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Buprenorphine/suboxone is safe in pregnancy: substance use and stigma in the healthcare professions

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ABSTRACT A clinical decision report using:

Mullins N, Galvin SL, Ramage M, et al. Buprenorphine and Naloxone Versus Buprenorphine for Opioid Use Disorder in Pregnancy: A Cohort Study. *J Addict Med.* 2020;14(3):185-192. https://doi.org/10.1097/ADM.0000000000000562

for a woman with opioid use disorder during pregnancy.

Keywords: *buprenorphine, naloxone, suboxone, opioid use disorder, pregnancy, stigma, withdrawal, mental health*

Clinical-Social Context

"Tammy Eldrige" is a 33-year-old woman with a medical history of opioid use disorder (OUD), depression, anxiety, hearing loss with cochlear implant, intrauterine pregnancy at 21 weeks and 1 day, by 11-week ultrasound, who presented to a hospital in Tennessee for treatment of opioid withdrawal during pregnancy. She reported a history of misusing medications from her job as a veterinary technician, which included oxycodone, propofol, and benzodiazepines. She also reported previous heroin and methamphetamine use and said she had used substances for over a decade. She said that her substance use would help her to escape from her anxiety. She reported inconsistent engagement with mental health services, including hospitalization for a suicide attempt by cutting in 2020. She said that when she found out she was pregnant, she attempted to discontinue use of all substances, in order to "keep my baby safe." She said she was able to abstain from substance use with the exception of opioids, saying that she would have "psychological withdrawals." Through her own internet research, she read that buprenorphine was the safest opioid to take during pregnancy and she started using intravenous buprenorphine from her veterinary clinic. She reported using about 0.3mg intravenous buprenorphine daily, with her last use the day prior to hospital admission.

When I first met Ms. Eldridge, she was anxious-appearing. She told me she was afraid someone in her life would find out about her use and that she felt uncomfortable in the hospital setting. She said she continued to hide her use of buprenorphine from her employer and those close to her, and that she was afraid she would lose her job if anyone found out she was misusing medications from her clinic. Her stated goals were to "get through detox" and to no longer use opioids. I assured her that I would not disclose any information about her substance use history to her employer or law enforcement, which she said was a significant relief. I asked her if she would be interested in taking medication for OUD and she was amenable. We discussed outpatient follow-up planning, and she expressed concern that it may be difficult to attend appointments, given the distance from her residence and the need to take time off work. Typically, buprenorphine as a mono-product or methadone are preferred treatments for OUD

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in pregnancy.[1] Given her history of intravenous buprenorphine use, she worried about the temptation to misuse the medication intravenously. For methadone, she did not believe she would be able to attend daily appointments at a methadone clinic with her work schedule.

Buprenorphine/naloxone is a preferred agent for the treatment of opioid use disorder in non-pregnant patients, as the naloxone component makes the medication less likely to be misused intravenously.[2-4] Currently, buprenorphine/naloxone is less commonly administered in pregnancy, as this combination product was introduced after many of the pregnancy safety trials were performed using the buprenorphine monoproduct.[5-7] There is also a theoretical concern that the naloxone component could precipitate a withdrawal state that would harm the fetus, though when taken sublingually, systemic levels are low.[8,9] The concern for opioid withdrawal causing fetal harm, such as miscarriage, appears to be based primarily on older case reports from the 1970's, and buprenorphine or naloxone were not used in any of the reports.[10-12] Through conversations with other providers, I was informed that more recent studies suggest buprenorphine/naloxone is safe in pregnancy, and I wanted to further investigate.

I spoke with the other members of the Addiction Consult Team about Ms. Eldridge's case. Given that she expressed an inability to attend daily methadone appointments, we thought buprenorphine monoproduct or buprenorphine/naloxone would be the best treatment options for her OUD. We agreed that the buprenorphine monoproduct would carry a higher risk of misuse, as she had been misusing buprenorphine prior to admission. The other team members acknowledged that buprenorphine/naloxone is most likely safe in pregnancy, while also expressing apprehension about ordering buprenorphine/naloxone for a pregnant patient, as it deviates from convention. I informed the team that I would review the relevant literature on the topic and report back to them.

