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Opioid Dependency in Pregnancy and Length of Stay for Neonatal Abstinence Syndrome

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Abstract

Objective—To examine opioid replacement therapy in pregnancy and maternal effects on neonatal outcomes including length of hospital stay for neonatal abstinence syndrome.

Design—Retrospective descriptive study.

Setting—Labor and Delivery Unit and Neonatal Intensive Care Unit (NICU), Eastern Maine Medical Center, Bangor, Maine.

Participants—One hundred fifty two opioid dependent pregnant women on methadone maintenance therapy (MMT) (n = 136) or buprenorphine maintenance therapy (BMT) (n = 16) during pregnancy and their neonates. The neonates were born between January 1, 2005 and December 31, 2007.

Methods—A review of the electronic medical records (EMR) was conducted of all opioid dependent women who were maintained on MMT or BMT at the time of admission for labor and delivery and their neonates.

Results—Maternal methadone dose and concomitant *in-utero* exposure to benzodiazepines prolonged the length of hospital stay for neonates. Length of stay was shorter in breastfed neonates as compared to formula fed neonates or neonates who received formula and breast milk. Neonates with a prenatal exposure to MMT as compared to BMT spent more days in the hospital (21 vs. 14 days) for treatment of neonatal abstinence syndrome (NAS).

Conclusion—These findings are consistent with previous research on the simultaneous use of methadone and benzodiazepines during pregnancy and provide further direction for the treatment of opioid dependency during pregnancy. Harm reduction strategies for opioid dependent pregnant women in substance abuse treatment with MMT may one day include guidance on daily treatment doses and recommendations to avoid the concomitant use of benzodiazepines to lessen NAS. Breastfeeding should be recommended to shorten LOS. Understanding perinatal and neonatal outcomes of pregnant women on methadone or buprenorphine will help to identify optimal treatment for opioid dependency in pregnancy.

Keywords

Opioid dependency; neonatal abstinence syndrome; methadone maintenance therapy; buprenorphine maintenance therapy; selective serotonin reuptake inhibitors; benzodiazepines; neonatal length of stay; breastfeeding

Opioid dependency in pregnancy is linked to physical, mental, and psychological problems for the pregnant women and their offspring (Kaltenbach, Berghella, & Finnegan, 1998) and increases the risk for preterm delivery and low birth weight (Fajemirokun-Oduzeyi et al.,

2005). To lower health risks, pregnant women who are opioid dependent have been treated with methadone maintenance therapy (MMT), the standard of care for several decades (Jones et al., 2005). Another treatment option became available when the United States (U.S.) Food and Drug Administration (FDA) approved the use of buprenorphine maintenance therapy (BMT) in 2002 as a treatment for opioid dependence (Rayburn & Bogenschutz, 2004). However, neonates with intrauterine opioid exposure are at risk for withdrawal and prolonged length of hospital stay (LOS). Strategies to optimize therapy for opioid dependent pregnant women to improve neonatal outcomes are essential. One approach has been to compare the two synthetic opioid replacement therapies on perinatal and neonatal outcomes, particularly neonatal abstinence syndrome (NAS) however, findings continue to be inconclusive (Jones et al., 2010; Kakko, Heilig, & Sarman, 2008; Minozzi, Amatao, Vecchi, & Davoli, 2008). Hence, the current study examined the experience of opioid replacement therapies in a large rural sample.

Twenty-one to 94% of neonates with *in utero* exposure to opioids experience withdrawal symptoms characterized by central nervous system hyperirritability, gastrointestinal dysfunction, respiratory distress and vague autonomic symptoms such as yawning, sneezing, mottled color and fever (Ebner et al., 2007; Jansson, Velez, & Harrow, 2009) with a 46%–78% likelihood of receiving pharmacologic treatment with an extended hospital stay (Dashe et al., 2002; McCarthy, Leamon, Parr, & Anania, 2005). Prolonged hospitalization of neonates with NAS may affect infant attachment, disrupt families, and increase health care costs. Long term effects of such exposures and the consequences of NAS remain unclear (Sanchez, Bigbee, Fobbs, Robinson, & Sato-Bigbee, 2008).

Methadone Maintenance Therapy

The use of methadone in opioid dependent pregnant women lowers maternal morbidity and mortality rates and promotes fetal stability and growth compared to women who use heroin (Ludlow, Evans, & Hulse, 2004). Continuous methadone treatment during pregnancy is associated with improved earlier antenatal care (Burns, Mattick, Lim, & Wallace, 2007), compliance with prenatal care and better preparation for infant care and parenting responsibilities (Dawe, Harnett Rendalls, & Staiger, 2003). However, the neonate exposed to methadone *in utero* is at risk for neonatal abstinence syndrome (NAS) and prolonged hospital stay (Arlettaz et al., 2005). The higher the maternal methadone dosages the more severe the NAS (Dashe et al., 2002; Isemann, Meinzen-Derr, & Akinbi, 2011; Lim, Prasad, Samuels, Gardner, & Cordero, 2009; Sharpe & Kuschel, 2004) although Kuschel, Austerberry, Cornwell, Couch, and Rowley, (2004) and Pizarro et al. (2011) found that the maternal methadone dose did not predict the need for NAS treatment. McCarty et al. (2005) showed that pregnant women on higher doses of methadone had significantly less illicit drug use at delivery even when the women had longer histories of drug addiction. Gravid women on MMT who use more than two illicit substances have higher preterm birth rates compared to the national average (Almario, Seligman, Dysart, Berghella, & Baxter, 2009). They found that the incidence of preterm birth was 29.1% with MMT alone and higher in women who abused illicit drugs and/or alcohol while on MMT.

