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Opioid Agonist Therapy and Detoxification: Improving Outcomes for Fetuses Born to Addicted Mothers

Kao Lee
Augsburg University

Opioid Agonist Therapy and Detoxification:

Improving Outcomes for Fetuses Born to Addicted Mothers

By

Kao Lee, PA-S2

Advisor: Eric Barth, PA-C

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Introduction

The use of opioids has increased significantly in the last decade. Concern for the undertreatment of pain emerged in the mid-1990s, prompting providers to treat pain as a fifth vital sign. The pharmaceutical industry marketed their products as having significantly less abuse potential than reality. Prescriptions for pain medications soared with prescription opioids leading the way. Prescription opioids became ubiquitous in medicine cabinets and reports of abuse rose. Casually administered, illicit sale, theft, and doctor shopping became more common as reports of overdose also rose. By 2010, the United States government was issuing strategies to combat the opioid crisis.[1]

People from all demographics were affected by the opioid crisis, including pregnant women and their fetuses. Use of opioids during pregnancy can lead to many complications, including neonatal abstinence syndrome (NAS) which results when an infant suffers withdrawal after cessation of gestational exposure to addictive substances like opioids. [2] Opioid agonist therapy (OAT) has long been the recommended treatment of choice for pregnant women with opioid use disorder (OUD).[3] However, the use of opioids to combat the poor outcomes of opioids seems counterproductive. This study aims to explore if the use of medically assisted withdrawal and opioid detoxification are as effective as OAT in improving outcomes for fetuses born to women who were addicted to opiates during pregnancy.

Background

Methadone

Methadone is a long-acting, high-affinity, full mu-opioid receptor agonist that prevents withdrawal symptoms while limiting euphoric side effects.[3] The typical length of effect is 24 hours or longer. It is available as oral solution, tablet, or injectable solution.[4]

Methadone drug therapy is recommended to be initiated as early in the pregnancy as possible to maximize fetal outcomes. Due to potential for serious side effects, hospitalization is suggested during initiation. Unlike buprenorphine, there is no need for withdrawal symptoms before starting therapy. The starting dose varies according to the symptoms of the patient; however, the typical dose is 20 to 30 milligrams (mg). Incremental titration of 5 to 10 mg every three hours may be performed as needed according to withdrawal symptoms on the first day. Day two dosing is the equivalent of the sum of the previous day's dosing. If withdrawal symptoms are observed, the dose may be increased until no additional increases are needed to prevent withdrawal. Stabilization may require a week or more with the possibility of continued dose adjustment. Once stabilized, the patient may be discharged, and care is continued at outpatient treatment centers.[4]

Methadone administration is tightly controlled. Opioid treatment programs manage the daily dosing of methadone. Administration of the drug is conducted using the oral solution form so it can be observed, and diversion or misuse can be minimized. Office setting or at-home administration is not practiced.[5] The physiological changes of pregnancy may require dose adjustments which can be managed by addiction specialists at treatment centers.[3] Average maintenance dosing is 120 mg per day with evidence indicating better outcomes for those who are dosed at higher daily amounts.[4] According to the American College of Obstetricians and Gynecologists (ACOG), methadone dose has no correlation with incidence or duration of NAS.[3]

A significant portion of women enrolled in methadone programs continue to abuse substances during pregnancy, requiring high index of suspicion for polysubstance use. Drug monitoring is conducted by weekly urine drug testing. The urine drug screen-9 will test for methadone and other naturally occurring opioids, but not synthetic opioids such as buprenorphine or fentanyl which may need to be ordered separately. Index of suspicion for polysubstance use should remain high due to its role in reducing the benefits of OAT and increasing harm to the fetus.[4]