I explained to Ms. Eldrige that the buprenorphine/naloxone medication is less commonly given during pregnancy for the theoretical concern of precipitating opioid withdrawal, which may adversely affect her pregnancy. I informed her that treatment with buprenorphine monoproduct, and buprenorphine/naloxone carry a risk of her child experiencing neonatal abstinence syndrome (NAS), and that the condition is commonly treated during a short neonatal intensive care unit course.[6,7] Ultimately, both Ms. Eldrige and I agreed that buprenorphine/naloxone would be the preferred treatment for her OUD. I told her that I would speak with other physicians on the Addiction Consult Team and review the relevant literature on the topic. If the literature suggests safety during pregnancy, we would proceed with induction of buprenorphine/naloxone for her opioid use disorder. She was amenable to this plan.

Clinical Question

Is buprenorphine/naloxone a safe and effective alternative to buprenorphine monoproduct during pregnancy?

Research Article

Mullins N, Galvin SL, Ramage M, et al. Buprenorphine and Naloxone Versus Buprenorphine for Opioid Use Disorder in Pregnancy: A Cohort Study. *J Addict Med.* 2020;14(3):185-192. https://doi.org/10.1097/ADM.0000000000000562 [13]

Description of Related Literature

A literature search was performed using the Pubmed database. A search was built using the terms "pregnan*", "infant, newborn [mesh]", and "buprenorphine, naloxone drug combination [MeSH Terms] ". The combined search term, "(pregnan* OR "Infant, Newborn"[Mesh]) AND ("buprenorphine, naloxone drug combination"[MeSH Terms] OR buprenorphine naloxone[Text Word] OR "buprenorphine and naloxone")" produced 50 results. After screening by title and abstract, 13 articles were selected for further review. An additional two articles were identified from citations in the reviewed manuscripts for a total of 15 articles. Of these, three were systematic reviews, and 12 were original research studies. Supplemental information was obtained from articles cited by the reviewed studies, PubMed and Google searches, and previous publications in *Clinical Research in Practice*.

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A systematic review of and meta-analysis by Link, et al. compared pregnancy outcomes for patients with OUD that were treated with buprenorphine/naloxone to other forms of medications for opioid use disorder (MOUD).[14] Based on the five studies selected for analysis, the authors concluded that there is no difference in neonatal or pregnancy outcomes in patients taking buprenorphine/naloxone compared to other forms of MOUD. Another systematic review and meta-analysis by Ordean, et al. published in 2023 found no increase in adverse neonatal outcomes between methadone, buprenorphine monotherapy, and buprenorphine/naloxone in the analysis of seven selected studies.[15] Additionally, lower rates of NAS requiring pharmacotherapy were found in buprenorphine/naloxone exposed groups compared to methadone. An additional review article by Lund, et al. concluded that there appears to be no difference in maternal or neonatal outcomes, though only one observational study involving buprenorphine/naloxone in pregnancy was cited.[16] These articles were not selected as they are review articles and not original research. All studies incorporated into these reviews were identified in the literature search and are described in greater detail in this section.

Debelek et al. performed a small, retrospective chart review in 2010 of 10 pregnant patients treated with buprenorphine/naloxone.[17] No adverse maternal outcomes were appreciated and 40% of neonates experienced NAS, which the authors describe as comparable to other forms of MOUD. Another retrospective chart review by Nguyen observed 26 mother-infant dyads in West Virginia that were exposed to burpenorphine/naloxone in pregnancy showing a lower rate of NAS (19%).[18] Higher doses of buprenorphine were significantly positively associated with gestational age and neonatal length. These studies were not selected as they were purely observational and did not have a comparator group.

A Finnish cohort study from 2023 by Kanervo, et al. observed 67 mother-infant dyads with OUD who were treated with methadone, buprenorphine, or buprenorphine/naloxone.[19] Newborns in the methadone group were found to have significantly greater severity of NAS and were smaller compared to the combined buprenorphine and buprenorphine/naloxone groups. Urinary tract abnormalities were found in two of the neonates exposed to buprenorphine/naloxone. This study was not selected because of its relatively small sample size, and differences in baseline demographics of study groups that were not controlled and may have biased results.

Nechanská, et al. was a retrospective cohort study that compared infants born to mothers treated with methadone, buprenorphine, or buprenorphine/naloxone in the Czech Republic and Norway.[20] Buprenorphine exposed neonates were found to have marginally more favorable outcomes than those exposed to methadone, though no significant differences were observed between the three exposure groups. This study was not selected as it sought primarily to compare methadone and buprenorphine, and the number of neonates exposed to buprenorphine/naloxone in utero was relatively small. The study also did not address maternal outcomes.