A majority of opioid dependent women on maintenance treatment use tobacco, which plays an important role in perinatal outcomes, particularly preterm birth (Kearney, 2008). Those who smoked more than 20 cigarettes per day had the added risk of having neonates with significantly higher NAS peak scores and took longer to peak than those who smoked less (Choo, Huestis, Schroeder, Shin, & Jones, 2004). Beyond the neonatal period, maternal cigarette smoking has been found to be a precursor to neuro-psychological deficits in offspring and these deficits have been associated with problematic behaviors, including early onset criminal offenses (McGloin, Pratt, & Piquero, 2006).

Among pregnant women on MMT, tobacco use has also been found to be significantly associated with maternal mood disorders (Chisolm, Tutuen, Brigham, Strain, & Jones, 2009). Treatment of co-occurring psychiatric disorders with antidepressants, benzodiazepines or antipsychotics may further impact NAS. The concomitant use of benzodiazepines and MMT was associated with longer stays for the neonates with NAS (Seligman et al., 2008). Benzodiazepines used by women during pregnancy can accumulate in the fetal tissue, especially if the use was chronic or at high doses (Guthrie & Augustin, 2008) and this may delay neonatal withdrawal symptoms (Oei & Lui, 2007).

Another factor that impacts NAS is the concentration of opioids in fetal circulation, which is influenced by gestational age and placental function (Farid, Dunlop, Tait, & Hulse, 2008; Nanovskaya et al., 2002, 2004, 2005; Nekhayeva et al., 2005). As pregnancy progresses, there is a reduction in maternal methadone blood levels and the placenta affects the concentration of methadone in fetal circulation. This may account for the variability seen in the incidence and intensity of NAS among exposed infants, specifically at different gestational ages. Furthermore, breastfeeding is speculated to ameliorate the potential for severe NAS and the need for NAS treatment (Jansson et al., 2007; 2008). The concentrations of methadone and buprenorphine found in human milk are low; therefore, women on opioid maintenance therapy should be permitted to breastfeed if desired and stable (Jansson, 2009). Taken together, there is variability in neonatal outcomes when MMT is used during pregnancy due to a number of maternal behaviors and physiological changes in pregnancy.

Buprenorphine Maintenance Therapy

Buprenorphine hydrochloride was approved by the FDA for treatment of opioid dependent patients in 2002 but not for pregnant patients (Comer & Annitto, 2004). Women in treatment for opioid dependence that have conceived while on BMT have been permitted to continue with BMT for the duration of their pregnancy if stable. It is hypothesized that BMT may be equally effective to MMT and yield less intense NAS in the neonate (Jones et al., 2005; 2010; Fischer et al., 2006; Kayemba-Kay's & Lacllyde, 2003; Nanovskaya, Deshmukh, Brooks, & Ahmed, 2002; Schindler et al., 2003). The placenta acts as a depot for buprenorphine thus lowering transplacental transfer to fetal circulation and lessening the incidence and intensity of NAS (Nanovskaya et al., 2002, 2004, 2005; Nekhayeva et al., 2005). Significant differences in urinary disposition of buprenorphine metabolites between trimesters in nine pregnant women points to other possible causes for the variability seen in neonatal NAS from BMT (Kacinko, Jones, Johnson, Choo, & Huestis, 2008).

Methadone Versus Buprenorphine in Pregnancy

Findings from a number of comparative studies on the use of methadone and buprenorphine in pregnancy have led to the increased use of buprenorphine among pregnant women despite lack of FDA approval. Buprenorphine exposed fetuses had higher levels of fetal heart rate variability and accelerations, greater coupling between fetal heart rate and fetal movement, and less suppression of motor activity and longer duration of movement than the methadone exposed fetuses (Jansson et al., 2011). Kahila, Saisto, Kivitie-Kallio, Haukkamaa, and Halmesmaki (2007) compared outcome measures of women on BMT to national statistics and found that the pregnancies and deliveries were uneventful; however, severe NAS occurred in 57% of the newborns and there were two deaths from sudden infant death syndrome (SIDS). Kakko et al. (2008) followed BMT exposed neonates and MMT exposed neonates and found significant advantages with BMT over MMT. Birth weight was higher in the BMT exposed group due to longer gestation and the incidence of NAS of any intensity, as well as the incidence of NAS that received pharmacologic treatment, was lower. The duration of hospitalization was shorter for the BMT exposed neonates which was

consistent with previous research (Jones, 2005; Johnson, Jones, & Fisher, 2003; Kayemba-Kay's & Laclede, 2003; Lejeune, Simmat-Durand, Gourarier, & Aubisson, 2006). When BMT was started pre-conception, NAS was less frequent than in subjects with post conception initiated treatment (Kakko et al., 2008). The prognosis for the infants improved because of the specialized prenatal care that the mothers received regardless of the type of opioid substitution (Simmat-Durand, Lejeune, & Gourarier, 2008; Vavrinková & Binder, 2007). A prospective comparative study of the effect of buprenorphine, methadone, and street heroin on the course of pregnancy and NAS found that substitution therapy decreases street heroin use but methadone increases NAS severity (Binder & Vavrinková, 2008).

Findings from the Maternal Opioid Treatment: Human Experimental Research (MOTHER) project, a multicenter, randomized clinical trial comparing buprenorphine with methadone for the treatment of opioid dependent pregnant women, supports the use of BMT in pregnancy (Jones et al., 2010). Neonates exposed to BMT required significantly less morphine to treat NAS, had a significantly shorter hospital stay and experienced a significantly shorter duration of treatment for NAS. The researchers concluded that BMT should be considered as a safe alternative to methadone and perhaps even as a first-line treatment option for opioid dependency during pregnancy. Clinicians are reminded to consider the ceiling effect of buprenorphine and the possibility of lowered adherence to treatment in comparison to methadone (Jones et al., 2010). Significant gaps in knowledge remain in the treatment of opioid dependent pregnant women particularly in regard to the type and dose of opioid replacement therapy and the effects of concomitant exposures to tobacco, marijuana, SSRIs and benzodiazepines on NAS.