Buprenorphine

Buprenorphine is a partial mu-opioid receptor agonist that was approved for use in 2002.[6] It has a high affinity for the receptor, meaning it binds stronger to but with lower activity than full opioid agonists such as heroin, morphine, or methadone resulting in similar pharmacologic effects but with a ceiling effect at high doses. This results in lowered risk of adverse side effects such as respiratory depression, overdose, and death. Typical administration is done sublingually or buccally due to greater bioavailability as compared to oral administration.[4] Buprenorphine is available as a monoproduct or in combination with naloxone, an opioid antagonist that is used to counteract symptoms of opioid overdose. The purpose of naloxone is to deter users from injecting the drug in order to achieve a greater euphoric effect or diverting the drug so others can do the same. Naloxone has no effect if taken sublingually, buccally, or orally but will have full effect if injected. Concern for possible adverse side effects of naloxone on the fetus has influenced discouragement of use of the combination product in pregnant patients[5], however recent guidance from ACOG has indicated that naloxone may have no adverse effects and may be safe for use in pregnancy as time goes on and more data are collected.[3]

Initiation of buprenorphine treatment may lead to withdrawal symptoms, particularly if the patient has been exposed to opioids recently. It should be initiated when the patient shows signs of moderate withdrawal: chills alternating with flushing or diaphoresis, nausea, yawning, anorexia, lacrimation, rhinorrhea, or moderate muscle or joint aches. The effects of buprenorphine last from 24 to 48 hours, resulting in once daily or every other day dosing. Initial dosing is typically 2 to 4 mg with titration of an additional 2 to 8 mg after two hours of observation if withdrawal symptoms persist. Day two dosing is the equivalent of the sum of the previous day's dosing. If withdrawal symptoms are observed, the dose may be increased in 4 mg increments for a maximum daily dose of 16 mg. Dosing for the average patient stabilizes at 8 to 16 mg per day with possible need to adjust the dosing throughout pregnancy.[4] Due to its partial agonist action, increasing the dose to more than 32 mg may not add to its efficacy.[7]

Dispensation and monitoring of buprenorphine differ from methadone. Though buprenorphine may be administered through opioid treatment programs like methadone, it can also be dispensed through office-based means by trained U.S. Drug Enforcement Administration-approved providers. Weekly or monthly prescriptions are possible.[5] Monitoring is conducted by urine drug testing with buprenorphine and/or its metabolite norbuprenorphine specified on the order. Frequency determined clinically.[4]

Naltrexone

Naltrexone is an opioid antagonist. It competitively binds to opioid receptor sites with the highest affinity for mu-opioid receptors, blocking the euphoric effects of opioids and reducing craving which aid in abstinence efforts.[8] Its forms include oral and injectable. The oral form has demonstrated poor adherence with no efficacy over placebo. Intramuscular naltrexone is long-acting and is effective for four weeks.[9] Currently, there is limited research on the effects of

naltrexone on the fetus and pregnancy outcomes and guidance is to determine treatment on a case by case basis. A woman currently on naltrexone should be counseled on the limited safety data of the effects of naltrexone on the fetus if she chooses to continue treatment as well as the risk of relapse if she chooses to discontinue treatment to pursue complete detoxification.[3] Initiation of therapy requires an opioid-free period of at least seven to 10 days in order to avoid full withdrawal upon administration of the drug, which could cause harm through fetal stress or relapse.[8]

Opioid Detoxification

Neonatal abstinence syndrome is a big motivator for the use of opioid detoxification during pregnancy. Successful detoxification results in no opiates in the mother's system which would prevent NAS from occurring after birth. This has been attempted through residential treatment programs, incarceration, involuntary institutionalization, and individually without any medical supervision.[10] Rates of relapse are high with one study showing at 96% positive urine toxicology at delivery as well as reports of postpartum maternal death due to overdose.[10] Slow tapering off opioid maintenance treatment (buprenorphine or methadone) during pregnancy to reach complete detoxification has similarly shown relapse and the necessary return to some level of the previous treatment.[11] Though detoxification is attractive, it will most likely result in the risk of NAS due to withdrawal.