A 2022 retrospective cohort study by Perry et al. retrospectively compared 106 mother-infant dyads, 73 of which received buprenorphine treatment and 33 of which received buprenorphine-naloxone.[10] Mothers taking buprenorphine-naloxone were found to have a greater rate of return to use compared to mothers taking buprenorphine monoproduct and infants exposed to buprenorphine-naloxone in utero were less likely to receive pharmacological treatment for NAS. These differences were not statistically significant. No significant differences in secondary neonatal outcomes were observed. This study was not selected because of its relatively small sample size, which likely rendered it underpowered.

A retrospective cohort study of mother-infant dyads in remote Northwestern Ontario, Canada compared 62 women who had been exposed to buprenorphine/naloxone during pregnancy to 855 women who had no opioid exposure during pregnancy and 159 women who had used non-prescribed opioids during pregnancy.[21] The study found no significant difference in rate of congenital malformations, stillbirth, or low birth weight between mothers who were exposed to buprenorphine-naloxone. Another Canadian study by Dooley, et al. compared outcomes of 30 maternal-neonatal dyads exposed to buprenorphine/naloxone to 134 dyads exposed to other opioids (non-MOUD), and 476 dyads that were not exposed to any opioids.[22] NAS was observed at a higher rate in the buprenorphine/naloxone and other opioid groups compared to non-exposed neonates. Additionally, lower birth weight was observed in neonates exposed to other opioids compared to buprenorphine. Otherwise, no differences in adverse maternal or neonatal outcomes were observed between the groups. These studies were not selected because they did not compare buprenorphine/naloxone to other forms of MOUD.

Four of the reviewed articles were retrospective cohort studies that compared buprenorphine/naloxone to methadone in pregnant women and exposed neonates.[23-26] Sample sizes ranged from 62 to 232 mother-neonate dyads. No significant differences in

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maternal outcomes were observed between the buprenorphine and methadone groups. All four studies found a lower rate of NAS in the buprenorphine/naloxone exposed groups compared to the methadone groups. These studies were not selected because they did not have a buprenorphine monoproduct comparison group.

Ultimately, a retrospective cohort study by Mullins, et al. comparing mother-infant dyads exposed to buprenorphine monoproduct and buprenorphine/naloxone was selected.[13] This study was selected because it directly compared buprenorphine monoproduct to buprenorphine/naloxone cohorts, included both maternal and neonatal outcomes, had a relatively large sample size compared to other studies, and had a study population from a similar geographic region to Ms. Eldridge. As a high quality cohort study, this research meets Level 2 study quality, based on SORT Taxonomy.[27] With a high level of consensus among multiple cohort studies, the SORT strength of recommendation is "A".

Critical Appraisal

Mullins, et al. was a retrospective cohort study that compared maternal-infant dyads receiving buprenorphine monoproduct to those taking buprenorphine/naloxone.[13] Data was collected through a chart review of all pregnant women who attended a community-based obstetrics and gynecology residency clinic in Western North Carolina and were prescribed buprenorphine monoproduct or buprenorphine/naloxone from 2014-2018. The decision to treat with buprenorphine monoproduct or buprenorphine naloxone was at the discretion of the provider. At this clinic, buprenorphine/naloxone was the preferred treatment modality for OUD in pregnancy. Patients were treated with buprenorphine monoproduct if they were already stable on this medication or reported adverse reactions to the combination product. Women who changed treatment modalities during pregnancy or had non-singleton pregnancies were excluded.

The primary outcome of this study was the incidence of NAS. Secondary neonatal outcomes included birth weight, length, head circumference, 5-minute Apgar score, congenital abnormality diagnosis, NICU admission, appropriate umbilical cord blood toxicology, hospital length of stay, and 30-minute hospital readmission. Secondary maternal outcomes included appropriate findings on urine drug screen at delivery, obstetrical care attendance, primary cesarean delivery, preterm delivery (<37 weeks gestation), and breastfeeding status.