Generally, opioid dependent pregnant women are advised to initiate or continue with opioid replacement therapy over illicit drug use to improve perinatal and neonatal outcomes. However, their neonates are at risk for NAS and prolonged hospital stays. The intent of the current study was to identify maternal and neonatal factors that may influence or predict NAS and thus LOS in neonates exposed to opioid replacement therapy. Although BMT was less commonly used to treat opioid dependent pregnant women during this research period (January 1, 2005– December 1, 2007), neonates in the current study included those with buprenorphine exposure. In the large methadone exposed sample, we hypothesized that concomitant prenatal exposures, such as tobacco, alcohol, marijuana, selective serotonin reuptake inhibitors (SSRIs), and benzodiazepines may increase LOS. Further, we hypothesized that the neonates of opioid dependent pregnant women on buprenorphine, as compared to methadone, would have reduced LOS. Specific aims were to:

1. Examine the effect of methadone dose on neonatal LOS;
2. Examine neonatal LOS in the presence of other exposures (tobacco, marijuana, benzodiazepines, SSRIs and alcohol) and with infant feeding method;
3. Compare MMT to BMT in this small sample.

Method

Institutional Review Board approval was obtained from Eastern Maine Medical Center (EMMC), Bangor, Maine and the University of Maine, Orono, Maine. A retrospective chart review was conducted of medical records for opioid dependent pregnant women on MMT or BMT and their newborns delivered between January 1, 2005 and December 31, 2007. The electronic medical records (EMRs) were queried at EMMC and a list of women on prescribed MMT or BMT when admitted for labor and delivery was generated. Similarly, a list of neonates diagnosed with NAS was generated as a cross reference. Women on MMT (n = 136) or BMT (n = 16) who labored and delivered at EMMC or at an outlying community hospital during the same time-period and whose neonates were directly admitted

to the EMMC Neonatal Intensive Care Unit were used for the study. Opioid dependent women not on prescribed replacement therapy with MMT or BMT were excluded from the study. Neonates less than 28 weeks gestation were excluded ($n = 2$) as the ability of the placenta to metabolize methadone or store buprenorphine prior to the third trimester is unclear (Nanovskaya et al., 2004).

A data collection worksheet developed by the nurse researcher was approved for use by a panel of expert researchers as a research tool prior to the start of this study. This tool was used solely by the nurse researcher to document demographic data obtained on each mother-neonate dyad as well as information regarding the variables of interest in the study. Some EMRs were reviewed twice for accuracy.

Maternal Measures

Maternal age, gravidity, parity, gestational age when prenatal care was initiated, number of prenatal visits, form of maintenance treatment (MMT or BMT) and dose, number of cigarettes smoked during pregnancy (none, 0-½ pack per day [PPD], ½ PPD-1 PPD and >1PPD) and self reports of alcohol consumed while pregnant were extracted from prenatal, intrapartum and neonatal EMRs. In most cases, mothers' use of substances was queried on the initial prenatal visit. Subsequent antepartum and intrapartum assessments of maternal drug exposures (prescribed and illicit) and urine drug screen results for benzodiazepines, cannabinoids and other opioids were noted.

Neonatal Measures

Neonatal date of birth, gender, type of feeding (breast milk, formula, or both), gestational age at the time of birth, birth weight, head circumference, size for gestational age, LOS, need for pharmacologic therapy for NAS (yes vs. no), age (measured in days) when infant first started pharmacologic treatment for NAS, type of treatment used (phenobarbital [first line therapy]) and age when second line therapy (diluted deodorized tincture of opium [dDTO]) was started during initial hospitalization.

Statistical Analyses

The data analysis was generated using the Statistical Package for the Social Sciences (SPSS™) version 19. Descriptive statistics were used on demographic factors. Adequate power to examine the influence of maternal lifestyle and infant feeding method was afforded in the methadone group, which was examined separately using multiple linear regression statistics. The model examined variables hypothesized to affect LOS: maternal methadone dose, smoking, SSRIs, benzodiazepines, alcohol, other opioids and marijuana. In addition we added infant feeding method because of the association with LOS in other studies (Jansson, et al, 2007; 2008a; 2008b; Jansson, 2009). Significance was set at $p = .05$.

Results

Table 1 shows the demographics comparing MMT and BMT maternal samples for antenatal variables related to comorbid prenatal drug, nicotine and alcohol use. The mean maternal age was 25.3 years (standard deviation [SD] = 3.9, range 18–37). Other demographic variables and outcome in terms of means, SDs and percents for MMT and BMT groups are presented. Group contrasts were examined with t-test means comparisons or Chi square for categorical variables. All demographics measures were similar between the MMT and BMT groups; with the exception that marijuana use during pregnancy was reported as significantly higher in the MMT group ($p < .05$).

All of the women qualified for MaineCare, Medicaid health insurance for low-income families and therefore deemed socio-economically disadvantaged. The demographic characteristics of the two groups of women, those on methadone and those on buprenorphine, were similar for age, gravidity, parity, gestational age at first prenatal visit, number of prenatal visits, reported use of tobacco, alcohol, and marijuana, and documentation of prescribed SSRIs and/or illicit use of benzodiazepines and other opioids.

Neonatal Outcomes

Table 2 displays the descriptive statistics that were calculated for the 152 neonates exposed prenatally to MMT (n = 136) or BMT (n = 16); one of the MMT neonates had exposure to BMT in early pregnancy then the mother was converted to MMT by the time of delivery. Despite the group size differences, we found that the MMT group had significantly smaller head circumference (p < .03). There were also differences by group in size for gestational age (p < .03) with MMT group showing more SGA and BMT showing more neonates with LGA diagnosis. However, the group size differences are a caution in interpreting the demographic findings.