Neonatal Abstinence Syndrome

Neonatal abstinence syndrome is a constellation of symptoms experienced by the newborn while undergoing withdrawal due to the abrupt discontinuation of opioids upon birth. Gestational exposure to such substances as methadone, buprenorphine, cocaine,

benzodiazepines, alcohol, nicotine, and other opioid-containing drugs like fentanyl, hydrocodone, or oxycodone can result in NAS. Additionally, other factors may contribute to the presentation of NAS such as polysubstance abuse, maternal psychiatric comorbidities, exposure to violence and other maternal stressors, inadequate nutrition, and poor prenatal care.[12] Though rarely fatal, complications of NAS can cause illness and subsequent prolonged hospital stays.[2]

The clinical presentation of NAS can be varied. The infant may display emphasis of one or a few symptoms with little or no expression of others, or they may display each symptom. The specific symptoms include hyperirritability, excessive high-pitched crying, exaggerated Moro reflex, myoclonic jerks, hypertonicity, tremors, poor sleep, uncoordinated sucking reflexes, gastrointestinal disturbances, and autonomic disturbances such as fever, sweating, sneezing, and yawning. Not all symptoms are immediately obvious. Infants whose symptoms are primarily autonomic will be more subtle to detection and require more astute observation. In these cases, diagnosis is further complicated by a less pronounced response to treatment.[12]

Neonatal abstinence syndrome symptoms generally start within the first 72 hours of life for infants exposed to methadone and last for several days to weeks. Infants exposed to buprenorphine, NAS symptoms usually appear within 12 to 48 hours and last for seven days. Currently, the modified Finnegan Scoring System is the most commonly used tool to diagnose NAS. Neonates are observed for various central nervous, gastrointestinal, and autonomic disturbances every three to four hours while awake after feeding. Typically, a score of above eight is considered pathological and requires pharmacological treatment, however that score may vary according to the institution.[13] Diagnosis is clinical, but toxicological confirmation may be necessary to rule in or out other substances that may have been present during pregnancy. This may be done with meconium or urine testing.[2]

Treatment for NAS can be both pharmacological and nonpharmacological. Nonpharmacological treatment consists of soothing techniques and manipulation of the environment to calm the mother and infant.[12] Transfer of methadone or buprenorphine into breast milk is minimal regardless of dose, therefore breastfeeding is indicated for mothers who are stable on their opioid agonist, are not abusing illicit or licit drugs, and are not infected with human immunodeficiency virus (HIV). It has been associated with lowered severity of NAS symptoms in infants, shorter hospital stays, and a lowered need for pharmacotherapy.[3]

Pharmacological treatment is indicated when signs and symptoms are not controlled, severe dehydration results from withdrawal, serious side effects occur such as seizures, or Finnegan scores remain high. The goal of treatment is to reduce severity of NAS symptoms to a level that allows for the infant to eat, sleep, and interact.[12] The most common agent used is morphine. Its short half-life requires frequent dosing, but dose adjustment can be made quickly if necessary. However, weaning must be done slowly. Hospital stays may be prolonged if morphine is used. Methadone is another option. Unlike morphine, it is dosed twice daily due to its long half-life, making it difficult to titrate. Buprenorphine is a newer alternative but lacks enough data to support its use. Adjuvants include phenobarbital or clonidine.[2]

Methods

PubMed was searched between May 24, 2019 and July 22, 2019. Keywords included in the search were: pregnancy, opioids, buprenorphine, methadone, naltrexone, detoxification, neonatal abstinence syndrome, and OUD. Studies that were included were in English, contained information pertaining to human studies, and focused on pregnant women using OAT or detoxification and neonatal outcomes.

Discussion

Opioid Agonist Therapy Alternatives

Opioid detoxification is an option that is ideal in theory, but difficult to execute in practice. The goal is to decrease the chances of NAS and therefore decreasing the lengths of hospital stays and associated negative outcomes for the infant. Successful detoxification has been linked to absence of NAS, higher birth weights in comparison to those with ongoing illicit drug use, preterm birth rates and fetal loss comparable to the general population, and normal physical development. However, the studies showing these outcomes had high variability with fair to poor overall quality of evidence. Accurate interpretation of the data was limited due to the retrospective studies and lack of randomized controls.[12]

