Developmental outcome in methadone and buprenorphine-exposed infants:

A retrospective study

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Specific aims:

The purpose of this study is to compare the outcomes of mothers and infants treated with or exposed to methadone versus buprenorphine. A query of the existing FAHC quality assurance database regarding prenatal, infant, and maternal characteristics will be performed to evaluate relative effects of methadone and buprenorphine on developmental outcomes of infants exposed to methadone or buprenorphine in utero. In a recently published randomized controlled trial, several immediate neonatal benefits for using buprenorphine over methadone were established (Jones et al. 2010). However, as of yet no study has determined how buprenorphine exposure impacts later developmental outcomes of exposed infants. After seven years of clinical use at FAHC, our hypothesis is that maternally prescribed buprenorphine results in equivalent or improved developmental outcomes when compared to methadone.

Background/Significance:

Neonatal abstinence syndrome is generally caused by intrauterine exposure to opioids or similar agents which result in withdrawal after birth. It is characterized by “…signs and symptoms of central nervous system irritability, gastrointestinal dysfunction, respiratory distress, and vague autonomic symptoms, which include yawning, sneezing, sweating, stuffy nose, mottling, increased lacrimation, and fever” (Kaltenbach K and Finnegan LP 1986). Other symptoms of NAS include difficulty feeding, loose stools leading to dehydration and electrolyte imbalance, tremors, and irritability.

Methadone is the current recommended approach to treating opioid dependence during pregnancy as it has been shown to increase durations of maternal drug abstinence, increase prenatal care compliance, reduce other risk-related behaviors, reduce fetal exposure to illicit drugs, and increase infant birth weight (Jones HE et al. 2012). While buprenorphine was approved for treating opioid dependence by the FDA in 2002 (Hudak 2012), little evidence in the literature exists for the recommendation of one over the other. However, a randomized multicenter trial has demonstrated less severe NAS in infants exposed to buprenorphine in comparison to methadone for some patients, including shorter infant hospital stays, shorter treatment durations following birth, and lower required doses of morphine following birth (Jones H et al. 2010). The Children’s Specialty Center of the Vermont Children’s Hospital was one of the first clinical care centers to use buprenorphine in a pregnancy setting and as such we are well positioned to use a large bank of collected data in a clinically useful manner with a high potential for affecting drug treatment recommendations.

In 2010, the Vermont Department of Health reported that 2.5% of all infants (157 infants) born to Vermont residents were born with neonatal abstinence syndrome (Vermont Department of Health 2013). The number of infants born to opioid-dependent mothers on methadone or buprenorphine maintenance at the Vermont Children’s Hospital at FAHC has been increasing, and between 2002 and 2011 the total number exceeded 600. Because of the need to work with the State of Vermont for follow-up in treating opioid-exposed infants and for coordination with
the Vermont Child Health Improvement Program (VCHIP) for health care of women receiving Medicaid, FAHC has maintained a database for quality purposes that includes all infants and mothers who have received care. All deliveries and admissions of opioid-exposed infants are included in the database. It is currently used to report activities to the state and to develop treatment protocols to assist communities throughout Vermont in the treatment of opioid dependence during pregnancy, some of which have already been based on some of the analyses of this dataset. The database is also used to coordinate the ongoing care of newborns, making its primary usefulness quality improvement and clinical care. It now includes data for over 900 methadone, buprenorphine, or opioid-exposed infants and after a search of the literature, to our knowledge no retrospective cohort study evaluating the effects of buprenorphine versus methadone on infants has yet been conducted of this size. None have addressed the issue of continued effects of buprenorphine on developmental outcomes.

**Method**

This is a retrospective cohort study, which is a fitting study design for evaluating the issue at hand because exposure and outcome have already occurred. Despite the increased potential for confounding and random error, this study will cost next to nothing to perform in comparison to a randomized controlled trial. A large bank of valuable data already exists and with a potential sample size of 900 it is highly unlikely to be underpowered. Though a tremendous amount of data needs to be evaluated and analyzed, we anticipate being able to finish the bulk of the work in a seven week time frame.

Secondary data analysis will follow the collection of variables (all recorded throughout standard clinical care) as they pertain to three aspects of perinatal care: infant characteristics, maternal characteristics, and prenatal characteristics.

1. Infant characteristics consist of EGA at delivery (weeks), year of delivery (####), sex, birth weight (grams), APGAR score, head circumference (cm), duration of hospital stay (days), duration of treatment period (days) for NAS, dose (mg) and treatment type (morphine or methadone), weight during treatment period (g), number of visits during treatment period, adverse events, breastfeeding status, growth during postpartum period, and developmental outcomes at 8 to 10 months (corrected age) as measured by Bayley III scales (gross motor, fine motor, receptive language, expressive language, and cognitive ability).

2. Maternal characteristics include age (years) at delivery, BMI at delivery, BMI at initial prenatal care visit, cigarette use during pregnancy, and hepatitis C status.

3. Prenatal characteristics are estimated gestational age (EGA) at initial prenatal care visit, number of prenatal care visits, EGA at initiation of opioid treatment, type of maternal opioid treatment (methadone or buprenorphine), and daily dose of maternal opioid treatment (mg).
The quality assessment database is maintained on the FAHC shared drive with multiple layers of password protection and will be accessed via an office on Smith 5. Data for this study will be de-identified and then maintained in a separate study data set which will be stored in the password protected electronic file storage. All results will be reported in aggregate without identifiers.

Statistical considerations include basic descriptive techniques such as means and standard deviations for normally-distributed continuous variables and medians and interquartile ranges for non-normal data. Confidence intervals will also be calculated when appropriate. Categorical data will warrant the use of proportions. When developing the predictive model, we will first analyze the association between study variables and developmental outcomes using a univariate approach. Any variable that demonstrates a potential predictive value as defined by \( p < 0.20 \) will be forwarded to a multivariate logistic regression model, from which variables will also be removed via a backward stepwise regression model. The final multivariate model will contain only variables of significant predictive value as defined by \( p < 0.05 \).

**Future directions in which the project may lead**

After this initial retrospective study we will be able to transition into a prospective cohort design and begin following this growing patient population in real time. A large number of possibilities exist for further research regarding buprenorphine versus methadone regimens here in the community, including a long term comparative assessment of developmental outcomes throughout childhood, a more detailed look at risk assessment and postpartum outcomes for mothers, and evaluations of family demographics as well as other risk factors as they contribute to buprenorphine versus methadone prescription, compliance, and outcome.

**References**


