0–50.1 | 47.9–49.0 | 0.98 (−0.14 to 2.10) |
| Birthweight, g | 3 | 405 | 2905.0–3174.0 | 2904.0–3010.0 | 36.15 (−72.02 to 144.33) |
| Neonatal HC, cm | 3 | 405 | 33.0–34.4 | 32.9–34.0 | 0.39 (−0.65 to 1.42) |

Data are presented as number of buprenorphine users/number of naloxone users (percentage) or reported mean range.

*CI*, confidence interval; *GA*, gestational age; *HC*, head circumference; *LOS*, length of stay; *MAT*, medication-assisted treatment; *NAS*, neonatal abstinence syndrome; *NICU*, neonatal intensive care unit; *OR*, odds ratio; *SD*, standard deviation.

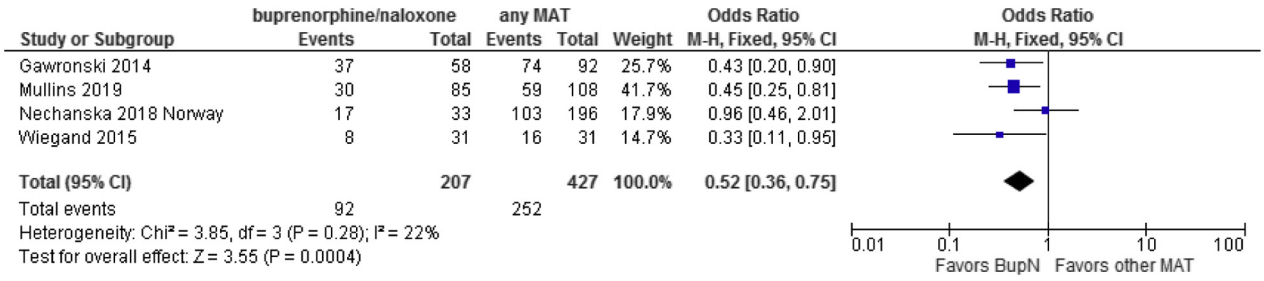
[a] Other MAT is composed solely of methadone; [b] Values are statistically significant.

*Link. Buprenorphine-naloxone use in pregnancy: a systematic review and metaanalysis. AJOG MFM 2020.*

In 2018, Nguyen and colleagues[22] reported maternal and neonatal outcomes from a retrospective case series of 26 women utilizing exclusively buprenorphine-naloxone for MAT in pregnancy. They observed that neonatal birth outcomes were within normal range; however, there was a higher than expected prevalence of PTB (23%) and low birthweight (10%) among these neonates, along with a lower than expected prevalence of NAS requiring treatment (19%).[22] The authors were unable to account for this observation; however, they hypothesized that unmeasured confounders such as smoking, nutrition, psychiatric comorbidity, and stress could have contributed to these results. Our results did not demonstrate significant differences in birthweight and prematurity when comparing neonates exposed to buprenorphine-naloxone to other forms of MAT. Although there was a significant decrease in the rate of NAS requiring treatment, the rate in our study (44%) is more in line with previously reported literature on NAS among neonates exposed to buprenorphine alone, and the significant decrease is likely due to the comparison group of other MAT being composed of more than 50% methadone.[13]

Although the theoretical advantage of a combination product with naloxone is decreased potential for abuse, introducing a new agent into an obstetrical population requires strict scrutiny. Concerns that naloxone exposure during pregnancy could contribute to fetal stress and adverse pregnancy outcomes (because of the potential to induce withdrawal) are likely influenced by historic case reports from the 1970s

**FIGURE 2**
**Forest plot for need for neonatal abstinence treatment**




*CI*, confidence interval; *MAT*, medication-assisted treatment; *M-H*, Mantel-Haenszel.

*Link. Buprenorphine-naloxone use in pregnancy: a systematic review and metaanalysis. AJOG MFM 2020.*

suggesting fetal harm from maternal opioid withdrawal.[4,31,32] Multiple subsequent studies have established that these risks were likely overstated, and recent systematic reviews have not demonstrated any increased risk of poor fetal outcome from tapering or detoxification in pregnancy.[33,34] Our findings further support that historic concerns regarding naloxone exposure in pregnancy are unfounded and should not drive MAT choice today.