NAS is a painful consequence of opioid use. It is painful for the neonate to suffer through and witnessing can induce feelings of guilt and anxiety in the mother. This can lead to high rates of relapse, which is harmful for the health of the mother as well as contribute to poor outcomes for her infant. Relapse rates were high in most studies, resulting in continued gestational opioid exposure and increased risk of HIV and hepatitis infection; some studies reported maternal death due to overdose in the postpartum period. Behavioral therapy and ongoing support are crucial to success throughout the perinatal and postpartum periods. In addition to high relapse rates, fetal stress in response to maternal withdrawal has limited data but remains a high concern that should be discussed with every potential candidate for detoxification. Current evidence indicates there is not enough data to support detoxification as a superior option to OAT.[12]

Naltrexone, an opioid antagonist, is another alternative to OAT. It is not an opioid, thus NAS and its associated neonatal outcomes such as low birth weight and extended hospital stays

are decreased in comparison to mothers treated with OAT if it is utilized faithfully. However, in the study conducted by Kelty and Hulse, NAS was not eliminated. This was attributed to the mother relapsing during pregnancy. The study did not find an association between naltrexone and perinatal mortality or neonatal mortality. Rates of congenital birth abnormalities are comparable to the general population; however, rates of urogenital abnormalities are higher.[14] Given these positive outcomes, naltrexone seems a superior option, but consideration must be given to the process of initiation of treatment. If the woman is not already on naltrexone at the time of pregnancy, an opioid-free period of seven to 10 days is required, and she must exhibit signs of withdrawal prior to initiation.[8] This period is problematic for its high risk of relapse as well as the limited data on the effect of maternal withdrawal on the fetus. Current naltrexone use and the reliability of the woman must be heavily weighed when considering naltrexone as a means of opioid avoidance maintenance during pregnancy. Attempts at detoxification should be counseled against.[3]

Opioid Agonist Therapy

Methadone has been studied extensively and has been the medication of choice for opioid addiction therapy for over 40 years. It has been shown to be highly effective in treating OUD and has been recommended over detoxification due to the evidence of longer maternal abstinence, higher compliance leading to lower rates of relapse and subsequent fetal illicit drug and associated HIV and hepatitis exposure, and better neonatal outcomes.[7] However, methadone use is highly controlled, requiring its users to visit a treatment center daily and submit to frequent urine monitoring. This may be beneficial to patients who require the rigid structure in order to maintain discipline but may detract from compliance of those whose daily activities are disrupted. Additionally, though it is a preferable alternative to heroin or fentanyl addiction,

methadone itself is an addictive opioid. Buprenorphine, being a partial mu-agonist that doesn't require the rigidity of methadone administration, can be a more attractive option.[5]

In addition to convenience, there are other factors to consider when comparing methadone to buprenorphine. In most studies, both methadone- and buprenorphine-exposed neonates exhibited NAS requiring pharmacological intervention. However, neonates exposed to buprenorphine had lower incidences of NAS, required less medication and lower duration for NAS as compared to neonates exposed to methadone.[7, 15-18] In some studies that compared the two maintenance agonist treatments, it was found that incidences of NAS was comparable between buprenorphine and methadone, though there was no mention regarding severity or duration of hospital stay. Regarding birth weights, those same review found that birth weights were higher for neonates exposed to buprenorphine when compared to those exposed to methadone.[6, 19] As compared to women who used methadone for OAT, women on buprenorphine were more likely to initiate OAT before or during early pregnancy, deliver at full term, have longer rates of gestation, and deliver newborns with higher birth weight and bigger head circumference.[15]

Though most studies showed better neonatal outcomes for neonates exposed to buprenorphine, it should be noted that dropout and switch rates from buprenorphine to methadone during treatment was higher than the reverse.[6, 15, 19] The most cited reason was due to suboptimal control of their withdrawal symptoms.[15] Attrition rates for buprenorphine treatment was generally higher than methadone treatment however, the data indicating reasons why is limited as most studies did not track that information. It is an area worth additional research in order to guide best practices for appropriate induction and maintenance dosing.[7]

Opioid agonist therapy during pregnancy, regardless of which medication is used, is an important component of overall maternal, fetal, and neonatal health when compared to uncontrolled opioid addiction during pregnancy. While buprenorphine has been shown in multiple studies to be at least comparable, and in some cases superior, to methadone in terms of neonatal outcomes, all studies concluded that both buprenorphine and methadone are important components of treatment for opioid-dependent women at the time of pregnancy.[3, 7, 15, 19]

