Buprenorphine: A Better Option for Opioid Use Disorder Treatment in Pregnancy Compared to Methadone

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Buprenorphine, rather than methadone, should be considered the preferred first-line therapy for opioid use disorder in pregnancy due to its more favorable neonatal outcomes.[1] (J Am Board Fam Med 2025;38:188–191.)

Keywords: **Buprenorphine, Methadone, Opioid Overdose, Opioid-Related Disorders, Prenatal Care**

Strength of Recommendation: B

Based on a retrospective cohort study.[1]

Illustrative Case

A 34 year old nulliparous patient with a past medical history of unintentional opioid overdose, currently in her 16th week of pregnancy, presents for her initial prenatal care and wishes to discuss treatment options for her opioid use disorder. Should buprenorphine be considered the preferred first-line treatment option over methadone for opioid use disorder treatment in pregnancy?

Clinical Context

Opioid use disorder (OUD) diagnosed by a pattern of opioid use characterized by tolerance, craving, and uncontrolled and continued use despite adverse effects has substantially increased among pregnant people in the United States.[2,3] The national rate of maternal OUD at delivery increased from 1.1 to 6.5 per 1000 hospital deliveries between 2000 and 2014.[3] Further, opioid exposure in pregnancy is linked to unfavorable maternal and neonatal outcomes.[4] Between 2000 and 2014, the neonatal abstinence syndrome (NAS) rate secondary to prenatal opioid exposure, increased from 1.2 to 8.0 per 1000 hospital births resulting in a longer hospital length of stay and higher estimated mean health care cost.[3]

The American College of Obstetrics and Gynecologists recommends early universal screening of pregnant women for OUD and referral for treatment with an opioid agonist medication to improve maternal and newborn outcomes.[5] Methadone and buprenorphine are the 2 medications for OUD with the highest efficacy for reducing opioid use and, subsequently, opioid-related mortality.[6] Methadone has historically been the preferred first-line treatment due to increased treatment supervision at opioid treatment programs, also known as methadone clinics, and retention rate.[5,7]

Emerging evidence suggests that buprenorphine, while as effective as methadone for OUD treatment, is associated with better neonatal outcomes, and may be more cost-effective over time.[1,7] A systematic review and meta-analysis of 18 studies (n = 2146) that compared safety of methadone to buprenorphine in the treatment of OUD in pregnancy concluded buprenorphine was associated with lower risk of preterm birth, greater birth weight, and larger head circumference. Although, there were no

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differences in fetal death, congenital anomalies, or other measures of fetal growth.[8] A different systematic review and meta-analysis of 20 studies (n = 7251) that compared the effect of buprenorphine and methadone in pregnancy on maternal and neonatal outcome found that buprenorphine was consistently associated with improved birth weight and increased gestational age.[9] Finally, in a population-based retrospective cohort study among pregnant women (n = 400), prenatal methadone early (0 to 20 weeks) and late (≥20 weeks) exposure was associated with a substantially higher risk of preterm birth (<37 gestational weeks), low birth weight, neonatal intensive care unit admissions, and extended maternal hospital stay >7 days compared with buprenorphine.[10] Although the evidence suggests that buprenorphine may improve neonatal outcomes, the studies had limited sample sizes or were not fully controlled for potential confounders over time to make significant practice changes.

Methods

This article was identified as a potential PURL through the standard systematic methodology.[22] An additional literature search was conducted by searching PubMed with the terms buprenorphine, methadone, OUD, and pregnancy to find additional literature to place this research into the context of current clinical practice.

Study Summary

This retrospective cohort study investigated the neonatal and maternal outcomes of buprenorphine treatment compared with methadone treatment for opioid use disorder (OUD) during pregnancy among women who were enrolled in the United States Medicaid insurance programs between 2000 and 2018.[1] Pregnancies were included in the study if they resulted in a live birth in women ages 12 to 55 years, and had Medicaid insurance 3 months before their last menstrual period (LMP) and 1 month after delivery, and had Medicaid-insured infants through 3 months after delivery (or until death if death occurred before 3 months of age). Pregnant women who received both medications at some point from 90 days before their LMP through the end of the exposure window were excluded. Buprenorphine and methadone exposure during the study period was determined through medication dispensing data. Exposure was defined as having occurred within the 30 days preceding delivery to analyze neonatal abstinence syndrome. For other outcomes, exposure was defined as having occurred in early pregnancy (from LMP through 19 weeks of pregnancy), or late pregnancy, (from 20 weeks of pregnancy through the day before delivery). For preterm birth, exposure during late pregnancy was evaluated until 36 weeks of pregnancy. Neonatal outcomes included neonatal abstinence syndrome, preterm birth, small size for gestational age [SGA], and low birth weight [LBW], while maternal outcomes included cesarean section delivery and severe maternal complications, such as a composite of potentially life-threatening conditions caused or aggravated by pregnancy and were ascertained at delivery or 30 days postpartum.[1]