The pharmacokinetics of naloxone are such that following oral ingestion and metabolism, the drug remains inactive; however, intravenous or intramuscular injection will precipitate withdrawal.[17,35] Sublingual administration of buprenorphine-naloxone in pregnancy, the typical method of ingestion, results in low levels of absorption and transplacental passage. Although transplacental transfer does occur, bioavailability is poor, with neonatal levels significantly lower than that required for therapeutic effect.[36] Data on the human teratogenicity risks of naloxone exposure are minimal; however, animal studies have not demonstrated teratogenicity.[37]

One of the advantages of buprenorphine-naloxone is that it can be dispensed as an outpatient multiday prescription from most pharmacies. In comparison, federal law limits the distribution of methadone to government-accredited outpatient treatment programs.[38] Licensing of methadone clinics is controlled at the state level, and some states have laws limiting clinic expansion of methadone treatment clinics, making it harder for more rural residents to access care. Further complicating access, methadone is typically distributed in single doses requiring daily clinic visits, which introduce additional barriers to treatment.[39,40]

According to the 2000 Drug Abuse Treatment Act, buprenorphine can be prescribed by waivered healthcare providers in private offices and in quantities sufficient for up to 30 days treatment, making it more desirable and accessible to many patients than methadone.[38] With increased accessibility comes an increased risk of diversion or illicit use of the buprenorphine alone that has resulted in restrictions on use in some areas. For example, to obtain the buprenorphine-alone medication in Canada, a request must be made to the national government and, if approved, must be stored according to strict regulations. This severely restricts access for pregnant women in rural areas and has been the reason for buprenorphine-naloxone maintenance during pregnancy for women living in these areas despite the lack of data.[19,41]

Buprenorphine diversion and illicit use has been increasing both in the United States and around the world since its introduction to the market.[42,43] Although there is no evidence at present to suggest that the United States will respond to this problem by restricting access to the buprenorphine-alone medication as other countries have done, there is increased emphasis on alternative formulations as first-line treatment, with prioritization of buprenorphine-naloxone or other formulations less susceptible to misuse.[43,44] Among women with OUD, unintended pregnancy rates are significantly higher than the general obstetrical population.[45] It is reasonable in this environment for healthcare providers to anticipate that more women will conceive while maintained on buprenorphine-naloxone and they will require thoughtful counseling on how best to treat their OUD in these circumstances. Our data support that pregnancy outcomes among women using buprenorphine-naloxone do not differ significantly from women who use alternative forms of MAT. Rather than running the risks of interrupting MAT or increasing the barriers to treatment, providers should use this information to reassure women who have been exposed to buprenorphine-naloxone. Consideration of switching MAT to buprenorphine alone should be based on an individual woman's circumstances and not simply a blanket recommendation.

### Strengths and limitations

Strengths of our analysis include a thorough and systematic review of all available published studies. We were able to synthesize the results of smaller existing studies and managed to show that neonates born to women taking

buprenorphine-naloxone did not experience significantly different pregnancy outcomes and were less likely to be treated for NAS than those utilizing other forms of MAT. These findings are consistent with the case reports and previously published studies.

As with any metaanalysis, we were limited by the type and quality of evidence available to us as well as the fact that our screening process was conducted by a single investigator. Although our buprenorphine-naloxone study data were derived from 5 study populations in relatively similar proportions, the comparison groups of buprenorphine alone and methadone were more limited in their sources, and the 2 national registry groups accounted for more than half of the data. We were limited by the inconsistent comparison groups among the available studies as well as the fact that only 2 studies reported results adjusted for known confounders.[20] Although we attempted to examine the risk of bias across the 6 groups with our analysis in Table 2, we recognize that our approach was necessarily limited, given the small sizes of the included groups, the retrospective nature of the studies included, and the inability to assess unknown confounders (attrition, self-selection, etc.). Thus, our analysis of risk of bias should not be considered to be comprehensive of the potential for bias but rather a reflection of what could be assessed in light of the limitations of the available data. The ability to assess for publication bias was limited owing to the number of studies resulting from the systematic review. Our ability to draw definitive conclusions regarding the safety of buprenorphine-naloxone use in the first trimester was limited both by lack of consistent reporting of the timing of treatment initiation and by the limited reporting on congenital anomalies or birth defects as an outcome, but the limited bioavailability of naloxone suggests that there is no strong biologically plausible reason to believe naloxone would be harmful when used as prescribed and even the risks associated with withdrawal because of misuse are likely overstated. Only 2 studies evaluated congenital anomalies; one of these was by Jumah et al,[19] which lacked an appropriate control group, whereas the other study was by Mullins et al,[23] which reported no difference in congenital anomalies among buprenorphine-naloxone–exposed neonates, Nonetheless but information regarding the timing of treatment initiation or duration of exposure was not provided making it difficult to determine the extent of first-trimester exposure. The lack of difference in congenital anomalies among buprenorphine-naloxone–exposed neonates reported within these studies aligns with the reports from the case series by Debelak of which all women were either on buprenorphine-naloxone before conception or started in the first trimester and is further supported by animal studies on teratogenicity of naloxone.[18,19,37] Despite this, these studies are all limited by small sample size in their ability to fully assess for the risk of congenital anomalies.