Limitations

Further research is needed in many areas. Information regarding the effects of maternal withdrawal on the fetus would be invaluable in guiding treatment for those who wish to initiate naltrexone treatment or detoxification but is very limited due to ethical constraints. Until that data is gathered, non-opioid treatment during pregnancy will not be a viable option for most mothers despite the superior neonatal outcomes as well as the fact that buprenorphine and methadone have quickly become drugs of abuse themselves. The optimal dosing for buprenorphine also needs to be studied further as attrition rates for buprenorphine treatment is higher than those for methadone, but evidence indicates better neonatal outcomes for mothers treated with buprenorphine over methadone. One factor that this study did not take into heavy consideration was the multifaceted nature of low birth weights and its other possible contributors, such as gestational age at birth, polysubstance abuse, cigarette smoking, and alcohol use. However relevant, it was outside the scope of this paper. Lastly, the population of affected children has grown due to the opioid epidemic, yielding an opportune time to study the long-term effects of OAT. Some areas of interest may be behavioral, psychosocial, and pain perception.

Treatment Recommendations

Recommendations on treating pregnant women who use opioids or have OUD place heavy emphasis on screening. Early universal screening is highly advocated in order to both give patients the care they need as well as to give options to women of reproductive age before they become pregnant. Universal screening for every pregnant woman should also be conducted regardless of their demographic or prior medical and social history to reduce stigma and avoid missing cases. There are many recommended screening tools available such as CRAFFT (for women 26 years or younger), 4Ps, NIDA Quick Screen.[3]

Opioid agonist therapy is the treatment of choice for pregnant women with OUD. The outcomes are better for both mother and fetus. It is recommended over medically assisted withdrawal or detoxification due to concerns over high relapse rates and the unknown effects of withdrawal on the fetus. Behavioral therapy should also be initiated in conjunction with OAT and extended into the postpartum period. During prenatal care, the clinician should expand treatment to meet the special needs of both mother and fetus including additional fetal monitoring to track fetal weight and development as well as additional maternal monitoring for diseases common to substance abusers.[3]

Monitoring infants born to mothers who used opioids during pregnancy is important given the possible subtle presentations of NAS. Infants should be monitored and treated by a pediatric care provider. Breastfeeding should be encouraged if the mother is stable on OAT, not abusing licit or illicit drugs, and have no other contraindications such as HIV infection. Contraceptive counseling should be provided for any woman of reproductive age, particularly those who abuse opioids or other drugs to avoid unintended pregnancy. Discussions should be had prior to delivery regarding the possibility of long-term contraceptive devices such as an intrauterine device which could be inserted immediately after delivery.[3]

Conclusion

Opioid agonist therapy is the treatment of choice for pregnant women with OUD. Neonatal outcomes are better with lower rates of NAS and higher birth weights as compared to outcomes for neonates born to mothers with untreated OUD. Medically assisted withdrawal or detoxification have high failure rates and put the mother and fetus at risk for continued gestational opioid exposure and subsequent poor outcomes.

The guidelines that have been outlined can result in high rates of NAS, which can be mentally and emotionally draining for all involved. Additionally, the concept of continuing to give opioids to people who are addicted to opioids runs counter to intuition as well as the precepts of some of the country's most successful addiction recovery and support groups.[20] This can influence people who are pregnant to insist on medically assisted withdrawal or detoxification. It can also put heavy pressure on the provider to advise their patients of the same. However, the data that were investigated for this study show that the nature of opioid addiction can often overcome the nature of sheer willpower. Ultimately, NAS is more treatable than overdose, severe fetal deformities, or fetal death. As a physician assistant, I will give healthy respect to what this study has found and follow the guidelines issued by ACOG. I will advise my prepartum and postpartum patients to consider medically assisted withdrawal or detoxification if I have assessed that it is appropriate on a case-by-case basis.

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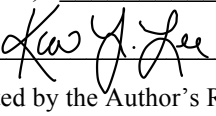
Author's Signature:  Date: 8/8/2019

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