Methadone Group Analyses

A multiple regression model was developed to examine LOS in relation to maternal methadone dose and the hypothesized concomitant exposures associated with maternal lifestyle and health. The following predictors were entered into the model: maternal methadone dose, smoking (none, 0-½ pack per day [PPD], ½ PPD-1 PPD and >1PPD), marijuana (yes vs. no), benzodiazepines (yes vs. no), SSRIs (yes vs. no), alcohol (yes vs. no), use of other opioids (yes vs. no) and infant feeding method (dummy coded as formula, mixed [formula and breast milk] and breast milk only). Table 3 shows that the overall model was statistically significant, $F(8,101) = 3.93$, $p < .000$, $R^2 = .24$ with effects detected for methadone dose (p = .022), benzodiazepine exposure (p = .006), and feeding method (p = .052). Maternal methadone dose and concomitant use of benzodiazepines increased LOS by 8.6 days while women on MMT who breastfed their neonates shortened their infants' LOS. In this model, LOS in methadone exposed neonates was increased by maternal methadone dose and concomitant exposure to benzodiazepines. Infants with prenatal exposure to methadone who were breastfed were discharged home earlier than those infants who were formula fed.

Discussion

The main findings of this retrospective study suggest that maternal methadone dose was associated with neonatal LOS. These findings are similar to those of Woules and Woodward (2010) who reported a positive relationship between maternal methadone dose and NAS. Most recently, Pizarro (2011) found that higher methadone doses were not associated with increased rate or severity of NAS or other adverse perinatal outcomes; therefore, dosing should not be restricted or lowered during pregnancy. Controversy over methadone dosing for maintenance therapy in pregnancy persists and warrants further investigation. Individual variations in body weight, rates of metabolism and interactions between tobacco, methadone and other medications being taken simultaneously must be considered.

Seligman et al. (2008) reported that maternal benzodiazepine use is a predictor variable for length of treatment for NAS. Neonates exposed to methadone and benzodiazepines while *in utero* and who were born at term had significantly longer length of treatment for NAS when compared with unexposed neonates or to exposed neonates born prematurely (Seligman et al.). Symptoms of benzodiazepine withdrawal confound NAS treatment and scoring because of the potential for delayed onset of withdrawal symptoms by 12–21 days of life (Oei & Lui,

2007). Concomitant exposure to SSRIs with MMT did not prolong LOS and this confirmed reports by Seligman et al. (2008) that SSRIs were not associated with longer length of treatment of neonatal NAS.

Infant feeding method was negatively related to LOS, suggesting that breastfeeding may be protective for neonates withdrawing from opioids. This finding might have been statistically significant with a larger sample. Although Jansson et al. (2008) found that concentrations of methadone in breast milk were low and not related to maternal dose, increasing evidence from our group (Brown, Hayes, & LaBrie, 2011; Pritham, 2011) found that breastfeeding was associated with a decreased rate of infant treatment for withdrawal from prenatal methadone or buprenorphine exposure. Breastfeeding is permitted and encouraged if the maternal urine drug screen is negative for illicit substances upon admission for active labor.

Although the study lacked equivalence of subjects in the two exposure groups (methadone and buprenorphine), neonates exposed to buprenorphine experienced less severe NAS and shorter LOS than those exposed to methadone by seven days, which is consistent with prior comparative studies (Binder & Vavrinkova, 2008; Fisher et al, 2006; Jones et al., 2005; 2006; 2010; Kakko et al., 2008; Minozzi et al., 2008). One of the limitations seen with previous comparative studies, as well as this study, is that the buprenorphine groups have been small and insufficiently powered to detect meaningful differences between methadone and buprenorphine. Evidence from the MOTHER project (Jones et al., 2010) suggests that BMT may be preferable over MMT in the treatment of opioid dependence during pregnancy as NAS is less severe. The outcome of the MOTHER project provides the FDA with additional longitude information about the safety and efficacy of BMT during pregnancy, but prospective studies on the immediate and long-term outcomes of neonates with exposure to both forms of opioid replacement therapies are necessary (Jones et al., 2008).

Limitations of the Study

This study had several limitations that should be considered when interpreting the findings. First, the researcher was dependent on the availability of medical records and accuracy of clinicians' documentation of exposure history to a number of substances of interest. Maternal drug use was mostly determined by self-report, which can be unreliable in pregnant women. Pregnant women often minimize their reported use of cigarettes and alcohol due to social stigma and shame. Opioid dependent pregnant women are under close scrutiny by social services and underreporting of prenatal alcohol use or abuse is likely to avoid the potential loss of infant custody to child protective services. Thus, the lack of tobacco or alcohol effects on neonatal length of stay may be due to a social desirability bias related to underreporting or false reports by the women.

It was difficult to determine from the obstetrical records when some of the women started opioid replacement therapy, SSRIs or benzodiazepines. Documentation pertaining to dose, frequency and duration of the SSRIs and benzodiazepines used in pregnancy was lacking. Examining the duration and amount of *in-utero* exposure to opioid replacement therapy, SSRIs and benzodiazepines by the neonates and subsequent LOS would have been valuable. Seligman (2008) found an association between term versus preterm birth and longer length of neonatal treatment for NAS after exposure to MMT. The explanation given was that term infants have a greater duration of intrauterine exposure to substances than preterm infants do.

Another limitation of the study was the presence of unmeasured confounders such as maternal length of time in addiction treatment, number of treatment relapses, time of initiation of MMT or BMT relative to gestational age and duration of such therapy. An examination of the women's lifetime history of substance abuse and family violence may

better explain continued drug use during pregnancy. Knowledge of addiction severity, length of time in treatment for addictions, and the frequency of relapse over a lifetime may help to distinguish women on MMT from women on BMT. Furthermore, BMT differs from MMT in opioid equivalence and may not be comparable. Most importantly, the study lacked equivalence of subjects in the two exposure groups, MMT and BMT. BMT is not FDA approved for use in pregnancy which constrained the number of pregnant women on BMT available during this study period. Some neonates with prenatal exposure to licit or illicit MMT or BMT without symptoms of NAS may have been inadvertently discharged home early and not identified as part of the sample.