## Conclusion

In summary, the current literature suggests that pregnant women undergoing treatment for OUD with buprenorphine-naloxone do not experience significantly different pregnancy outcomes than women undergoing treatment with other forms of MAT. The number and quality of these studies are limited; however, as the opioid crisis continues, it is expected that more women of reproductive age will conceive while taking buprenorphine-naloxone, and providers can use these results to reassure patients regarding pregnancy outcomes and to be thoughtful in any consideration for adjustment of MAT. For women who are geographically restricted in their access to MAT, it is hoped that these results can be utilized to further support their use of buprenorphine-naloxone when the alternative treatments available to them are less efficacious. For women utilizing buprenorphine-naloxone who are considering switching their medication regimen outside the window of organogenesis, our recommendation would be to continue with their current MAT if it is successful for them.

Future research is needed specifically for women beginning their pregnancy on buprenorphine-naloxone to fill the knowledge gaps of this study. Given the ethical barriers to randomizing pregnant women to treatment in the first trimester to settle any lingering concerns for teratogenicity, observational studies are expected to fill this gap. ■

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**SUPPLEMENTAL TABLE**

**Systematic manual searches conducted to identify all relevant studies and trials**

| Database | Search strategy |
|---|---|
| PubMed | ("Pregnant Women"[Mesh] OR "Pregnancy"[Mesh] OR Pregnant OR Pregnancy OR Pregnancies OR Gestation OR Gravidity) AND ("Analgesics, Opioid"[Mesh] OR Opioid OR Opioids OR Opiate OR Heroin OR "Opioid-Related Disorders"[Mesh] OR "Substance-Related Disorders"[Mesh] OR "Neonatal Abstinence Syndrome"[Mesh] OR (Neonatal Abstinence Syndrome) OR (Neonatal Abstinence Syndromes) OR (Neonatal Withdrawal Syndrome) OR (Neonatal Withdrawal Syndromes) OR (Neonatal Substance Withdrawal) OR (Neonatal Substance Withdrawals) OR (Neonatal Passive Addiction) OR (Neonatal Passive Addictions)) AND ("Buprenorphine, Naloxone Drug Combination"[Mesh] OR "Buprenorphine"[Mesh] OR "Naloxone"[Mesh] OR "Methadone"[Mesh] OR (Buprenorphine Naloxone) OR Buprenorphine OR Subutex OR Naloxone OR Suboxone OR Zubsolv OR Bunavail OR Sublocade OR Probuphine OR Methadone OR (Metabolic Inactivation) OR Detoxification OR Adanon OR Algidon OR Algolysin OR Algoxale OR Althose OR Amidon OR Amidona OR Amidone OR Amidosan OR (An 148) OR (An148) OR Anadon OR Biodone OR Butalgin OR Depridol OR Diaminon OR Dianone OR Dolamid OR Dolesone OR Dolmed OR Dolophine OR Dorex OR Dorexol OR Eptadone OR Fenadon OR Gobbidona OR Heptadon OR Heptanon OR (Hoe 10820) OR Hoe10820 OR Ketalgin OR Mecodin OR Mepecton OR Mephenon OR Metadol OR Metadon OR Metasedin OR Methaddict OR Methadon OR Methadose OR Methaforte OR Miadone OR Moheptan OR Pallidone OR Phenadon OR Physepton OR Physeptone OR Polamidon OR Polamivet OR Polamivit OR Sinalgin OR Symoron OR Westadone OR Win OR Methex OR Phenadone OR Phymet OR Antioplaz OR (En 1530) OR (En 15304) OR En1530 OR En15304 OR Evzio OR Maloxone OR Nalone OR Naloxon OR Naloxona OR Narcan OR Narcanti OR Narcon OR Narvcam OR Naxone OR Zynox OR (MRZ 2593) OR MRZ2593 OR (MRZ 2593Br) OR Anorfin OR Belbuca OR Buprenex OR Buprenorphine OR Buprex OR Buprine OR Butrans OR (Cl 112 302) OR (Cl 112302) OR (Cl112 302) OR (Cl112302) OR Finibron OR Lepetan OR (Nih 8805) OR (Nih8805) OR Norphin OR Pentorel OR Prefin OR Probuphine OR (Rx 6029 m) OR (Rx 6029m) OR Rx6029m OR Somnena OR Temgesic OR Transtec OR (Um 952) OR Um952) |
