Prenatal exposure to methadone or buprenorphine: Early childhood developmental outcomes

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Full length article

Background: Methadone and buprenorphine are recommended to treat opioid use disorders during pregnancy. However, the literature on the relationship between longer-term effects of prenatal exposure to these medications and childhood development is both sparse and inconsistent.

Methods: Participants were 96 children and their mothers who participated in MOTHER, a randomized controlled trial of opioid-agonist pharmacotherapy during pregnancy. The present study examined child growth and developmental outcomes over the three-year period yielded 2/37 significant findings for children. Similarly, tests of mean differences between children prenatally exposed to methadone vs. buprenorphine over the three-year period yielded 2/37 significant findings for children. Similarly, tests of mean differences between children treated for NAS relative to those not treated for NAS yielded 1/37 significant finding. Changes over time occurred for 27/37 child outcomes including expected child increases in weight, head and height, and overall gains in cognitive development, language abilities, sensory processing, and temperament. Moreover, findings suggest that prenatal opioid agonist exposure is not deleterious to normal physical and mental development.

Conclusions: Findings strongly suggest no deleterious effects of buprenorphine relative to methadone or of treatment for NAS severity relative to not-treated for NAS on growth, cognitive development, language abilities, sensory processing, and temperament. Moreover, findings suggest that prenatal opioid agonist exposure is not deleterious to normal physical and mental development.

1. Introduction

Methadone and buprenorphine, if taken in adequate doses, can stabilize pregnant women with opioid use disorder and prevent relapse (Hulse and O’Neil, 2002; Jones et al., 2010; Kaltenbach et al., 1998). However, concern is often raised regarding effects of such prenatal exposure to these medications on the developmental outcome of the children. Studies to date have produced inconsistent findings. A review by Maguire and colleagues (Maguire et al., 2016) suggests that prenatal exposure to opioids may be associated
with deficits in cognition, psychomotor, and behavioral processes in infants and young children. However, a review by Behnke and Smith (2013) found long-term effects on behavior but no consensus on cognition and suggest studies with positive findings were usually confounded by environmental factors. Most publications included in the reviews have concerning methodological limitations (e.g., conflating different opioid exposures, not controlling for tobacco and alcohol exposure) (Jones et al., 2015) and reported on cross-sectional case-control studies in small, heterogeneous samples, with few prospective longitudinal studies (Konijnenberg and Melinder, 2011).

Systematic reviews and meta-analyses (Brogly et al., 2014; Zedler et al., 2016) have generally supported the contention that buprenorphine is superior to methadone in terms of neonatal outcomes. Zedler and colleagues (Zedler et al., 2016) concluded that prenatal exposure to buprenorphine relative to methadone has a lower risk of preterm birth, greater birth weight, and larger head circumference. Brogly and colleagues (Brogly et al., 2014) also report greater birth weight and larger head circumference as well as a higher mean gestational age and a lower risk for treatment for neonatal abstinence syndrome (NAS) and shorter length of hospital stay for buprenorphine than methadone-exposed neonates. Neutrons treated for NAS had a shorter duration of NAS treatment and a lower total dosage of morphine dose in buprenorphine- than methadone-exposed neonates. Yet there are only two studies to date that compare the outcome of children prematurely exposed to buprenorphine to children prenatally exposed to methadone, both of which were retrospective pediatric clinical chart reviews at birth and 4 months of age (Bier et al., 2015) and through 2 years of age (Humbarger et al., 2016). To date, there are no studies that prospectively examine developmental outcomes of children prematurely exposed to buprenorphine compared to children prenatally exposed to methadone, although a longitudinal study assessed visual evoked potential scores at 4 months of age (Whitham et al., 2010) and at 3 years of age (Whitham et al., 2015) and found little difference between buprenorphine and methadone exposure.

The question of the long-term effect of NAS has recently received new emphasis given the rising opioid epidemic and the significant increase in prenatal opioid exposure (Patrick et al., 2015). NAS has been used as an index of risk in recent legislation (Child Abuse Prevention Act (CAPTA) of 2010; the Comprehensive Addiction and Recovery Act (CARA) of 2016) resulting in potential consequences for mothers receiving opioid medication for treatment of OUD while pregnant. However, the only study that has examined if developmental outcome differs for infants who required treatment for NAS compared to infants who exhibited mid NAS and required no treatment found no difference in development at 6 months of age (Kaltenbach and Fnnegan, 1986). There are no data regarding the effect of severity of NAS on development during late infancy and early childhood.

