5-2020

Comparison of Buprenorphine-Naloxone and Buprenorphine Monotherapy in Opioid Dependent Pregnant Women

Ellie Gillund
University of North Dakota, ellie.gillund@und.edu

Comparison of Buprenorphine-Naloxone and Buprenorphine Monotherapy in Opioid Dependent Pregnant Women

by

Ellie A. Gillund, PA-S

Bachelor of Science, University of Mary, 2016

Contributing Author, Russell Kauffman, PA-C

A Scholarly Project

Submitted to the Graduate Faculty of the University of North Dakota

in partial fulfillment of the requirements for the degree of

Master of Physician Assistant Studies

Grand Forks, North Dakota

May 2020

TABLE OF CONTENTS

Acknowledgements

I would like to thank the UND Physician Assistant Program faculty for their guidance, knowledge, and encouragement throughout the program. I would also like to acknowledge the providers at Essentia Health Fosston, who shared their knowledge and helped guide my research during this project, as they become suboxone certified. Thank you to Ryan Laposki, PharmD for his time and interdisciplinary discussion related buprenorphine.

Abstract

Opioid use disorder during pregnancy has continued to rise, and more primary care providers are being encouraged to prescribe opioid agonist pharmacotherapy. Such medications include methadone, buprenorphine, and naloxone. Many studies have been done to compare these medications' role in medication assisted treatment (MAT) in pregnant women with opioid use disorder.

The purpose of this literature review is to compare the use e of buprenorphine, with and without naloxone, as MAT for opioid dependent pregnant women. Specific outcomes compared in this study include maternal and neonatal safety, neonatal abstinence syndrome, and peripartum pain management. This review included three electronic search databases: PubMed, Clinical Key, and Cochrane library from September 1, 2019 to March 1, 2020. The search included randomized control trials, systematic reviews, and meta-analysis that were published in the last 25 years.

Several of the presented studies show evidence to support of buprenorphine monotherapy and buprenorphine-naloxone combination therapy. Majority of the research suggest overall insufficient evidence to declare one therapy superiority compared to the other. Many studies discuss the complications and limitations with regards to medication trials in pregnant and opioid dependent populations. Ultimately, more research and clinical trials are needed in order to claim the safety and efficacy in the use of buprenorphine as MAT in pregnant women with opioid dependence.

Key terms: buprenorphine in pregnancy, buprenorphine-naloxone in pregnancy, naloxone in pregnancy, buprenorphine safety, suboxone, Subutex, buprenorphine and neonatal abstinence syndrome, pain management buprenorphine, peripartum pain management buprenorphine.

Introduction

In recent studies by the Center for Disease Control (2019), opioid use disorder during pregnancy has continued to rise. From 1999 to 2014 the number of women with opioid use disorder at the time of delivery has quadrupled. Opioid agonist pharmacotherapy, also referred to as medication assisted treatment (MAT) first began in the 1970s for pregnant women with heroin addiction. Since then, such medications have been used in pregnant women with opioid use disorder. The two primary medications of MAT include Methadone and Buprenorphine. The goal of MAT during pregnancy is to prevent maternal opioid withdrawal, prevent relapse, reduce neonatal opioid exposure, and improve fetal outcomes. One main concern of opioid use and MAT is neonatal abstinence syndrome (NAS). Neonatal abstinence syndrome is a range of symptoms that may result from chronic maternal opioid use during pregnancy and can occur in 30-80% of MAT mothers.

The purpose of this literature review is to further understand the role of buprenorphine, with and without naloxone, as MAT for opioid dependent pregnant women. Furthermore, the specific outcomes compared include maternal and neonatal safety, neonatal abstinence syndrome, and peripartum pain management. This knowledge will help providers to make an educated an appropriate choice when choosing MAT therapy for pregnant mothers with opioid dependence.