| Cochrane Central Register of Controlled Trials | (Pregnant OR Pregnancy OR Pregnancies OR Gestation OR Gravidity) AND (Opioid OR Opioids OR Opiate OR Heroin OR (Neonatal Abstinence Syndrome) OR (Neonatal Abstinence Syndromes) OR (Neonatal Withdrawal Syndrome) OR (Neonatal Withdrawal Syndromes) OR (Neonatal Substance Withdrawal) OR (Neonatal Substance Withdrawals) OR (Neonatal Passive Addiction) OR (Neonatal Passive Addictions)) AND ((Buprenorphine Naloxone) OR Buprenorphine OR Subutex OR Naloxone OR Suboxone OR Zubsolv OR Bunavail OR Sublocade OR Probuphine OR Methadone OR (Metabolic Inactivation) OR Detoxification OR Adanon OR Algidon OR Algolysin OR Algoxale OR Althose OR Amidon OR Amidona OR Amidone OR Amidosan OR (An 148) OR (An148) OR Anadon OR Biodone OR Butalgin OR Depridol OR Diaminon OR Dianone OR Dolamid OR Dolesone OR Dolmed OR Dolophine OR Dorex OR Dorexol OR Eptadone OR Fenadon OR Gobbidona OR Heptadon OR Heptanon OR (Hoe 10820) OR Hoe10820 OR Ketalgin OR Mecodin OR Mepecton OR Mephenon OR Metadol OR Metadon OR Metasedin OR Methaddict OR Methadon OR Methadose OR Methaforte OR Miadone OR Moheptan OR Pallidone OR Phenadon OR Physepton OR Physeptone OR Polamidon OR Polamivet OR Polamivit OR Sinalgin OR Symoron OR Westadone OR Win OR Methex OR Phenadone OR Phymet OR Antioplaz OR (En 1530) OR (En 15304) OR En1530 OR En15304 OR Evzio OR Maloxone OR Nalone OR Naloxon OR Naloxona OR Narcan OR Narcanti OR Narcon OR Narvcam OR Naxone OR Zynox OR (MRZ 2593) OR MRZ2593 OR (MRZ 2593Br) OR Anorfin OR Belbuca OR Buprenex OR Buprenorphine OR Buprex OR Buprine OR Butrans OR (Cl 112 302) OR (Cl 112302) OR (Cl112 302) OR (Cl112302) OR Finibron OR Lepetan OR (Nih 8805) OR (Nih8805) OR Norphin OR Pentorel OR Prefin OR Probuphine OR (Rx 6029 m) OR (Rx 6029m) OR Rx6029m OR Somnena OR Temgesic OR Transtec OR (Um 952) OR Um952) |
| PsycINFO | (Pregnant OR Pregnancy OR Pregnancies OR Gestation OR Gravidity) AND (Opioid OR Opioids OR Opiate OR Heroin OR (Neonatal Abstinence Syndrome) OR (Neonatal Abstinence Syndromes) OR (Neonatal Withdrawal Syndrome) OR (Neonatal Withdrawal Syndromes) OR (Neonatal Substance Withdrawal) OR (Neonatal Substance Withdrawals) OR (Neonatal Passive Addiction) OR (Neonatal Passive Addictions)) AND ((Buprenorphine Naloxone) OR Buprenorphine OR Subutex OR Naloxone OR Suboxone OR Zubsolv OR Bunavail OR Sublocade OR Probuphine OR Methadone OR (Metabolic Inactivation) OR Detoxification OR Adanon OR Algidon OR Algolysin OR Algoxale OR Althose OR Amidon OR Amidona OR Amidone OR Amidosan OR (An 148) OR (An148) OR Anadon OR Biodone OR Butalgin OR Depridol OR Diaminon OR Dianone OR Dolamid OR Dolesone OR Dolmed OR Dolophine OR Dorex OR Dorexol OR Eptadone OR Fenadon OR Gobbidona OR Heptadon OR Heptanon OR (Hoe 10820) OR Hoe10820 OR Ketalgin OR Mecodin OR Mepecton OR Mephenon OR Metadol OR Metadon OR Metasedin OR Methaddict OR Methadon OR Methadose OR Methaforte OR Miadone OR Moheptan OR Pallidone OR Phenadon OR Physepton OR Physeptone OR Polamidon OR Polamivet OR Polamivit OR Sinalgin OR Symoron OR Westadone OR Win OR Methex OR Phenadone OR Phymet OR Antioplaz OR (En 1530) OR (En 15304) OR En1530 OR En15304 OR Evzio OR Maloxone OR Nalone OR Naloxon OR Naloxona OR Narcan OR Narcanti OR Narcon OR Narvcam OR Naxone OR Zynox OR (MRZ 2593) OR MRZ2593 OR (MRZ 2593Br) OR Anorfin OR Belbuca OR Buprenex OR Buprenorphine OR Buprex OR Buprine OR Butrans OR (Cl 112 302) OR (Cl 112302) OR (Cl112 302) OR (Cl112302) OR Finibron OR Lepetan OR (Nih 8805) OR (Nih8805) OR Norphin OR Pentorel OR Prefin OR Probuphine OR (Rx 6029 m) OR (Rx 6029m) OR Rx6029m OR Somnena OR Temgesic OR Transtec OR (Um 952) OR Um952) |