A total of 241 women were treated with buprenorphine/naloxone or buprenorphine monoproduct during the study period. Three patients were excluded for non-singleton pregnancies, and 15 patients were excluded because they changed MOUD during pregnancy. 14 patients in the buprenorphine/naloxone group and 19 patients in the buprenorphine monoproduct group did not deliver at the local hospital and were also excluded. After exclusion, 108 maternal-infant dyads receiving buprenorphine monoproduct and 85 receiving buprenorphine/naloxone were included in the final analysis. The women in the both cohorts were predominantly white with an average age (in years) of 27.5 ± 4.4 in the buprenorphine monoproduct group and 28.0 ± 4.6 in the buprenorphine/naloxone group. The proportion of women prescribed buprenorphine/naloxone was greater among those treated at the residency program compared to other providers. Women treated with buprenorphine/naloxone had a lower average buprenorphine dose than women taking buprenorphine monoproduct. Otherwise, no significant demographic differences were noted between the two groups.

The rate of NAS was significantly lower among infants exposed to buprenorphine/naloxone (35.3%) compared to buprenorphine monoproduct (54.6%). Adjusting for dose of buprenorphine product at delivery, year of expected delivery, prescriber type, hepatitis C diagnosis, and preterm delivery, buprenorphine/naloxone was not associated with significantly lower odds of NAS compared to buprenorphine monoproduct (OR 0.627, 95% CI 0.309 - 1.275). Significantly more mothers in the buprenorphine monoproduct cohort developed gestational hypertension (11.8%), compared to the buprenorphine/naloxone cohort (2.0%). Otherwise, no other statistically significant differences in maternal or neonatal outcomes were observed between groups.

Overall, the study appears to be a well-designed retrospective cohort study. This study had a relatively large sample size compared to other studies investigating buprenorphine/naloxone in pregnancy and the two cohorts appeared to be comparable in demographic characteristics. Patients in this trial appeared to be similar to Ms. Eldrige in age, race, and geographic location in the American Southeast. Limitations of this study include those inherent to retrospective cohort studies, such as confounding variables not controlled for by randomization. While larger than similar studies on the topic, the sample size remains relatively small compared to more robust drug trials and may have rendered the study underpowered and unable to detect rarer treatment

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complications. Additionally, this study was also conducted prior to fentanyl becoming more prevalent in the drug supply, which may have impacted results.

Clinical Application

Physicians are often tasked with making the best clinical decision for their patient without the clarity of a large randomized control trial for every clinical question. For this case, the best available studies were retrospective cohort studies, which is not uncommon for research investigating medication effects in pregnancy. The findings of the Mullins study suggest that buprenorphine/naloxone is no more harmful to mothers and infants than buprenorphine monoproduct, and had a similar rate of successful OUD treatment. Additionally, none of the 14 other reviewed articles demonstrated evidence of worse maternal or neonatal outcomes for those treated with buprenorphine/naloxone compared to buprenorphine monoproduct.[10,14-26] Some studies also suggested lower risk of NAS in neonates exposed to buprenorphine/naloxone compared to methadone.[15,19,23-26] Recently, Health Canada removed pregnancy as a contraindication for buprenorphine/naloxone after reviewing many of the aforementioned studies.[28] A sufficiently powered, multi-center, randomized control trial would be helpful in providing more definitive evidence to guide practice. Until such a study is conducted, physicians can refer to the available body of evidence and create treatment plans that are catered to each individual patient's situation.

After reviewing the available evidence, I explained to Ms. Eldridge that, based on the available evidence, buprenorphine/naloxone appears to be as safe as other first line treatments for OUD in pregnancy. Using shared decision making with Ms. Eldrige and other members of the Addiction Consult Team, all parties ultimately agreed that buprenorphine/naloxone would be the best treatment for her OUD. It was surmised that buprenorphine/naloxone has a similar safety profile to buprenorphine monoproduct, would reduce her risk of returning to non-prescribed opioid use, and would have less misuse potential than buprenorphine monoproduct. She agreed and was started on buprenorphine/naloxone 2mg/0.5mg every one hour, with a maximum total daily dose of 12mg the first day, in order to determine appropriate dosing. She was given a total of 8mg/2mg buprenorphine/naloxone on day one. She showed signs of mild sedation, so further doses were not given. When I saw her the next day, she said she felt significantly less anxious and was grateful that she chose to get help. She was continued on buprenorphine/naloxone 4mg/1mg twice daily.

I saw Ms. Eldrige at the Recovery Clinic one week after hospital discharge. She reported doing well overall and continued to take buprenorphine/naloxone. She said she was still grateful she chose to come to the hospital. She reported no return to use since hospital discharge, with the exception of smoking marijuana one time. I told her that I would not judge her for her one-time marijuana use, and provided affirmation for abstaining from opioid use and continuing to seek care. Initially, she expressed concern about her ability to make appointments because of the distance to the hospital and the need to take off work, but said her job had been supportive. She told her employer that the appointments were pregnancy related, but did not disclose that they were related to substance use, out of fear of repercussions.