Statement of the Problem

According to the Substance Abuse and Mental Health Services Administration (SAMHSA), in 2013 there were an estimated 1.8 million people with opioid use disorder related to prescription medications and 517,000 related to heroin. SAMHSA reports there are currently

less than 100,000 providers nationwide that have undergone the buprenorphine wavier program under the Drug Addiction Treatment Act of 2000 (DATA). It is clear to see there is not a enough providers certified for MAT when looking at the number of individuals suffering with opioid use disorder. Thus, as an increasing number of providers are advised to undergo MAT training and certification. Furthermore, these providers should be informed on the use of such medication in pregnant women to make the safest and most effective choice. The FDA has approved two medications for use of opioid dependent pregnant women, methadone and buprenorphine. Furthermore, buprenorphine can be used as monotherapy, or combination therapy of buprenorphine and naloxone. Previous research has compared the use of methadone to buprenorphine. This literature review will compare buprenorphine monotherapy to buprenorphine-naloxone combination therapy in opioid dependent pregnant women. Specific outcomes in this comparison include maternal adherence, neonatal abstinence syndrome, and peripartum pain management to aid in determining the treatment option with greatest benefits and least risk for mother and baby.

Research Questions

In opioid dependent pregnant women, how does use of buprenorphine-naloxone compare to buprenorphine monotherapy in maternal and neonatal safety?

In opioid dependent pregnant women, how does use of buprenorphine-naloxone compare to buprenorphine monotherapy in reduction of NAS?

In opioid dependent pregnant women, how does use of buprenorphine-naloxone compared to buprenorphine monotherapy effect management of peripartum pain?

Methodology

A literature review was performed using electronic search databases: PubMed, Clinical Key, and Cochrane library. Keyword and mesh terms included: *buprenorphine in pregnancy, buprenorphine-naloxone in pregnancy, naloxone in pregnancy, buprenorphine safety, suboxone, Subutex, buprenorphine and neonatal abstinence syndrome, pain management buprenorphine, peripartum pain management buprenorphine*. Many articles used the same research studies and were not original studies, so some were excluded. Several studies compared buprenorphine to methadone, looking at similar outcomes, many of these studies were also excluded. PubMed served as the primary database for this literature review. Several studies were excluded as they did not solely look at use of buprenorphine as MAT or its use in pregnant women. The data search time frame included studies completed in the last ten years.

Review of Literature

A review of the literature has been conducted which shows that there is evidence to support use of methadone or buprenorphine in pregnant women with opioid dependence. Furthermore, buprenorphine can be used with or without naloxone. There are many concerns about the use of naloxone in pregnancy as it is an opioid antagonist, however buprenorphine monotherapy has higher potential for misuse (ACOG, 2017). The goal of selecting the best medication for opioid dependent mothers includes several factors including maternal adherence and risk of withdrawal, obstetric complications, impaired fetal development, and neonatal abstinence syndrome. Limitations to the study include small sample size, maternal adherence, natural variants in maternal and neonatal pregnancy outcomes, duration and dosing of MAT.

Maternal and neonatal safety outcomes with buprenorphine monotherapy versus buprenorphine-naloxone combination therapy.

A 2018 article in *American Family Physician* by Zoorob et al., discusses use of buprenorphine in opioid use disorder. Buprenorphine is a schedule III medication and is manufactured in two formulations, buprenorphine monotherapy and combination buprenorphine-naloxone. Combination therapy is preferable over monotherapy in most patients due to its lower risk of misuse. However, monotherapy is preferred in pregnant and lactating women because neonatal exposure to naloxone is not very well studied and misuse, such as injecting, naloxone containing product can induce opioid withdrawal. Both monotherapy and combination therapy are well tolerated with the most common side effects including anxiety, constipation, dizziness, drowsiness, headache, nausea, and sedation. More serious adverse effects include accidental ingestion and overdose, hepatitis and hepatic events, opioid withdrawal effects particularly in combination products, perinatal effects, or respiratory depression in patients with compromised respiratory function. This article serves to provide baseline knowledge and understanding of the medication, use, and potential side effects.