*Link. Buprenorphine-naloxone use in pregnancy: a systematic review and metaanalysis. AJOG MFM 2020.* *(continued)*

**SUPPLEMENTAL TABLE**

**Systematic manual searches conducted to identify all relevant studies and trials** *(continued)*

| Database | Search strategy |
|---|---|
| Embase | ('Pregnant Women'/exp OR 'Pregnancy'/exp OR Pregnant OR Pregnancy OR Pregnancies OR Gestation OR Gravidity) AND ('Opiate'/exp OR Opioid OR Opioids OR Opiate OR Heroin OR 'Opiate Addiction'/exp OR 'Drug Dependence'/exp OR 'Neonatal Abstinence Syndrome'/exp OR (Neonatal Abstinence Syndrome) OR (Neonatal Abstinence Syndromes) OR (Neonatal Withdrawal Syndrome) OR (Neonatal Withdrawal Syndromes) OR (Neonatal Substance Withdrawal) OR (Neonatal Substance Withdrawals) OR (Neonatal Passive Addiction) OR (Neonatal Passive Addictions)) AND ('Buprenorphine Plus Naloxone'/exp OR 'Buprenorphine'/exp OR 'Naloxone'/exp OR 'Methadone'/exp OR (Buprenorphine Naloxone) OR Buprenorphine OR Subutex OR Naloxone OR Suboxone OR Zubsolv OR Bunavail OR Sublocade OR Probuphine OR Methadone OR (Metabolic Inactivation) OR Detoxification OR Adanon OR Algidon OR Algolysin OR Algoxale OR Althose OR Amidon OR Amidona OR Amidone OR Amidosan OR (An 148) OR (An148) OR Anadon OR Biodone OR Butalgin OR Depridol OR Diaminon OR Dianone OR Dolamid OR Dolesone OR Dolmed OR Dolophine OR Dorex OR Dorexol OR Eptadone OR Fenadon OR Gobbidona OR Heptadon OR Heptanon OR (Hoe 10820) OR Hoe10820 OR Ketalgin OR Mecodin OR Mepecton OR Mephenon OR Metadol OR Metadon OR Metasedin OR Methaddict OR Methadon OR Methadose OR Methaforte OR Miadone OR Moheptan OR Pallidone OR Phenadon OR Physepton OR Physeptone OR Polamidon OR Polamivet OR Polamivit OR Sinalgin OR Symoron OR Westadone OR Win OR Methex OR Phenadone OR Phymet OR Antioplaz OR (En 1530) OR (En 15304) OR En1530 OR En15304 OR Evzio OR Maloxone OR Nalone OR Naloxon OR Naloxona OR Narcan OR Narcanti OR Narcon OR Narvcam OR Naxone OR Zynox OR (MRZ 2593) OR MRZ2593 OR (MRZ 2593Br) OR Anorfin OR Belbuca OR Buprenex OR Buprenorphine OR Buprex OR Buprine OR Butrans OR (Cl 112 302) OR (Cl 112302) OR (Cl112 302) OR (Cl112302) OR Finibron OR Lepetan OR (Nih 8805) OR (Nih8805) OR Norphin OR Pentorel OR Prefin OR Probuphine OR (Rx 6029 m) OR (Rx 6029m) OR Rx6029m OR Somnena OR Temgesic OR Transtec OR (Um 952) OR Um952) |
