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Is Maternal Buprenorphine Use During Pregnancy Effective In Preventing Neonatal Abstinence Syndrome?

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ABSTRACT

OBJECTIVE: The objective of this systematic review is to determine whether or not maternal buprenorphine use during pregnancy is effective in preventing neonatal abstinence syndrome (NAS).

STUDY DESIGN: Review of three English language primary studies published in 2005, 2006 and 2008.

DATA SOURCES: Two randomized, double blind (with flexible dosing) trials and one case series comparing methadone maintenance and buprenorphine maintenance during pregnancy were found using Ovid MEDLINE and CINAHL databases.

OUTCOME MEASURED: Incidence of neonates requiring treatment for NAS and amount of medication used, total length of hospital stay and peak NAS scores using the Finnegan Scale and a modified 19 item Finnegan Scale. The Finnegan Scale assess infants for the most common signs and symptoms of neonatal withdrawal including: High pitched cry, restlessness, hyperactive moro reflex, tremors, increased muscle tone, excoriation, myoclonic jerks, convulsions, sweating, fever, yawning, mottling, nasal stuffiness, sneezing, nasal flaring, increased respiratory rate, excessive sucking, poor feeding, regurgitation/vomiting, lose/watery stools.

RESULTS: The two RCTs included in this review did not find maternal buprenorphine use to be effective in preventing NAS. The case series included did find a significant relationship between maternal buprenorphine use and a reduction in NAS symptoms.

CONCLUSIONS: The results of the two RCTs demonstrate that maternal buprenorphine use is not effective in preventing NAS symptoms. The case series did find a significant relationship, however because of the nature of the study (case series) the results must be interpreted with caution and additional RCTs are needed to evaluate the effectiveness of maternal buprenorphine use and NAS.

KEY WORDS: Neonatal abstinence syndrome, withdrawal, buprenorphine, methadone, pregnancy.

INTRODUCTION

Illicit drug use among pregnant women is on the rise, resulting in over 225,000 infants in the past year to be exposed to illegal substances prenatally[1]. Neonates exposed to illicit drugs are at greater risk of developing neonatal abstinence syndrome (NAS) as an astounding 50%-95% of infants exposed to heroin in utero will exhibit signs and symptoms of NAS[2]. While NAS is becoming more prevalent, there remains controversy regarding the most effective way to prevent and treat this illness.

Approximately 5.2% of pregnant women and 9.2% of non-pregnant women report past-month illicit drug use[1] making maternal substance abuse and NAS an all too relevant topic in medicine today. The prevalence of opioid use during pregnancy ranges from 1-21% of women[2]. While an exact cost of treating NAS has not been identified, neonatal withdrawal results in longer hospital stays and ultimately increased costs as 60-80% of all infants exposed to methadone will present with some symptoms of NAS[6].

Neonatal withdrawal can occur when a fetus is exposed to a variety of illicit drugs or medications such as opiates, tobacco, alcohol and sedatives. Signs and symptoms of NAS are generally seen within 2-3 days of birth, but may not present for up to one month[1]. Infants are evaluated using the Finnegan Scale, a standardized scoring system that identifies 21 signs and symptoms of withdrawal, such as decreased sleep, tremors, excessive suck, sweating and loose stools[3,4,5].

NAS is generally treated using diluted tincture of opium (DTO)[1], however methadone and morphine are alternatives. In addition to DTO, oral Phenobarbital is often used adjunctively. While these treatments are effective, more information is needed regarding the prevention of NAS. Methadone is the only recommended treatment for opiate dependence in pregnant women,

however over half of methadone exposed infants require treatment for NAS[1]. Buprenorphine, an opioid substitute that has both mixed agonist and antagonist properties may provide an alternative to methadone in pregnant patients. Because buprenorphine has high opioid receptor affinity and low intrinsic activity adults experience fewer signs and symptoms of withdrawal upon discontinuation, it is theorized that infants exposed to buprenorphine in utero may experience fewer signs and symptoms of withdrawal when compared to methadone.[1].