New Knowledge Related to Clinical Decision Science

In addition to the incorporation of clinical research to create an individualized care plan for Ms. Eldrige, this case required both the patient and physician to navigate a complex social situation. One of the key underlying questions in her case is, "why did she not get help for her substance use earlier?" She reported years of substance use that placed her at risk of job loss and legal action. It was not until she became pregnant and, out of concern for her unborn child, she finally sought treatment. When I asked her why she was so reluctant to get help, she expressed fear of employment termination and the judgment she would face surrounding her use. She was determined to protect her baby and, at the same time, so hesitant to get help, that she researched how to best treat her condition and was self-administering treatment taken from her workplace.

Ms. Eldridge is now able to take medication that helps her refrain from full-agonist opioid use. Creating a supportive environment is helpful in facilitating the care of patients with substance use disorders (SUD). In caring for her, I was intentional about using non-stigmatizing language. I asked her if she had, "any return to substance use," rather than, "did you relapse?," and I tried not to shame

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her for taking medications from her employer. Had a more punitive approach been taken by her obstetrician or hospital care team hospital, it is possible that she would have decided to no longer seek treatment, placing her at higher risk for employment termination, overdose, and incarceration - all of which would be detrimental to her and her child. She and her baby are in a much safer situation now. So why does our healthcare culture make it so daunting to get treatment?

Fear of being reported presents a substantial barrier for those with SUD's to seek treatment. Not long after caring for Ms. Eldridge, I was speaking with a nurse sitting next to me on a plane. She told me about her previous struggle with morphine addiction. She relayed how she was afraid to seek help because of the professional repercussions. She told me that if her Nursing Board had found out she had a substance use disorder, they would permanently flag her license for any employer to see. It wasn't until she was at dinner with another nurse who told the waiter "No wine for me, I'm in recovery," that she realized she wasn't alone and decided to pursue treatment. "I knew my addiction was going to kill me," she said. "But I was too afraid to get help."

Working in the field of Addiction Medicine, I have quickly learned that substance use can affect anyone. It is estimated that 10-15% of healthcare workers who have misused substances during their career. Among physicians, 14% meet criteria for an alcohol use disorder, and 6-8% meet criteria for another SUD.[29] How often do we as healthcare providers look to the nurse, the tech, the doctor next to us and not know that they are struggling with a SUD? Moreover, how often do we realize our colleagues need help, but we feel we are unable to address the situation? If one of our co-workers were doubled over with abdominal pain, we would recommend they seek medical attention without hesitation. But if we suspect they have a SUD, we pause: Is it the fear of having an uncomfortable conversation? Not wanting to jeopardize that person's career? Or maybe viewing it as "their problem" and not wanting to intervene? It is no small task. It is a deeply personal condition, and the societal and professional stigma that is placed on substance use makes taking steps to help our colleges all the more difficult. Attempts to address substance use should come from a place of compassion and refrain from judgment.[30] All fifty states have physician treatment programs, and contacting the state medical society can be a good first step to familiarize oneself with available treatment options.[29]

In addition to my fellowship training in Addiction Medicine, I am also a practicing Emergency Medicine Physician. In my experience, it is not uncommon for healthcare workers to view patients with substance use disorders as "difficult" or "unworthy." The provider-patient relationship can become adversarial, causing patients to experience iatrogenic trauma and increasing their apprehension to seek care.[31-34] As physicians, we are not judges, we are not law enforcement. We are healers. By taking a compassionate approach, familiarizing myself with treatments and resources for SUD's, and treating each patient as a unique individual going through a powerful human experience, I am now able to see these patients as opportunities for change. Not only has this approach benefited my patients, it has allowed me to take greater joy in my work. When I talk to other providers who take a similar stance to patients with substance use disorders, they have consistently echoed my sentiments about improved career satisfaction. Any healthcare provider can take this approach as long as they are open to it. My experience caring for Ms. Eldridge affirmed this mentality for me. There is a certain beauty in working with another person who is afraid of being looked down upon, treating them with compassion, and helping them to change their life for the better. It is worth pursuing.

Conflict Of Interest Statement

The author declares no conflicts of interest.

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