The primary interest of the present study was threefold. First, to determine whether changes in child growth parameters, cognition, language abilities, sensory processing, and temperament over the 36-month period were differentially related to prenatal buprenorphine versus methadone exposure. Significant results would indicate that the children develop differently over the first three years of life as a result of exposure to one of the two opioid agonists. Second, to determine whether changes in child developmental outcomes over this 36-month period were differentially related to treatment for NAS. Significant results would suggest that children who were treated for NAS as neonates develop differently over the first three years of life as a result of NAS severity and/or exposure to morphine treatment. Third, to determine the extent to which young children prenatally exposed to opioid agonist medication follow a normal course of development and the extent to which maternal perceptions of parenting stress, home environment, and addiction severity might have changed over the three-year period.

This study examined secondary outcomes of child growth parameters, cognitive development, language abilities, sensory processing, and temperament, and maternal perceptions of parenting stress, home environment, and addiction severity during the child’s first 36 months of life in a sample of 96 children and their mothers who participated in a randomized controlled trial of opioid-agonist pharmacotherapy during pregnancy. This study has multiple strengths relative to previous research: (1) the maternal sample is clearly defined by study eligibility criteria; (2) use of substances other than either methadone or buprenorphine during pregnancy was minimal; (3) both child and maternal functioning are examined; (4) the potentially adverse impact on development of neonatal abstinence syndrome (NAS) that requires treatment following prenatal exposure to either methadone and buprenorphine is examined; and (5) it is longitudinal and prospective.

2. Methods

2.1. Maternal opioid treatment: human experimental research (MOTHER) study

Methodological aspects of the MOTHER trial relevant to this article, including the inclusion/exclusion criteria and the CONSORT diagram, as well as maternal baseline characteristics and secondary neonatal and maternal outcomes (i.e., amount of prenatal care, positive drug screen at delivery, etc.) have already been published (Jones et al., 2012; Jones et al., 2010). MOTHER (Jones et al., 2010) was a double-blind, double-dummy, flexible-dosing, two-group randomized controlled trial. Either methadone or buprenorphine was provided to 175 opioid-dependent pregnant women with a singleton fetus (6–30 weeks), of whom 58 women in the buprenorphine and 73 in the methadone condition delivered an infant while enrolled in the study. Buprenorphine (2–32 mg) and methadone (20–140 mg) dosing followed a flexible dose protocol (Jones et al., 2010).

NAS assessment was performed for all infants for a minimum period of 10 days post-delivery. The MOTHER NAS Scale (MNS) (Jones et al., 2010) measured NAS. Supplementary Material (Jones et al., 2010) and Table 2 in Weaver et al. (Weaver et al., 2014) provide MNS development and scoring principles. Jones et al. (Jones et al., 2010) provide rater training and inter-rater agreement information. The NAS treatment protocol was based on MNS scores. Neonates requiring pharmacotherapy were treated with oral morphine sulfate.

2.2. Procedures

The present study was approved by the Institutional Review Boards of the participating sites: Brown University, Johns Hopkins University, The Medical University of Vienna, the University of Vermont, Thomas Jefferson University and the City of Philadelphia, Vanderbilt University, and Wayne State University. Study participants were recruited at study sites following completion of MOTHER participation. Examiners trained in developmental evaluations assessed infants and research staff assessed mothers. All assessments were conducted at the hospital sites and all examiners were blind to the maternal-infant Medication Condition.

2.3. Measures and assessment schedule

Measures were a multidimensional set of well-validated instruments that are widely used both for clinical diagnoses and research assessment, with child measures of developmental outcomes focusing on growth parameters, cognitive development, sensory processing, temperament, and language abilities. Maternal measures focused on perceptions of parenting stress, home environment, and addiction severity. Assessments were conducted when infants were 3, 6, 12, 24, and 36 months of age. Table 1 includes descriptions of measures and their assessment schedule. Because first enrollment in MOTHER occurred in May 2005 and the follow-up National Institute on Drug Abuse supplement award for this study was not received until Spring 2008, some infants were too old to be administered the assessment battery at the
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