An article from 2003 in Drug and Alcohol Dependence Journal by Johnson et al., outlines information for providers regarding information about the formulations, use, and side effects of both buprenorphine-monotherapy and buprenorphine-naloxone. Buprenorphine is a mu-receptor agonist, with high affinity, low intrinsic activity, and slow dissociation. These qualities allow buprenorphine to have a good safety profile, low physical dependence, and flexibility in dose scheduling. Furthermore, buprenorphine has been formulated into a combination sublingual tablet with naloxone in a 4:1 ratio. Naloxone is an opioid antagonist, however, has poor sublingual absorption, therefore provides minimal opioid antagonist effects. The combination

product of buprenorphine-naloxone was developed to decrease the risk of diversion and abuse of buprenorphine monotherapy, in the event the medication is used parenterally, naloxone will cause the predominant effect resulting in withdrawal. The 2003 article by Johnson et al. reports that buprenorphine-naloxone has been tested in over 5,000 opioid-dependent individuals in the U.S., and no apparent side effects have been reported. Similar to that of opioids however, buprenorphine can cause constipation. Additionally, there have been some reports of individuals whom experience elevated liver enzymes. Liver toxicity has been associated with intravenous buprenorphine misuse, due to the increased bioavailability when administered parenterally.

In 2016, Jumah et al. preformed an observational, retrospective study of 855 pregnant women, including 62 women expose to buprenorphine-naloxone, 618 women with no opioid exposure, and 159 women with opioid exposure other than buprenorphine-naloxone. The outcomes assessed included birth weight, preterm delivery, congenital anomalies, still birth, Apgar score at 1 and 5 minutes, NAS score >7, and treatment of NAS. Maternal outcomes included cesarean sections, postpartum hemorrhages, and out of hospital deliveries and transfer of care. Results showed no difference between Apgar scores and caesarean section rates between buprenorphine-naloxone exposure and no opioid exposure. Additionally, mothers using buprenorphine-naloxone had higher birth-weight babies compared to mothers taking other opioids ($p=0.001$). This study suggests that buprenorphine-naloxone use by opioid dependent mothers during pregnancy causes no significant harm. This study is beneficial in understanding the benefits versus risks of buprenorphine use during pregnancy for both mother and baby, and additionally includes use of naloxone. Overall, no significant complications or safety concerns were identified. This study strongly supports use of buprenorphine-naloxone in pregnancy (Jumah et al., 2016).

Lund et al. performed a comparison review in 2013 of previously published studies on buprenorphine pharmacotherapy during pregnancy. A comparison study was done to evaluate maternal and neonatal outcomes with use of buprenorphine-naloxone compared to buprenorphine monotherapy in treatment of opioid dependent mothers. Maternal outcomes reported included cesarean sections, days of maternal hospital stay, maternal weight gain, non-normal delivery presentation, analgesia during delivery, drug-screen at delivery, medication complications at deliver, number of prenatal obstetrical visits, fetal presentation at delivery, and breast feeding. Despite limitations including small sample size and retrospective study, there were no obvious adverse maternal or neonatal outcomes related to the use of buprenorphine-naloxone combination therapy in the treatment of opioid-dependent mothers. The maternal outcomes assessed were similar to those previously identified in women using buprenorphine monotherapy. This study is beneficial as it evaluates maternal and neonatal safety with use of buprenorphine-naloxone and concludes there were no significant differences compared to use of buprenorphine monotherapy in the pregnant population (Lund et al., 2013).

Poon et al. conducted a study in 2014 with the goal of comparing the safety of newer opioid antagonists used in pregnancy, including buprenorphine and buprenorphine-naloxone. The main concern with buprenorphine- naloxone is its potential for abuse used intravenously or intranasally, in which case the naloxone causes severe withdrawal in opioid dependent patients. Regarding maternal safety, a retrospective chart review of opioid dependent mothers treated with buprenorphine-naloxone was done. The study included women who began treatment prior to conceptions (n = 8) or within the first trimester (n= 2). Of these mothers, no significant adverse maternal or neonatal outcomes were reported compared to the mothers receiving buprenorphine monotherapy. Although sample size is small, it was concluded that both buprenorphine

monotherapy and combination therapy are safe and effective treatment options for opioid dependent mothers. Furthermore, they recommend women who become pregnant while taking buprenorphine-naloxone treatment are advised to transition to buprenorphine monotherapy, as there is greater risk of withdrawal caused by improper use of combination therapy. Despite small sample size, this study is beneficial as it compares safety outcomes and includes recommendations. There are many contradictory recommendations regarding whether it is safe or appropriate to switch from one treatment to another after becoming pregnant. Additionally, there are contradictory beliefs on whether buprenorphine-monotherapy or buprenorphine-naloxone have greater all-around risk if there is potential for abuse. Monotherapy abuse can cause increased fetal opioid exposure, while combination therapy abuse can result in withdrawal.