The mean LOS at EMMC was examined to evaluate the neonates' severity of NAS, although another marker of the severity of NAS was the initiation of first line therapy with phenobarbital and second line therapy with dDTO to treat NAS. Beyond this, further analysis of NAS drug regimen and doses, was not conducted although the treatment pharmacotherapy was standardized for all infants in both groups during the period of data collection. We did not examine neonatal drug regimen and it was not controlled for across groups.

Implications for Practice

Educating pregnant women on opioid replacement therapy and their clinicians that the concomitant use of benzodiazepines may potentiate NAS in their neonates is an essential harm reduction strategy. Jones et al. (2008), through collective clinical and research experience, summarized many of the key issues in the treatment of opioid dependent pregnant women and offered general recommendations for antepartal, intrapartal, and postpartal care but standardized protocols are necessary. Evidence from the MOTHER project (Jones et al., 2010) suggests that BMT may be preferable over MMT in the treatment of opioid dependence during pregnancy as NAS is less severe. However, without FDA approval, clinicians remain reluctant to prescribe buprenorphine for pregnant women. New models for providing care to opioid dependent pregnant women are needed that address poly-substance abuse, co-occurring psychiatric disorders and possible medication interactions. Clearly, the integration of obstetrical care/primary care within substance abuse treatment programs would increase awareness of the risks of concomitant use of benzodiazepines with MMT and perhaps BMT on perinatal outcomes. Collaboration between the addiction treatment specialists, psychiatrists, and prenatal care providers is essential. Collective emphasis on nonpharmacologic alternatives for the management of depression and anxiety is needed to lessen any unnecessary fetal exposures.

NAS may prolong hospitalization of neonates with *in-utero* exposure to MMT or BMT and this may impact maternal-infant bonding and attachment and places additional burdens on families and the health care system. Breastfeeding, which has been associated with a decreased need for NAS treatment and promotes infant attachment and bonding, should be encouraged. Other interventions, such as infant swaddling and minimizing external stimuli, to lessen the severity of NAS and possibly the need for pharmacologic treatment of NAS, will shorten length of hospital stay as well and are cost effective.

Conclusion

There is growing evidence that demonstrates the superiority of BMT over MMT in pregnancy outcomes and NAS (Jones et al., 2010) and fetal neurodevelopmental indicators (Jansson et al., 2011). This has influenced decisions made by practitioners to allow women on buprenorphine prior to pregnancy to remain on buprenorphine while pregnant as long as they are not experiencing withdrawal symptoms. Ongoing individualized assessments of treatment response and dose adjustments throughout pregnancy with adjunct psychosocial

interventions will enhance the effects of MMT and BMT (Connock et al., 2007). One of the concerns when evaluating neonates of opioid dependent pregnant women is the impact of multiple substances, licit and illicit, used during pregnancy that may affect the expression of NAS (Jansson, 2008) and even worsen the withdrawal symptoms. Improved addiction treatment and prenatal care during the antepartal period is thought to mitigate this.

Nocon (2006) reported that a buprenorphine-managed mother might save at least \$25,000 in hospital expenses even though methadone is less expensive and in some cases is more effective in treatment retention than buprenorphine (Connock et al., 2007). Nocon states that minimal to no NAS from buprenorphine results in less morbidity to the newborn and fewer admissions to the NICU which is cost saving for patients and insurers.

Further research is needed to determine differences in NAS between neonates whose initial exposure to opioid replacement therapy occurred at different gestational ages and with different durations of exposure. Longitudinal studies of the neonates with *in-utero* exposure are necessary to identify potential long term effects on neurological development.

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References

- Almario CV, Seligman NS, Dysart KC, Berghella V, Baxter JK. Risk factors for preterm birth among opiate-addicted gravid women in a methadone treatment program. *American Journal of Obstetrics & Gynecology* 2009; 201:326.e1–6.
- Arlettaz R, Kashiwagi M, Das-Kundu S, Fauchere JC, Lang A, Bucher HU. Methadone maintenance program in pregnancy in a Swiss perinatal center (II): Neonatal outcome and social resources. *Acta Obstetrica et Gynecologica Scandinavica*. 2005; 84:145–150. [PubMed: 15683374]
- Binder T, Vavrinkova B. Prospective randomized comparative study of the effect of buprenorphine, methadone and heroin on the course of pregnancy, birth weight of newborns, early postpartum adaptation and course of neonatal abstinence syndrome (NAS) in women followed up in the outpatient department. *Neuroendocrinology Letters*. 2008; 29(1):80–86. [PubMed: 18283247]
- Brown, M.; Hayes, M.; LaBrie, S. Breast feeding is associated with decreased risk and length of treatment for neonatal abstinence syndrome (NAS) in methadone and buprenorphine exposed infants [Poster]. Presented at Pediatric Academic Societies and Asian Society for Pediatric Research 2011 Joint Meeting; Boston, MA. 2011 Apr-May.
- Burns L, Mattick RP, Lim K, Wallace C. Methadone in pregnancy: Treatment retention and neonatal outcomes. *Addiction*. 2007; 102(2):264–270. [PubMed: 17222281]
- Chisolm MS, Tuten M, Brigham EC, Strain EC, Jones HE. Relationship between cigarette use and mood/anxiety disorders among pregnant methadone-maintained patients. *American Journal of Addictions*. 2009; 18(5):422–429.
- Choo RE, Huestis MA, Schroeder JR, Shin AS, Jones HE. Neonatal abstinence syndrome in methadone-exposed infants is altered by level of prenatal tobacco exposure. *Drug and Alcohol Dependence*. 2004; 75:253–260. [PubMed: 15283946]
- Comer VG, Annitto WJ. Buprenorphine: A safe method for detoxifying pregnant heroin addicts and their unborn. *The American Journal on Addictions*. 2004; 13:317–318. [PubMed: 15370952]
- Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, Taylor R. Methadone and buprenorphine for the management of opioid dependence: A systematic review and economic evaluation. *Health Technology Assessment*. 2007; 11(9) Executive Summary.
- Dashe J, Sheffield JS, Olscher DA, Todd SJ, Jackson GL, Wendel GD. Relationship between maternal methadone dosage and neonatal withdrawal. *The American College of Obstetricians and Gynecologists*. 2002 Dec.100:1244–1249.