The study included pregnant women who received buprenorphine (n = 10,704) or methadone (n = 4,387), the majority of whom were white, and approximately 28 years old. The occurrence of neonatal abstinence syndrome was lower with buprenorphine exposure (52%, n = 5,188) compared with methadone exposure (69.2%, n = 3,182) 30 days before delivery (adjusted relative risk [aRR], 0.73; 95% CI, 0.71–0.75). In early pregnancy exposure, preterm births occurred at 14.4% in buprenorphine versus 24.9% in methadone (aRR, 0.58; 95% CI, 0.53–0.62), SGA occurred at 12.1% in buprenorphine versus 15.3% in methadone exposure (aRR, 0.72; 95% CI, 0.66–0.8), and LBW occurred at 8.3% in buprenorphine versus 14.9% in methadone exposure (aRR 0.56; 95% CI, 0.5–0.63). These inverse associations were similar in late pregnancy exposure as well.

Maternal outcomes were comparable in both buprenorphine and methadone groups. Cesarean section delivery occurred in 33.6% of pregnancies exposed to buprenorphine in early pregnancy versus 33.1% of those exposed to methadone (aRR, 1.02; 95% CI, 0.97–1.08), and severe maternal complications developed in 3.3% of pregnancies exposed to buprenorphine versus 3.5% of those exposed to methadone (aRR, 0.91; 95% CI, 0.74–1.13).

What Is New

Although previous studies implied that buprenorphine, when compared with methadone, may be associated with more favorable maternal and neonatal outcomes, the existing data were limited to support this evidence. This study shows substantial evidence that buprenorphine

effectively treats OUD in pregnancy and is associated with a lower risk of adverse neonatal outcomes than methadone.

Caveats

This study only included pregnant patients enrolled in public Medicaid insurance programs, potentially limiting its applicability to those with private insurance or underinsured with a history of OUD. In addition, there were notable characteristic differences between the 2 groups. For example, pregnant women in the buprenorphine group were more likely to be white, which may have positively biased pregnancy outcomes.[11] However, the prevalence of coexisting conditions, and, opioid-related complications were similar across the groups.

The study did not account for lifestyle and behavioral factors during the pregnancy, which could have confounded the study results. However, propensity-score overlap weights were used to adjust for confounders in the maternal and neonatal outcomes risk ratios. In addition, there was no comparison of dose amounts between methadone and buprenorphine or medication dose adjustment, as the dosing for methadone was unavailable. Hence, assessment for dose equivalence effect was not possible.

Although buprenorphine is associated with better neonatal outcomes and should be considered first-line treatment for OUD in pregnancy, some patients may have buprenorphine intolerance or prefer methadone.[12] Hence, treatment recommendations should be patient-centered and depend on patient preference, medication tolerability, and availability.[13]

Challenges to Implementation

Due to a lack of well-trained, qualified clinicians and clinic staff to provide service, patients' ability to access buprenorphine for OUD remains a challenge, particularly in rural areas.[14] A 2020 study suggested that only 2.2% of the 545,723 Medicare Part D outpatient primary care clinicians between 2013 and 2016 were buprenorphine prescribers.[15]

The removal of the Drug Addiction Treatment Act of 2000 (DATA) waiver (X-waiver) requirement in the 2023 Omnibus bill is promising because it removes bureaucratic access barriers.[16] However, it remains to be seen how prescribing rates will evolve considering this change.

In addition, the use of buprenorphine, a partial mu-opioid receptor agonist, has become increasingly challenging due to the rising prevalence of illegally manufactured fentanyl, which has a significantly higher potency than heroin and morphine.[13,17] This poses a significant barrier to treatment as buprenorphine doses need to be higher in the era of synthetic opioids to alleviate severe opioid cravings or varying induction practices to avoid precipitating withdrawal symptoms in these patients.[13,17] However, there are reasons to believe that buprenorphine initiation and retention rates could improve by providing prescribing guidelines concerning effective doses of buprenorphine.[18,19] In patients who prefer buprenorphine over methadone treatment for OUD, clinicians should provide education regarding the need to initiate treatment after exhibiting clinical withdrawal symptoms, to prevent precipitated withdrawal during pharmacotherapy induction.[20] In addition, pregnant patients already receiving methadone therapy should not routinely transition to buprenorphine because of the unpleasant and undesirable precipitated withdrawal risk.[5]

Lastly, the cost of buprenorphine compared with methadone is often higher and might create a significant access barrier for patients without health insurance. The out-of-pocket price for the lowest dose of buprenorphine is approximately $1.3 to $2.5 per day compared with methadone which is approximately $0.5 to $0.8 per day.[21] However, in the long-term, buprenorphine treatment during pregnancy is more cost-effective, saving more than $102 million in health care dollars as well as 563 quality-adjusted life-year.[7]

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