OBJECTIVE

The objective of this systematic review is to determine whether or not maternal buprenorphine use during pregnancy is effective in preventing neonatal abstinence syndrome.

METHODS

Included in this analysis were two randomized controlled trials (RCTs) and a case series, all of which compared maternal buprenorphine use to methadone. The criteria used to select each study included pregnant women who were at least 18 years of age[3] or between the ages of 21-43[4,5] that met the DSM-IV criteria for opioid dependence. The intervention used was sublingual buprenorphine 4-24 mg. Comparison to this intervention was oral methadone HCL 20-100 mg. To assess outcomes a variety of methods were used including the Finnegan Scale and modified Finnegan Scale to assess for signs and symptoms of NAS, need for pharmacologic intervention and length of neonatal hospital stay.

A detailed inquiry was performed by the author using the search engines OVID Medline and CINAHL. The key words "Neonatal abstinence syndrome", "Buprenorphine" and "Pregnancy" were used in combination to search for articles. The articles chosen were published in English and in peer-reviewed journals from 2005-2008. Articles were selected based on their relevance and the importance of outcomes to the patient (Patient Oriented Evidence that Matters,

or POEMS). Studies included in this review were two randomized, prospective, controlled, double blind/double dummy and one case series, all of which included patient oriented outcomes. Table 1 includes the demographics of the included studies. Studies that were excluded included those that used combination treatment with buprenorphine or methadone and those with participants under the age of 18. The statistics utilized in the studies were relative risk reduction (RRR), absolute risk reduction (ARR), numbers needed to treat (NNT) and p-value.

OUTCOMES MEASURED

The primary outcome measured in all three studies was the severity of neonatal withdrawal using either the Finnegan scale[3,6] or modified 19-Item Finnegan scale[5]. The Finnegan scale is a 21 item standardized scoring system that assess for signs and symptoms of opioid withdrawal in neonates[4]. The Finnegan scale includes the following signs and symptoms of withdrawal: Increased/high pitched cry, decreased sleep, hyperactive moro-reflex, tremors (disturbed and undisturbed), increased muscle tone, excoriation, myoclonic jerks, convulsions, mottling, nasal stuffiness, nasal flaring, sweating, fever, increased respiratory rate, excessive suck, regurgitation/vomiting, poor feeding and loose/watery stools[4]. Jones et al utilized a modified Finnegan scale that did not include myoclonic jerks, mottling and excessive suck as part of the evaluation[5]. Other outcomes measured included the number of infants requiring medication management and the total days of neonatal hospital stay [5,6]. In addition Jones et al included total amount of morphine needed to treat NAS symptoms[5].

Table 1: Demographics of included studies

Study	Type	# pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Jones[4], 2005	Double blind with flexible dosing RCT	30	21-40	Gestational age of 16-30 wks; opioid dependence with request for maintenance therapy; recent opioid use; opiate positive urine	Urine positive for undocumented methadone; ETOH abuse/dependence; use of benzos; serious concurrent medical illness; pre-term labor; fetal malformation; HIV +; sickle cell trait	10	Randomized to receive SL buprenorphine HCL (4-24 mg) or methadone HCL (20-100 mg)
Fischer[3], 2006	Double blind with flexible dosing RCT	18	Age ≥ 18	Opioid dependence; gestational age of 24-29 wks; opioid positive urine, but neg for benzos and methadone; negative ETOH breath test	Severe somatic or other psychiatric distress; high risk pregnancies	4	Randomized to receive buprenorphine (8-24 mg) or methadone (40-100 mg)
Kakko[5], 2008	Case series	65	Age ≥ 18	Buprenorphine arm: one year of documented opioid dependence; methadone arm: four years of documented opioid dependence	Less than one year of documented opioid use (buprenorphine arm); less than four years of documented opioid dependence (methadone arm)	0	Buprenorphine maintenance to methadone maintenance during pregnancy

RESULTS

The studies performed by Fischer et al and Jones el al were RCTs that utilized double blind, double dummy with flexible dosing methods in which the neonates were observed in-patient under blinded conditions regarding the mothers treatment. Kakko et al utilized data that was analyzed retrospectively, as it was a case series. Results reported by Fischer et al were presented as continuous data that could not be converted to dichotomous data, where as results reported by Jones et al and Kakko et al were presented in dichotomous format.