Tran et al. conducted a review in 2017 to compare pregnancy outcomes with use of methadone, buprenorphine, and naltrexone in clinical trials. Between methadone and buprenorphine, buprenorphine is the preferred agent due to is shorter treatment duration, less pharmacotherapy needed in treatment of NAS symptoms, and shorter hospitalizations needed for neonates. Furthermore, buprenorphine monotherapy is preferable to buprenorphine-naloxone during pregnancy due to avoidance of prenatal naloxone exposure. There is greater risk of detoxification with use of naloxone during pregnancy. This study too shows skepticism of including naloxone in pregnancy and uses naltrexone as a comparative treatment in MAT of pregnant women. Additionally, this study expresses buprenorphine monotherapy as the preferable treatment over buprenorphine-naloxone, as the previously discussed studies favored combination therapy.

Neonatal abstinence syndrome with buprenorphine monotherapy versus buprenorphine-naloxone combination therapy.

The objective of Debelak et al, in 2013 was to compare maternal and neonatal outcomes following buprenorphine-naloxone exposure during pregnancy. A retrospective chart review used 10 opioid-dependent pregnant women using buprenorphine-naloxone sublingual film. Neonatal outcomes included measured-gestational age at delivery, 1- and 5-minute Apgar scores, head circumference, length and weight at birth, treatment for NAS, total amount of morphine sulfate needed for treatment of NAS, and length of hospital stay for treatment of NAS. Results found neonates were full-term with normal birth parameters. Four of the ten neonates were treated for NAS, and length of hospital stay for treatment of NAS were similar to that of buprenorphine monotherapy. This study is valuable in that it suggests there are not only no obvious significant maternal effects, but also no significant neonatal effects related to the use of buprenorphine-naloxone in pregnant women. Limitations of this study include small sample size (Debelak et al., 2013).

In the previously discussed study by Lund et al., comparing buprenorphine-naloxone and buprenorphine monotherapy, neonatal outcomes were additionally observed. Neonates exposed to buprenorphine-naloxone or buprenorphine monotherapy were born with comparable head circumferences, both within normal range according to the World Health Organization (WHO). The second significant neonatal outcome was Apgar scores at 5 minutes, in which the buprenorphine-naloxone group was significantly lower than buprenorphine monotherapy group, however both groups remained in the normal rage. Limitations of this study included small sample size. This study is beneficial in revealing observed neonatal outcomes and concluding no significant adverse effects with use of buprenorphine-monotherapy or buprenorphine-naloxone. Although there were differences notes, neither group fell out of the normal ranges set by WHO.

Mullins et al, performed a retrospective cohort study in 2019 of mothers with opioid use disorder using buprenorphine monotherapy and buprenorphine-naloxone comparing maternal and fetal outcomes. The primary fetal outcome assess was neonatal abstinence syndrome (NAS) requiring treatment. Results found infants exposed to buprenorphine in utero experienced a significantly higher rate of NAS 59/108 (54.6%), compared to infants exposed to buprenorphine-naloxone in utero experiencing NAS 30/85 (35.3%). In conclusion, when comparing buprenorphine monotherapy to buprenorphine-naloxone, combination therapy had a lower rate of NAS and can be considered an acceptable alternative treatment for opioid dependent pregnant women. This retrospective study is very significant in comparing buprenorphine-monotherapy against buprenorphine-naloxone and their effects on neonatal abstinence syndrome. Reducing risk of NAS is one of the primary goals of MAT in pregnancy. The results of this study favor use of buprenorphine-naloxone combination therapy for greater reduction of risk of NAS in neonates born to mothers with opioid dependence receiving MAT (Mullins et al., 2019).

Another retrospective chart review performed by Nguyen et al. in 2018, includes 26 mothers in medication-assisted treatment programs using buprenorphine-naloxone during pregnancy. The goal of this review was to examine the relationship of neonatal outcomes with the use of buprenorphine-naloxone in pregnancy. Results demonstrated neonatal birth outcomes all within normal ranges. Additionally, only 19% of the neonates includes required pharmacological treatment for neonatal abstinence syndrome. This study concluded use of buprenorphine- naloxone shows relative safety in pregnancy. This study also supports buprenorphine-naloxone for its safety in pregnancy, improved neonatal birth outcomes, and reduced requirement for treatment of NAS (Nguyen et al.,2018).