- Dawe S, Harnett PH, Rendalls V, Staiger P. Improving family functioning and child outcomes in methadone maintained families: The parents under pressure programme. *Drug and Alcohol Review*. 2003; 22:299–307. [PubMed: 15385224]
- Ebner N, Rohmeister K, Winklbaur B, Baewert A, Jagsch R, Peternell A, Fischer G. Management of neonatal abstinence syndrome in neonates born to opioid maintained women. *Drug Alcohol Dependence*. 2007; 87(2–3):131–138.
- Fajemirokun-Odudeyi O, Sinha C, Tutty S, Pairedeau P, Armstrong D, Phillips T, Lindow SW. Pregnancy outcome in women who use opiates. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2005; 126:170–175. [PubMed: 16202501]
- Farid WO, Dunlop SA, Tait RJ, Hulse GK. The effects of maternally administered methadone, buprenorphine and naltrexone on offspring: Review of human and animal data. *Current Neuropharmacology*. 2008; 6:125–150. [PubMed: 19305793]
- Fischer G, Ortner R, Rohmeister K, Jagsch R, Baewer A, Langer M, et al. Methadone versus buprenorphine in pregnant addicts: A double-blind, double dummy comparison study. *Addiction*. 2006; 101:275–281. [PubMed: 16445556]
- Guthrie, SK.; Augustin, SG. Psychiatric disorders. In: Koda-Kimble, MA.; Young, LY.; Kradjan, WA.; Guglielmo, BJ.; Alldredge, BK.; Corelli, RL.; Williams, BR., editors. *Applied Therapeutics: The Clinical Use of Drugs*. 9. Philadelphia: Wolters Kluwer Lippincott Williams & Wilkins; 2008. p. 76-17.
- Isemann B, Meinzen-Deer J, Akinbi H. Maternal and neonatal factors impacting response to methadone therapy in infants treated for neonatal abstinence syndrome. *Journal of Perinatology*. 2011; 31:25–29. [PubMed: 20508596]
- Jansson LM. Commentary neonatal abstinence syndrome. *Acta Paediatrica*. 2008; 97(10):1321–1323.
- Jansson LM. ABM clinical protocol #21: Guidelines for breastfeeding and the drug-dependent woman. The Academy of Breastfeeding Medicine Protocol Committee. *Breastfeeding Medicine*. 2009; 4(4):225–228. [PubMed: 19835481]
- Jansson LM, Choo RE, Harrow C, Velez M, Schroeder JR, Lowe R, Huestis MA. Concentrations of methadone in breast milk and plasmas in the immediate perinatal period. *Journal of Human Lactation*. 2007; 23(2):184–190. [PubMed: 17478871]
- Jansson LM, Choo R, Velez ML, Harrow C, Schroeder JR, Shakleya DM, Huestis MA. Methadone maintenance and breastfeeding in the neonatal period. *Pediatrics*. 2008a; 121(1):1056–114.
- Jansson LM, Choo R, Velez ML, Lowe R, Huestis MA. Methadone maintenance and long-term lactation. *Breastfeeding Medicine*. 2008b; 3(1):34–37. [PubMed: 18333767]
- Jansson LM, Dipietro JA, Velez M, Elko A, Williams E, Milio L, Jones HE. Fetal neurobehavioral effects of exposure to methadone or buprenorphine. *Neurotoxicology and Teratology*. 2011; 33(2): 240–243. [PubMed: 20868741]
- Jansson LM, Velez M, Harrow C. Methadone maintenance and lactation: A review of the literature and current management guidelines. *Journal of Human Lactation*. 2004; 20(1):62–71. [PubMed: 14974702]
- Johnson RE, Jones HE, Fischer G. Use of buprenorphine in pregnancy: Patient management and effects on the neonate. *Drug and Alcohol Dependence*. 2003; 70:S87–S101. [PubMed: 12738353]
- Jones HE, Johnson RE, Jasinski DR, O’Grady KE, Chisholm C, Choo RE, Milio L. Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: Effects on the neonatal abstinence syndrome. *Drug and Alcohol Dependence*. 2005; 79(1):1–10. [PubMed: 15943939]
- Jones HE, Kaltenbach K, Heil SH, Stine S, Coyle M, Arria AM, Fischer G. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *The New England Journal of Medicine*. 2010; 363(24):2320–2331. [PubMed: 21142534]
- Jones HE, Suess P, Jasinski DR, Johnson RE. Transferring methadone-stabilized pregnant patients to buprenorphine using an immediate release morphine transition: An open label exploratory study. *The American Journal on Addiction*. 2006; 15:61–70.
- Kacinko SL, Jones HE, Johnson RE, Choo RE, Huestis MA. Correlations of maternal buprenorphine dose, buprenorphine, and metabolite concentrations in meconium with neonatal outcomes. *Clinical Pharmacology and Therapeutics*. 2008; 84(5):604–612. [PubMed: 18701886]

