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Successful Buprenorphine/Naloxone Low-dose Induction in Pregnancy: A Case Report

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Background: Medication for opioid use disorder (OUD) with methadone or buprenorphine/naloxone is recommended for pregnant women with OUD. Traditional buprenorphine/naloxone induction requires patients to be in moderate withdrawal before the first dose of medication to minimize the chances of precipitated withdrawal. The low-dose buprenorphine "microinduction" (Bernese) method was described in 2016 and involves giving small doses of buprenorphine to patients for whom opioid withdrawal was not desirable. This method is being used widely in Vancouver in the context of high rates of overdose due to fentanyl poisoning.

Case Presentation: A 24-year-old woman, in her first pregnancy, with severe opioid and stimulant use disorder successfully started on buprenorphine/naloxone through a low-dose-induction protocol. The dose was started at 0.5 mg sublingual daily and slowly increased to 18 mg over 17 days. She continued to use fentanyl/heroin during the induction. She did not experience precipitated withdrawal and was able to stop using nonprescribed opioids once at a therapeutic dose of buprenorphine/naloxone.

Discussion: This represents the first documented case of successful buprenorphine/naloxone low-dose induction in pregnancy. First-line recommendations still remain to use traditional buprenorphine/naloxone induction when patients present in withdrawal. Obtaining informed consent regarding the lack of research on low-dose induction in pregnancy as well as discussion of risks and benefits is essential.

Conclusion: Low-dose induction with buprenorphine/naloxone was successfully done in an outpatient setting. This represents a novel way of initiation of medication for OUD, which may enhance choice and collaboration between health care providers and women impacted by substance use in pregnancy.

Key Words: buprenorphine/naloxone, low-dose induction, microinduction, pregnancy

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The use of nonprescribed opioids during pregnancy has been associated with adverse maternal, neonatal, and obstetric outcomes,[1] and for many women, pregnancy represents an enhanced time of motivation for cessation or reduction of substance use.[2,3] Medication for opioid use disorder (MOUD), also known as opioid agonist therapy, is the recommended treatment[4–6] for opioid use disorder. Although methadone has traditionally been used, buprenorphine/naloxone has evidence of safety[7] and is now considered an alternate first-line agent.[5] Although access to MOUD varies widely across different communities in Canada, both methadone and buprenorphine/naloxone are widely available in Vancouver where the low-dose induction described in this case report took place.[8]

Infants of individuals taking buprenorphine may require less intense treatment for neonatal abstinence syndrome than those of individuals taking methadone.[9] In addition, maternal use of methadone or buprenorphine is considered compatible with breastfeeding.[5,6,10]

Because of the risk of precipitated withdrawal, manufacturer guidelines recommend that patients be in moderate withdrawal before taking their first dose of buprenorphine/naloxone during induction.[11] Although there have been concerns in pregnancy related to maternal opioid withdrawal leading to uterine irritability and risk of preterm labor, fetal hypoxia, and fetal demise,[3] these concerns may be less significant than previously thought.[12] However, the discomfort associated with precipitated withdrawal, increased risk of return to substance use,[12] and possible obstetric concerns should be included in the informed consent discussion with pregnant patients.

Low-dose induction is an alternate method of buprenorphine induction, which does not require patients to be in withdrawal prior to starting buprenorphine.[13] Several case series have been published on the use of low-dose induction,[14,15] and it is being used widely and successfully in patients in Vancouver in the context of the fentanyl-poisoning crisis.[16]

CASE DESCRIPTION

The patient is a 24-year-old woman, G1 P0, with a medical history of opioid and stimulant use disorders, endocarditis,

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and multiple opioid overdoses. Consent was obtained from the patient to write the case report.

Substance use history was positive for use of opioids, stimulants, cannabis, and nicotine. She first used opioids at the age of 16 years with oxycodone, later transitioning to intravenous heroin. In the months preceding the low-dose induction, she was using heroin/fentanyl one-quarter gram smoked or intravenous every 1 to 2 days shared with her partner. She had experienced approximately 20 overdoses requiring naloxone in the preceding year.

She started using stimulants at age 19 years and before low-dose induction was using one to one-and-three-quarters gram per day, shared with her partner. She used cannabis as a teenager, which she found helpful for anxiety, before transitioning to opioid use. Nicotine use included 15 cigarettes per day, which had been reduced to 2 cigarettes per day after transitioning to vaping.