Peripartum and postpartum pain management with buprenorphine monotherapy versus buprenorphine-naloxone combination therapy.

In 2018, Hoyt et al. preformed an observational study to assess the standard labor analgesia of fentanyl in bupivacaine epidural solution was substituted with clonidine in bupivacaine. Pain scores were recorded during labor and immediately post-surgical. The study included fourteen patients, seven presented in spontaneous labor and seven had elective cesarean delivery. Of the women whom had spontaneous vaginal delivery, pain scores immediately post-epidural ranged from 0/10-4/10. Of women having cesarean delivery, pain score after receiving the epidural infusion pre-surgery was 0/10 for all patients and at time of epidural removal the highest pain score was 5/10. This study revealed that clonidine and bupivacaine appear affective in parturient on buprenorphine therapy for opioid addiction maintenance. Limitations of this study include small sample size. Many challenges arise for providers when trying to manage pain in patients receiving MAT as these patients have greater opioid tolerance and are receiving opioid agonist and/or antagonists which can be difficult and dangerous. This study shows good support for use of non-opioid medication for labor related pain management in patients receiving buprenorphine (Hoyt et al., 2018).

A 2017 article by Pan et al. in the Journal of Clinical Obstetrics and Gynecology, discusses peripartum, intrapartum, and post-partum anesthetic management and implications. Pain management in individuals using buprenorphine products is a challenge. These patients may experience altered baseline pain levels, requiring higher dosing to manage their pain. Mothers should continue maintenance doses of buprenorphine produce; however this does not provide labor analgesia. Pain management should be based on the clinical situation. Because buprenorphine has high affinity for mu-receptors, it may interfere with peripartum opioid efficacy requiring higher dosing. For intrapartum management, neuraxial anesthesia, spinal, and

epidural methods are all appropriate for both labor pain and cesarean section. Fentanyl and morphine can be used as neuraxial narcotics to provide pain relief. Local anesthetics may require higher dosing to provide pain relief, however opioid tolerance may decrease the efficacy of local anesthetics. Postpartum pain management will vary based on clinical and psychological context of the mother's pain. Both vaginal and cesarean delivery mothers should continue maintenance of the opioid therapy, such as buprenorphine, postpartum. Additionally, postpartum pain medication will be needed to a greater extent than non-opioid mothers, due to opioid-tolerance. Postpartum medication options include NAIDs (ketorolac or ibuprofen). Mothers receiving neuraxial anesthesia for labor or anesthesia may benefit from neuraxial morphine to aid in reduction of postpartum breakthrough pain. Epidural catheters and peripheral nerve blocks are also beneficial for these patients. This article serves as a good foundation for knowledge and understanding of the challenges and complications that arise when caring for individuals receiving MAT.

TABLE 2. Pain Treatment Options Peripartum

	Illicit Opioids		Chronic Pain Opioid		Opioid Antagonist	
	CS	VD	CS	VD	CS	VD
Opioids to cover illicit opioid use	✓	✓				
Maintenance of current management			✓	✓	✓	✓
NSAIDS (eg, toradol, ibuprofen)	✓	✓	✓	✓	✓	✓
Acetaminophen	✓	✓	✓	✓	✓	✓
Neuraxial opioids	✓	✓	✓	✓		
TAP block	✓		✓		✓	
Pudendal block		✓		✓		✓
PCEA	✓	✓	✓	✓	✓	✓
NMDA antagonism (eg, magnesium, ketamine)	✓	✓	✓	✓	✓	✓
Neurologics (eg, gabapentin)	✓	✓	✓	✓	✓	✓
Opioids for breakthrough pain	✓	✓	✓	✓		

CS indicates cessarean section; NMDA, *N*-methyl D-aspartate; NSAIDs, non-steroidal antiinflammatory drugs; PCEA, patient controlled epidural analgesia; TAP, transverse abdominis plane; VD, vaginal delivery.

Figure 1 – Pan et al., discusses effective peripartum pain treatment options compatible with opioid antagonists in mothers for both cesarean section and vaginal delivery (2017).