| Web of Science All Databases (including KCI-Korean Journal Database, Russian Science Citation Index, and SciELO Citation Index) | (Pregnant OR Pregnancy OR Pregnancies OR Gestation OR Gravidity) AND (Opioid OR Opioids OR Opiate OR Heroin OR (Neonatal Abstinence Syndrome) OR (Neonatal Abstinence Syndromes) OR (Neonatal Withdrawal Syndrome) OR (Neonatal Withdrawal Syndromes) OR (Neonatal Substance Withdrawal) OR (Neonatal Substance Withdrawals) OR (Neonatal Passive Addiction) OR (Neonatal Passive Addictions)) AND ((Buprenorphine Naloxone) OR Buprenorphine OR Subutex OR Naloxone OR Suboxone OR Zubsolv OR Bunavail OR Sublocade OR Probuphine OR Methadone OR (Metabolic Inactivation) OR Detoxification OR Adanon OR Algidon OR Algolysin OR Algoxale OR Althose OR Amidon OR Amidona OR Amidone OR Amidosan OR (An 148) OR (An148) OR Anadon OR Biodone OR Butalgin OR Depridol OR Diaminon OR Dianone OR Dolamid OR Dolesone OR Dolmed OR Dolophine OR Dorex OR Dorexol OR Eptadone OR Fenadon OR Gobbidona OR Heptadon OR Heptanon OR (Hoe 10820) OR Hoe10820 OR Ketalgin OR Mecodin OR Mepecton OR Mephenon OR Metadol OR Metadon OR Metasedin OR Methaddict OR Methadon OR Methadose OR Methaforte OR Miadone OR Moheptan OR Pallidone OR Phenadon OR Physepton OR Physeptone OR Polamidon OR Polamivet OR Polamivit OR Sinalgin OR Symoron OR Westadone OR Win OR Methex OR Phenadone OR Phymet OR Antioplaz OR (En 1530) OR (En 15304) OR En1530 OR En15304 OR Evzio OR Maloxone OR Nalone OR Naloxon OR Naloxona OR Narcan OR Narcanti OR Narcon OR Narvcam OR Naxone OR Zynox OR (MRZ 2593) OR MRZ2593 OR (MRZ 2593Br) OR Anorfin OR Belbuca OR Buprenex OR Buprenorphine OR Buprex OR Buprine OR Butrans OR (Cl 112 302) OR (Cl 112302) OR (Cl112 302) OR (Cl112302) OR Finibron OR Lepetan OR (Nih 8805) OR (Nih8805) OR Norphin OR Pentorel OR Prefin OR Probuphine OR (Rx 6029 m) OR (Rx 6029m) OR Rx6029m OR Somnena OR Temgesic OR Transtec OR (Um 952) OR Um952) |

*Link. Buprenorphine-naloxone use in pregnancy: a systematic review and metaanalysis. AJOG MFM 2020.*