Previous MOUD included buprenorphine-naloxone (maximum dose 32 mg), a brief trial of injectable opioid agonist therapy with diacetylmorphine and later oral hydromorphone, slow-release oral morphine, and methadone. Of these, the patient found buprenorphine/naloxone most effective in decreasing nonprescribed opioid use.

Previous psychosocial treatment included admissions to a detoxification facility, 3 residential treatment programs, and multiple recovery homes. A pregnancy test in clinic was positive at approximately 7 weeks' gestational age. Prenatal care was provided through a community health center specialized in perinatal substance use, and pregnancy history was unremarkable.

During her second trimester, at approximately 16 weeks, she presented to a low-barrier community MOUD clinic requesting a buprenorphine-naloxone low-dose induction. Just before starting the induction, her urine drug screen was positive for fentanyl, amphetamines, and opioids. Follow-up appointments for the induction were provided at several community clinics that are connected by electronic medical record, and the potential risk of precipitated withdrawal and lack of research on low-dose induction in pregnancy were discussed. She received a prescription for the induction medication and went daily to a community pharmacy for her medication per her request.

Following buprenorphine/naloxone low-dose induction to 18 mg, she missed 4 days of medication and used nonprescribed opioids at low doses to minimize withdrawal. She then presented to the clinic in withdrawal and did a traditional buprenorphine/naloxone induction, titrating up to 12 mg on day 1 (2 mg every 2 hours). She stabilized and stopped using nonprescribed opioids at a dose of 24 mg. She was able to stabilize on buprenorphine/naloxone and was abstinent from nonprescribed opioids, as was her goal. She later decided to switch to methadone, because of not "liking how she felt" on buprenorphine/naloxone. She continued to be abstinent from nonprescribed opioids and gave birth to her infant at term by spontaneous vaginal delivery at 40 weeks and 4 days gestational age, with Apgar scores of 5 at 1 minute and 9 at 5 minutes Her newborn's birth weight was appropriate for gestational age at 3600 g.

She roomed in with her infant while they were treated with a short course of oral morphine for neonatal opioid withdrawal syndrome. She continues to be engaged in MOUD and is parenting.

The low-dose-induction protocol that was used in this case is outlined in Table 1, although many other variations of this protocol are being used successfully and can range from 1 to 3 weeks of dose titration, often based on patient preference.

TABLE 1. Low-dose Induction Protocol

Day	Buprenorphine-naloxone Dose	Tablet Division	Opioid Use From Nonprescribed Sources
1	0.5 mg	¼ of 2 mg	Fentanyl/heroin
2	0.5 mg	½ of 2 mg	
3	1 mg	½ of 2 mg	
4	1.5 mg	¾ of 2 mg	
5	2 mg	1 × 2 mg	
6	Missed pharmacy dose		4 mg of nonprescribed buprenorphine/naloxone, no withdrawal symptoms
7	4 mg	2 × 2 mg	Fentanyl/heroin
8	5 mg	2½ × 2 mg	
9	6 mg	3 × 2 mg	
10	7 mg	3½ × 2 mg	
11	8 mg	4 × 2 mg	
12	10 mg	8 mg + 2 mg	
13	12 mg	8 mg + 2 × 2 mg	
14	14 mg	8 mg + 3 × 2 mg	
15	16 mg	2 × 8 mg	
16	Missed dose		
17	18 mg	2 × 8 mg + 2 mg	

DISCUSSION

This represents an off-label use of buprenorphine/naloxone and a novel method of induction in pregnancy that has not previously been documented. Because of the lack of research on this method, it is essential to have a discussion and obtain informed consent from a patient by discussing risks and benefits before offering a buprenorphine/naloxone low-dose induction in pregnancy.

Galati et al[17] describe the use of a buprenorphine patch as a bridge to sublingual buprenorphine in pregnancy. Although this is also an alternate low-dose-induction method, in our practice context, buprenorphine patches are not feasible for most individuals because of financial barriers and lack of private insurance coverage.

Risks include lack of previous study of this method of induction, theoretical precipitated withdrawal, and an increased length of time to get to therapeutic dose of buprenorphine/naloxone compared with traditional induction. As low-dose induction takes longer than traditional induction, patients may be at increased risk of overdose for longer because of continued use of nonprescribed opioids. Consideration could be made to prescribe opioids during the low-dose-induction protocol to limit risks from nonprescribed opioids, particularly in the context of a poisoned drug supply.