Meyer et al., in 2010, conducted a study with the objective of determining whether buprenorphine maintenance in opioid dependent mothers effect intrapartum and postpartum pain or medication requirements. Sixty-three women taking buprenorphine, 44 with vaginal delivery and 19 with cesarean delivery, were matched to control women. Analgesic medication and pain scores were assessed. Results yield no differences in intrapartum pain or analgesia needs in buprenorphine mothers compared to control mothers. Buprenorphine mothers who underwent vaginal delivery reported increased pain postpartum but required no increase in opioid pain management. However, the buprenorphine mothers who underwent cesarean delivery had greater analgesia needs and experienced greater postpartum pain. This study helps providers understand that despite taking opioid agonist and/or antagonist, these individuals are still experiencing equivocal pain to those not receiving MAT for opioid dependence, and their pain is legitimate and requires management. There is additional complexity in managing these patients' pain, due to their increased analgesia needs. This information is beneficial for providers to help understand the needs of these patient and how to provide adequate care.

Discussion

In opioid dependent pregnant women how does use of buprenorphine-naloxone compare to buprenorphine monotherapy in maternal and neonatal safety?

Regarding adverse effects, the study done by Juma et al. in 2016 maternal and neonatal outcomes were compared in mothers taking buprenorphine-naloxone, mothers taking opioids, and mothers taking no opioids. Results showed no differences between Apgar scores and caesarean rates between buprenorphine-naloxone exposure and no opioid exposure. This suggests use of buprenorphine-naloxone use during pregnancy poses low risk to mother and

baby. Furthermore, Juma et al. found mothers using buprenorphine-naloxone had higher, healthy birth-weight babies compared to mothers taking other opioids, suggesting improved neonatal outcomes with MAT versus without.

Regarding maternal and neonatal adherence and risk of withdrawal, Tran et al further elaborates on inclusion of naloxone component. If the patient were to abuse the buprenorphine-naloxone product, there is potential for naloxone exposure to the neonate which then precipitate maternal and/or neonate withdrawal. For this reason, Tran et al. finds buprenorphine mono-product more favorable. On the contrary, Zoorob et al. finds buprenorphine-naloxone combination product preferred due to its lower risk of misuse by inclusion of naloxone.

In summary, buprenorphine has been well studied, and shows improved maternal and neonatal outcomes compared to opioid use. However, both monotherapy and combination therapy have risk for abuse and misuse, therefore providers should be well educated on both potential adverse effects and decide based each unique patient. Lastly, as discussed by Poon et al, whichever medication is decided upon, it should be continued throughout pregnancy, and should not be discontinued or transitioned.

In opioid dependent pregnant women how does use of buprenorphine-naloxone compare to buprenorphine monotherapy in reduction of NAS?

When comparing combination therapy and monotherapy in reduction of NAS, very few studies have identified significant difference. Mullins et al. 2019 found that combination therapy did have a lower rate of NAS when compared to monotherapy. With this information providers can reassure mothers that between monotherapy and combination therapy, no significant

difference has been found in reduction of NAS. The decision should be ultimately make to best suit the mother, as evaluated and decided by the trained provider.

In opioid dependent pregnant women how does use of buprenorphine-naloxone compared to buprenorphine monotherapy effect management of peripartum pain?

Few specific studies were found that evaluated the role of naloxone in MAT and assess postpartum pain management. However, if the medication is use appropriately there is poor oral absorption of naloxone making it essential non-existent systemically. Therefore, combination therapy including naloxone should not interact with systemic or neuraxial pain medications. The primary takeaway from the research done on MAT mothers and managing peripartum pain, is that these patients' pain is more difficult to manage. Both providers and anesthesia should be aware of this unique population and educated on how to best provide them with pain management.

Clinical Application

As the number of providers become MAT certified increase, the information provided in the literature review will assist the medical provider in making the safest and most efficacious decision for management of opioid dependence in pregnant women or women of childbearing age. With more providers becoming trained in prescribing MAT, it will be important to understand what form best fits the patient based on their lifestyle and needs. MAT during pregnancy has several layers of complexity, as it is researching a low compliance population, but also researching medication use during pregnancy which many mothers are opposed to. However, the evidence is sufficient in comparing MAT to opioid use in pregnancy for both maternal and neonatal outcomes.