Fischer et al did not report sufficient information to convert data to dichotomous format. The authors did report the following; the mean duration of treatment for neonates exposed to buprenorphine was 4.8 days and neonates exposed to methadone was 5.3 days, with a reported p-value of 0.766 (Table 2). Additionally, infants exposed to methadone required treatment for NAS approximately 12 hours before those exposed to buprenorphine, with a reported p-value of 0.537. The amount of medication needed to treat symptoms of NAS did not vary widely as those exposed to buprenorphine required 2.00 mg (± 2.00) of morphine where as those exposed to methadone required 2.71 mg (±1.68) of morphine, with a reported p-value of 0.640 (Table 2). The authors also found that neonates from mothers with high rates of cigarette use (more than 10 cigarettes per day) had higher Finnegan scores than those who smoked less than 10 cigarettes per day. At the time of delivery the mean dose of buprenorphine given to subjects during pregnancy was 13.5 mg and the mean dose of methadone was 47.5 mg (Table 4).

Table 2: Reported data by Fischer et al.

Data Reported	Buprenorphine group	Methadone group	p-value
Mean duration of treatment (days)	4.8 days	5.3 days	0.766
Amount of medication needed to treat (mg of morphine)	2.00 mg (± 2.00)	2.71 mg (± 1.68)	0.640

Jones et al reported that 20% of neonates exposed to buprenorphine required treatment for NAS whereas 45% of infants exposed to methadone required treatment, with a reported p-value of 0.23. The RRR and ARR were calculated to be 56% and 25.5% respectively. NNT was -4, therefore for every 4 patients exposed to buprenorphine in utero there was one fewer incidence of NAS compared to the group exposed to methadone (Table 3). At the time of delivery the average dose of buprenorphine given to subjects during the pregnancy was 18.7 mg and the average dose of methadone was 79.1 mg (Table 4).

Kakko et al reported that 40.4% of neonates exposed to buprenorphine exhibited symptoms of NAS, whereas 77.8% of those exposed to methadone did, with a calculated p-value of 0.0008. RRR and ARR were calculated to be 48% and 37.4% respectively. NNT was -3, therefore for every 3 patients exposed to buprenorphine there was one fewer incidence of NAS than in the group exposed to methadone (Table 3). Kakko et al also reported that 14.9% of infants exposed to buprenorphine required treatment for NAS symptoms, where as 52.8% of those exposed to methadone did, with a p-value of 0.0004. Additionally the total hospital stay was significantly longer in infants exposed to methadone (19.7 ± 18.8 days) compared to infants exposed to buprenorphine (9.4 ± 8.4 days), with a reported p-value of 0.0009. At the time of birth, the mean amount of buprenorphine given to subjects during the pregnancy was 15.4 mg (± 6.4) and the mean amount of morphine was 71.3 mg (± 27.3) (Table 4).

Table 3-Efficacy of buprenorphine in prevention of NAS (Jones et al & Kakko et al)

Study	CER	EER	RRR	ARR	p-value	NNT
Jones[4]	45.5%	20%	-56%	-25.5%	0.23	-4
Kakko[5]	77.8%	40.4%	-48%	-37.4%	0.0008	-3

Table 4-Mean Doses of Maternal Buprenorphine and Methadone

Study	Mean Dose of Buprenorphine (mg)	Mean Dose of Methadone (mg)
Fischer[3]	13.5	47.5
Jones[4]	18.7	79.1
Kakko[5]	15.4 (± 6.4)	71.3 (± 27.3)