- Kahila H, Saisto T, Kivittie-Kallio S, Haukkamaa M, Halmesmaki E. A prospective study on buprenorphine use during pregnancy: Effects on maternal and neonatal outcome. *Acta Obstetrica et Gynecologica Scandinavica*. 2007; 84:145–150.
- Kakko J, Heilig M, Sarman I. Buprenorphine and methadone treatment of opiate dependence during pregnancy. Comparison of fetal growth and neonatal outcomes in two consecutive case series. *Drug & Alcohol Dependence*. 2008; 96(1/2):69–78. [PubMed: 18355989]
- Kaltenbach K, Berghella V, Finnegan L. Opioid dependence during pregnancy: Effects and management. *Obstetrics Gynecology Clinics of North America* 1998. 1998; 25:139–151.
- Kayemba-Kay's S, Laclede JP. Buprenorphine withdrawal syndrome in newborns: A report of 13 cases. *Addiction*. 2003; 98:1599–1604. [PubMed: 14616186]
- Kearney, M. March of Dimes Nursing Module. White Plains, NY: March of Dimes Education and Health Promotion; 2008. Tobacco, alcohol and drug use in childbearing families. Continuing education for registered nurses.
- Kuschel CA, Austerberry L, Cornwell M, Couch R, Rowley RSH. Can methadone concentrations predict the severity of withdrawal in infants at risk of neonatal abstinence syndrome? *Journal of Fetal Neonatology*. 2004; 89(5):390–393.
- Lacroix I, Berrebi A, Chaumerliac C, Lapeyre-Mestre M, Montastruc L, Damase-Michel C. Buprenorphine in pregnant opioid-dependent women: First results of a prospective study. *Addiction*. 2004; 99:209–214. [PubMed: 14756713]
- Lejeune C, Simmat-Durand L, Gourarier L, Aubisson S. Prospective multicenter observational study of 260 infants born to 259 opiate-dependent mothers on methadone or high-dose buprenorphine substitution. *Drug and Alcohol Dependence*. 2006; 82(3):250–257. [PubMed: 16257138]
- Levinson-Castiel R, Merlob P, Linder N, Sirota L, Klingler G. Neonatal abstinence syndrome after in utero exposure to selective serotonin reuptake inhibitors in term infants. *Archives of Pediatrics and Adolescent Medicine*. 2006; 160(2):173. Retrieved from <http://archpedi.ama-assn.org/cgi/content/full/160/2/173?eafg>. [PubMed: 16461873]
- Lim S, Prasad M, Samuels P, Gardner D, Cordero L. High-dose methadone in pregnant women and its effect on duration of neonatal abstinence syndrome. *American Journal of Obstetrics & Gynecology*, 2009. 2009; 200:70.e1–70.e5.
- Ludlow JP, Evans SF, Hulse G. Obstetric and perinatal outcomes in pregnancies associated with illicit substance abuse. *Australian and New Zealand Journal of Obstetrics and Gynaecology*. 2004; 44:302–306. [PubMed: 15282000]
- McCarthy JJ, Leamon MH, Parr MS, Anania B. High-dose methadone maintenance in pregnancy: Maternal and neonatal outcomes. *American Journal of Obstetrics and Gynecology*. 2005; 193:606–610. [PubMed: 16150249]
- McGloin JM, Prate TC, Piquero AR. A life course analysis of the criminogenic effects of maternal cigarette smoking during pregnancy. *Journal of Research in Crime and Delinquency*. 2006; 43(4): 412–426.
- Minozzi S, Amato L, Vecchi S, Davoli M. Maintenance agonist treatments for opioid dependent pregnant women. *Cochrane Database Systematic Review*. 2008 Apr 16.(2):CD006318.
- Nanovskaya T, Deshmukh S, Brooks M, Ahmed MS. Transplacental transfer and metabolism of buprenorphine. *Journal of Pharmacological Experimental Therapeutics*. 2002; 300:26–33.
- Nanovskaya T, Deshmukh S, Nekhayeva I, Zharikova O, Hankins &, Ahmed S. Methadone metabolism by human placenta. *Biochemical Pharmacology*. 2004; 68:583–591. [PubMed: 15242824]
- Nanovskaya T, Nekhayeva, Karunaratne N, Audus K, Hankins G, Ahmed M. Role of P-glycoprotein in transplacental transfer of methadone. *Biochemical Pharmacology*. 2005; 69:1869–1878. [PubMed: 15876424]
- Nekhayeva I, Nanovskaya T, Deshmukh S, Zharikova O, Hankins G, Ahmed M. Bidirectional transfer of methadone across human placenta. *Biochemical Pharmacology*. 2005; 69:187–197. [PubMed: 15588727]
- Oei J, Lui K. Management of the newborn infant affected by maternal opiates and other drugs of dependency. *Journal of Paediatrics and Child Health*. 2007; 43:9–18. [PubMed: 17207049]

- Pizarro D, Habli M, Grier M, Bombrys A, Sibai B, Livingston J. Higher maternal doses of methadone does not increase neonatal abstinence syndrome. *Journal Substance Abuse Treatment*. 2011; 40(3): 295–298.
- Pritham, U. Effects of breast and formula feedings on neonatal abstinence syndrome [Poster]. Presented at National Conference for Nurse Practitioners; Las Vegas, NV. 2011 May.
- Rayburn WF, Bogenschutz MP. Pharmacotherapy for pregnant women with addictions. *American Journal of Obstetrics and Gynecology*. 2004; 191(6) Retrieved from <http://www.ajog.org/scripts/om.dll>.
- Sanchez ES, Bigbee JW, Fobbs W, Robinson SE, Sato-Bigbee C. Opioid addiction and pregnancy: Perinatal exposure to buprenorphine affects myelination in the developing brain. *Glia*. 2008 Jul; 56(9):1017–1027. [PubMed: 18381654]
- Seligman NS, Salva N, Hayes EJ, Dysart KC, Pequignot EC, Baxter JK. Predicting length of treatment for neonatal abstinence syndrome in methadone-exposed neonates. *American Journal of Obstetrics & Gynecology*. 2008; 199:396.e1–396.e7. [PubMed: 18928986]
- Schindler SD, Eder H, Ortner R, Rohrmeister K, Langer M, Fischer G. Neonatal outcome following buprenorphine maintenance during conception and throughout pregnancy. *Addiction*. 2003; 98:103–110. [PubMed: 12492761]
- Sharp C, Kuschel C. Outcomes of infants born to mothers receiving methadone for pain management in pregnancy. *Archives of Disease in Childhood Fetal Neonatal Education*. 2004; 89:33–36.
- Simmat-Durand L, Lejeune C, Gourarier L. Pregnancy under high-dose buprenorphine. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2008 ejogrb.2008.10.012.
- Vavrinková B, Binder T. [Socioeconomic datas, the course of pregnancy and delivery in opioid-addicted women and women under substitution therapy.] Article in Czech; English Abstract. *Ceska Gynekologie*. 2007; 72(5):330–335. [PubMed: 18175516]
- Wouldes, TA.; Woodward, LJ. Maternal methadone dose during pregnancy and infant clinical outcome. *Neurotoxicology Teratology*; 2010. (Epub ahead of print). Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/20102736>
- Winklbaaur B, Jung E, Fischer G. Opioid dependence and pregnancy. *Current Opinion Psychiatry*. 2008; 21(3):255–259.
- Winklbaaur B, Kopf N, Ebner N, Jung E, Thau K, Fischer G. Treating pregnant women dependent on opioids is not the same as treating pregnancy and opioid dependence: A knowledge synthesis for better treatment for women and neonates. *Addiction*. 2008; 103:1429–1440. [PubMed: 18783498]