References

Debelak, K., Morrone, W., Ogrady, K., & Jones, H. (2013). Buprenorphine Naloxone in the Treatment of Opioid Dependence during Pregnancy-Initial Patient Care and Outcome Data. The American Journal on Addictions, 22(3), 252–254. https://doi: 10.1111/j.1521-0391.2012.12005.x

Hoyt, M., Shah, U., Cooley, J., & Temple, M. (2018). Use of epidural clonidine for the management of analgesia in the opioid addicted parturient on buprenorphine maintenance therapy: An observational study. International Journal of Obstetric Anesthesia, 34, 67-72. https://doi:S0959-289X(17)30330-8 [pii]

Johnson, R., Strain, E., & Amass, L. (2003). Buprenorphine: How to use it right. Drug and Alcohol Dependence, 70(2 Suppl), 59. https://doi:S0376871603000607 [pii]

Jumah, N., Edwards, C., Balfour-Boehm, J., Loewen, K., Dooley, J., Finn, L. G., & Kelly, L. (2016). Observational study of the safety of buprenorphine naloxone in pregnancy in a rural and remote population. BMJ Open, 6(10). https://doi:10.1136/bmjopen-2016-011774

Lund, I, Fischer, G., Welle-Strand, G. K., O'Grady, K. E., Debelak, K., Morrone, W. R., & Jones, H. E. (2013). A comparison of buprenorphine + naloxone to buprenorphine and methadone in the treatment of opioid dependence during pregnancy: Maternal and neonatal outcomes. Substance Abuse : Research and Treatment, 7, 61-74. https://doi:10.4137/SART.S10955 [doi]

Lund, I., Fischer, G., Welle-Strand, G., O'Grady, K.., Debelak, K., Morrone, W., & Jones, H. (2013). A comparison of buprenorphine + naloxone to buprenorphine and methadone in the treatment of opioid dependence during pregnancy: Maternal and neonatal outcomes. Substance Abuse : Research and Treatment, 7, 61-74. https://doi:10.4137/SART.S10955 [doi]

Lynne.walsh. (2020, February 12). Medication and Counseling Treatment. Retrieved March 15, 2020, from https://www.samhsa.gov/medication-assisted-treatment/treatment

Meyer, M., Paranya, G., Norris, A., & Howard, D. (2010). Intrapartum and postpartum analgesia for women maintained on buprenorphine during pregnancy. European Journal of Pain, 14(9), 939–943. https://doi: 10.1016/j.ejpain.2010.03.002

Mullins, N., Galvin, S., Ramage, M., Gannon, M., Lorenz, K., Sager, B., & Coulson, C. (2019). Buprenorphine and naloxone versus buprenorphine for opioid use disorder in pregnancy: A cohort study. Journal of Addiction Medicine, https://doi:10.1097/ADM.0000000000000562 [doi]

Nguyen, L., Lander, L., O'Grady, K., Marshalek, P., Schmidt, A., Kelly, A., & Jones, H. (2018). Treating women with opioid use disorder during pregnancy in appalachia: Initial neonatal outcomes following buprenorphine + naloxone exposure. The American Journal on Addictions, 27(2), 92-96. https://doi:10.1111/ajad.12687 [doi]

Pan, A., & Zakowski, M. (2017). Peripartum anesthetic management of the opioid-tolerant or buprenorphine/suboxone-dependent patient. Clinical Obstetrics and Gynecology, 60(2), 447-458. https://doi:10.1097/GRF.0000000000000288 [doi]

Poon, S., Pupco, A., Koren, G., & Bozzo, P. (2014). Safety of the newer class of opioid antagonists in pregnancy. Canadian Family Physician Medecin De Famille Canadien, 60(7), 63-9. https://doi:60/7/631 [pii]

Tran, T., Griffin, B., Stone, R., Vest, K., & Todd, T. (2017). Methadone, buprenorphine, and naltrexone for the treatment of opioid use disorder in pregnant women. Pharmacotherapy, 37(7), 824-839. https://doi:10.1002/phar.1958 [doi]

Zoorob, R., Kowalchuk, A., & Mejia de Grubb, M. (2018). Buprenorphine therapy for opioid use disorder. American Family Physician, 97(5), 313-320. https://doi:d13651 [pii]