The included studies required a maternal history of opioid dependence as defined by the DSM-IV. Participants in the study performed by Jones et al were randomized to receive sublingual buprenorphine 4-24 mg or methadone HCL 20-100 mg, which was titrated based on each individual's signs and symptoms of withdrawal. The study began with 30 participants, with 10 women withdrawing, reasons included a medical condition, missed consecutive dosing days and an elective withdrawal. Similarly, participants in the study performed by Fischer et al were randomized to receive 8-24 mg of buprenorphine or 40-100 mg of methadone; they began with 18 participants and had 4 withdrawals. Reasons for withdrawal included two participants who were non compliant with scheduled visits, one stillbirth and one late abortion. Kakko et al performed a case series, therefore retrospectively analyzed 39 pregnant women who were managed using buprenorphine therapy and 26 pregnant women who were managed using methadone therapy.

Co-morbid drug use was a common external factor in all three studies. Kakko et al noted that 15 out of 47 participants in the buprenorphine group utilized illicit substances (either opiates or cannibis) and 17 of the 35 participants receiving methadone did. Fischer et al reported at 14 weeks 66% of mothers were positive for opiates, 48% were positive for cocaine and 16% were positive for benzodiazepines; however between 36-38 weeks all participants were opioid positive, but negative for cocaine and benzodiazepines. Jones et al reported of those treated with buprenorphine 16.7% tested positive for opiates, 15.2% were positive for cocaine and 2.5% were positive for benzodiazepines at the time of birth. Similarly, of those treated with morphine 15.6% tested positive for opiates, 11.2% were positive cocaine, 0.4% were positive for benzodiazepines and 7.5% were positive for marijuana.

DISCUSSION

Buprenorphine is FDA approved for the treatment of opiate dependence by preventing symptoms of withdrawal. It is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor and is a Schedule III narcotic[4]. It is available in two formulations; Suboxone, which contains buprenorphine HCL and naloxone HCL and Subutex, which contain only buprenorphine HCL. Currently buprenorphine is classified under pregnancy category C and is indicated during pregnancy only if the benefit justifies the potential risk to the fetus[4]. Caution must be used when taking buprenorphine, as respiratory depression and death are potential adverse effects[4].

The study by Kakko et al appeared to show a significant relationship between maternal buprenorphine use and a decrease in NAS symptoms ($p=0.0008$). While these findings are clinically significant, one must use caution when interpreting these results due to the nature of the study (case series). The two RCTs reviewed (Fischer et al and Jones et al) did not show a

clinically significant correlation between maternal buprenorphine use and a decrease in NAS symptoms. Each of the studies included did have limitations. The study performed by Kakko et al was limited as it was a case series, the study was non-randomized, duration of previous drug abuse was unknown and NAS scoring and assessments were not blind. While the study by Jones et al was a RCT, it also had its limitations. The study included only 30 participants with 10 withdrawals and women were not enrolled into the study until 16 weeks gestational age therefore generalizations cannot be made regarding neonates conceived during already established maintenance therapy. Fischer et al similarly only had 18 participants with 4 withdrawals and concurrent tobacco use may have affected outcomes. All of the studies were limited by illicit drug use.

CONCLUSION

The studies reviewed demonstrate that maternal buprenorphine use during pregnancy is not effective in reducing signs and symptoms of NAS when compared to methadone. While Kakko et al did find a significant relationship these findings were limited due to the nature of the study (case series), the results would have been more significant if it had been a RCT. The two RCTs included did not find a significant correlation between maternal buprenorphine use and a reduction in NAS symptoms. Future studies are warranted to evaluate the efficacy of buprenorphine and NAS. Efforts should be made to reduce outside influences such as illicit drug use and tobacco use. Larger sample sizes are needed and ideally treatment with either buprenorphine or methadone should be started prior to conception. Additionally, efforts should also be made to standardize dosing of buprenorphine and methadone among participants.

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