Table 1

Demographics of Women on MMT and BMT

Variables	MMT Group (n = 136)			BMT Group (n = 16)			P
	n	Mean	SD	N	Mean	SD	
Maternal Dose (mg) on Admission*	136	131.3	69.9	16	18.6	14.3	-----
Maternal Age in Years	135	25.4	4.0	16	24.4	3.5	0.30
Gravidity with Current Pregnancy	135	3.2	2.4	16	2.8	1.8	0.44
Parity Prior to Delivery	134	2.5	0.99	16	1.8	0.98	0.15
GA When Prenatal Care Started in Weeks	113	13.5	6.9	10	14.2	9.2	0.79
Number of Prenatal Visits Attended	6	7.2	4.1	1	13		0.24
Reported Use of Tobacco:	131 (97%)			15(93.8%)			0.76
None	22 (16.8%)			3 (20.0%)			
0-1/2 PPD	47 (35.9%)			6 (40.0%)			
1/2 PPD-1 PPD	38 (29.0%)			4 (26.7%)			
> 1 PPD	24 (18.3%)			2 (13.3%)			
Reported Use of Alcohol	10 (8.3%)			1 (9.1%)			0.89
Use of SSRIs	13 (10.1%)			1 (8.3%)			0.67
Use of Benzodiazepines (prescribed or illicit)	21 (16.2%)			2 (16.7%)			0.76
Use of Marijuana	50 (42.7%)			2 (18.2%)			0.05
Use of Other Opioids	128 (94%)			14 (93%)			0.31

GA = gestational age; PPD = pack per day; SSRIs = selective serotonin reuptake inhibitors. Parametric variables (age, gravida, parity, prenatal visit measures) were analyzed with independent sample t-tests; χ^2 was used for the remaining variables.

* dose is not comparable between methadone and buprenorphine so is not statistically compared.

Table 2

Demographics of Neonates Exposed to MMT or BMT

Variables	MMT Group (n = 136)			BMT Group (n = 16)			p
	n	Means	SD	n	Means	SD	
Gender:							
Male	64 (47.4%)			6 (37.5%)			0.45
Female	71 (52.6%)			10 (62.5%)			
Feeding Method	132			16			0.38
Formula	96 (72.7%)			9 (56.2%)			
Breast	14 (10.6%)			3 (18.8%)			
Both Formula & Breast	22 (16.7%)			4 (25%)			
Gestation Weeks	133	37.7	2.1	15	38.3	1.8	0.36
Birth Weight (gr)	133	3,132.7	2,695.1	15	3,196.5	508.6	0.55
Head Circumference (cm)	129	32.9	2.6	15	33.8	1.2	0.03
Size GA:	133			15			0.03
Small For GA	14 (10.5%)			0 (0%)			
Appropriate for GA	113 (85.0%)			12 (80.0%)			
Large for GA	6 (4.5%)			3 (20.0%)			
Length of Stay (Days)	134	21.3	12.6	16	13.7	11.9	0.05
Treatment for NAS	115 (84.6%)			11 (68.8%)			0.11
No Treatment Required	21 (15.5%)			5 (31.3%)			
Age (Days) Treatment Started	135	1.84	1.35	15	1.87	1.88	0.91
Age (Days) Second Medication Started	135	2.59	2.67	15	1.53	2.39	0.20

MMT = methadone maintenance therapy; BMT = buprenorphine maintenance therapy; GA = gestational age; NAS = neonatal abstinence syndrome. Parametric variables were analyzed with independent sample t-tests (GA at birth, birth weight, head circumference, length of stay, age treatment started and age second medication started); the remaining variables are categorical and χ^2 was used.

Table 3

Regression of Methadone Group Predicting Length of Stay

LOS	Unstandardized Coefficients		Standardized Coefficients		t	p
	B	Std Error	Beta	Beta		
(Constant)	15.529	3.912			3.969	.00
Maternal Methadone Dose	.038	.016	.209		2.324	.02
Cigarette Smoking (Yes/No)	1.743	1.239	.135		1.407	.16
Marijuana (Yes/No)	1.255	2.349	.049		.534	.59
Benzodiazepines (Yes/No)	8.604	3.091	.256		2.784	.00
SSRIs (Yes/No)	3.247	3.713	.078		.875	.38
Alcohol Use (Yes/No)	-.528	4.201	-.012		-.126	.90
Opioid Use (Yes/No)	1.704	2.638	.058		.646	.52
Infant Feeding Method	-3.323	1.687	-.176		-1.970	.05

Note. $F(8, 101) = 3.93$, $p = .00$ $R^2 = .24$; LOS = length of stay; SSRIs = selective serotonin reuptake inhibitors.