Benefits of low-dose induction are that patients are not required to go into withdrawal before starting the first dose of buprenorphine/naloxone. This is an option for starting buprenorphine/naloxone in patients who cannot tolerate withdrawal, do not want to experience withdrawal, or are unable to stop using other types of opioids before the buprenorphine/naloxone induction.

Although this transition was done successfully in a closely monitored outpatient setting, with regular follow-up, an inpatient setting could also be considered. In the case of inpatient low-dose induction, prescribed opioids should be available during the

titration phase. If the patient presents to medical care in moderate opioid withdrawal, the traditional induction method would still be considered first line.

CONCLUSIONS

Buprenorphine/naloxone low-dose induction has successfully been used clinically in Vancouver with many patients, and this case report describes the first documented successful use of low-dose induction as an outpatient in our community during pregnancy. Since this first case study, low-dose-induction protocols have been used successfully in our community with other pregnant individuals, without precipitated withdrawal or obstetric complications. When used thoughtfully in appropriately selected circumstances with informed patient consent, this may enhance trauma informed care, by increasing the opportunity for patients to have choice in their treatment options and increase collaboration between health care providers and pregnant women with opioid use disorder.

REFERENCES

1. Maeda A, Bateman BT, Clancy CR, et al. Opioid abuse and dependence during pregnancy: temporal trends and obstetrical outcomes. *Anesthesiology*. 2014;121(6):1158–1165.
2. American Society of Addiction Medicine. Public Policy Statement on Substance Use, Misuse, and Use Disorders During and Following Pregnancy, With an Emphasis on Opioids. Bethesda, MD: American Society of Addiction Medicine, 2017.
3. McCarthy JJ, Leamon MH, Finnegan LP, et al. Opioid dependence and pregnancy: minimizing stress on the fetal brain. *Am J Obstet Gynecol*. 2017; 216(3):226–231.
4. Minozzi S, Amato L, Bellisario C, et al. Maintenance agonist treatments for opiate-dependent pregnant women. *Cochrane Database Syst Rev*. 2013; (12):CD006318.
5. Abrahams R, Ryan A, Berkman J, et al. Treatment of opioid use disorder during pregnancy: guideline supplement. *British Columbia Centre on Substance Use*. 2018. Available at: https://www.bccsu.ca/wp-content/uploads/2018/06/OUD-Pregnancy.pdf. Accessed July 15, 2022.
6. Ordean A, Wong S, Graves L. No. 349—substance use in pregnancy. *J Obstet Gynaecol Can*. 2017;39(10):922–37.e2.
7. Jumah NA, Edwards C, Balfour-Boehm J, et al. Observational study of the safety of buprenorphine+naloxone in pregnancy in a rural and remote population. *BMJ Open*. 2016;6(10):e011774.
8. Eibl JK, Morin K, Leinonen E, et al. The state of opioid agonist therapy in Canada 20 years after federal oversight. *Can J Psychiatry*. 2017; 62(7):444–450.
9. Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med*. 2010;363(24): 2320–2331.
10. Reece-Stremtan S, Marinelli KA. ABM clinical protocol #21: guidelines for breastfeeding and substance use or substance use disorder, revised 2015. *Breastfeed Med*. 2015;10(3):135–141.
11. Indivior. Product Monograph Including Patient Medication Information: Suboxone. Indivior UK Ltd, 2017.
12. Terplan M, Laird HJ, Hand DJ, et al. Opioid detoxification during pregnancy: a systematic review. *Obstet Gynecol*. 2018;131(5):803–814.
13. Hammig R, Kemter A, Strasser J, et al. Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method. *Subst Abuse Rehabil*. 2016;7:99–105.
14. Klaire S, Zivanovic R, Barbic SP, et al. Rapid micro-induction of buprenorphine/naloxone for opioid use disorder in an inpatient setting: a case series. *Am J Addict*. 2019;28(4):262–265.
15. Terasaki D, Smith C, Calcaterra SL. Transitioning hospitalized patients with opioid use disorder from methadone to buprenorphine without a period of opioid abstinence using a microdosing protocol. *Pharmacotherapy*. 2019;39(10):1023–1029.
16. Randhawa P, Brar R, Nolan S. Buprenorphine/naloxone 'micro-dosing': an alternate induction approach for the treatment of opioid use disorder in the wake of North America's increasingly potent illicit drug market. *CMAJ*. 2019;192(3):E73.
17. Galati BM, Carter EB, Perez M, et al. Buprenorphine patch as a bridge to sublingual treatment of opioid use disorder in pregnancy. *Obstet Gynecol*. 2021;137(4):713–716.