Please cite this article in press as: Podrebarac SK et al. Antenatal exposure to antidepressants is associated with altered brain development in very preterm-born neonates. Neuroscience (2016), http://dx.doi.org/10.1016/j.neuroscience.2016.11.025

Neuroscience xxx (2016) xxx–xxx

ANTENATAL EXPOSURE TO ANTIDEPRESSANTS IS ASSOCIATED WITH ALTERED BRAIN DEVELOPMENT IN VERY PRETERM-BORN NEONATES

SAMANTHA K. PODREBARAC,[a] EMMA G. DUERDEN,[a] VANN CHAU,[a,c] RUTH E. GRUNAU,[c] ANNE SYNNES,[c] TIM F. OBERLANDER[c] AND STEVEN P. MILLER[a,b]*

[a] *Department of Paediatrics, Research Institute, The Hospital for Sick Children, Toronto, Ontario, Canada*

[b] *The University of Toronto, Toronto, Ontario, Canada*

[c] *Department of Pediatrics, University of British Columbia, B.C. Children's and Women's Hospitals, BC Children's Hospital Research Institute, Vancouver, Canada*

Abstract—*Background:* Antenatal exposure to selective serotonin reuptake inhibitors (SSRI) is associated with an enhanced risk of preterm birth. Very preterm-born neonates (<32-week gestation) antenatally-exposed to SSRIs may show altered brain development.

Objective: To examine whether antenatal-SSRI exposure was associated with adverse neonatal brain microstructural and metabolic development using diffusion tensor and magnetic resonance spectroscopic imaging.

Design/Methods: Of 177 neonates enrolled, 14 (8%) were antenatally exposed to SSRIs. Neonates were scanned twice (median week 32; interquartile range [IQR]: 30.4–33.6) and again at term-equivalent age (40.1, IQR: 38.6–42.1). Using a region-of-interest approach, N-acetyl-aspartate to choline ratios (NAA/Cho), lactate-to-choline ratios, white and gray matter fractional anisotropy (FA), mean, axial, radial diffusivity (MD, AD, RD) values were extracted from white and gray matter subcortical regions. Neurodevelopment was assessed at 18-month corrected age.

Results: SSRI-exposed neonates exhibited increased FA and decreased MD, AD and RD values in the superior white matter ($p < 0.05$). FA values in the basal ganglia and thalamus were significantly lower in neonates antenatally exposed to SSRIs, compared to non-exposed ($p = 0.004$). Lower NAA/Cho values ($p = 0.04$) and higher Lactate/Cho values ($p = 0.004$) in posterior gray matter were evident in neonates exposed to SSRIs. No association with antenatal-SSRI exposure and neurodevelopment was evident.

Conclusions: Given the importance of treating depression in mothers at risk for preterm delivery, the impact of antenatal-SSRIs on early brain development requires further attention. Future research is directed at determining the mechanism of this relationship and the contribution of maternal mood.

This article is part of a Special Issue entitled SI: Early Adversity.

Key words: antidepressants, brain, prenatal, preterm, maternal mood.

INTRODUCTION

Depression in pregnant mothers is a significant and serious mental health issue affecting 13% of women (Gavin et al., 2005). Undertreated depression during pregnancy is associated with adverse neonatal outcomes including intrauterine growth restriction, slower rates of growth, low birth weight and preterm delivery (Andrade et al., 2008; Bakker et al., 2008; Munk-Olsen et al., 2012). Treatment with selective serotonin reuptake inhibitors antidepressants (SSRI) is frequently used to manage depression and anxiety during pregnancy. An estimated 6–13% of pregnant women receive pharmacological treatment for mood disorders and the number of women taking antidepressants during pregnancy has sharply increased (Andrade et al., 2008; Bakker et al., 2008; Munk-Olsen et al., 2012; Mitchell et al., 2011). SSRIs readily cross the placenta and are present in amniotic fluid (Calderon-Margalit et al., 2009). Fetal SSRI exposure has also been associated with adverse outcomes such as altered brain blood flow in late gestation (Karlsson et al., 1999), and in the newborn period behavioral disturbances resembling a drug withdrawal syndrome (Berman et al., 1978) and increased risk for PPHN (Clark et al., 1980) and congenital heart defects (Kim et al., 2006). The risk of poor growth and preterm labor related to SSRI exposure might be related to restricted oxygen delivery (Karlsson et al., 1999; Berman et al., 1978; Clark et al., 1980). Mothers treated for depression with SSRIs were more likely to deliver infants at younger gestational ages, with lower birth weight, who were more likely to exhibit respiratory distress, jaundice and poor feeding compared to the newborns of unmedicated depressed mothers (Kersbergen et al., 2014). Importantly, the impact of mood and drug is remarkably similar (Miller et al., 2002; Thayyil et al.,

*Correspondence to: S. P. Miller, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada. Fax: +1-416-813-6334.
E-mail address: steven.miller@sickkids.ca (S. P. Miller).

Abbreviations: 11β-HSD2, 11β-hydroxysteroid dehydrogenase type 2; FA, fractional anisotropy; HPA, hypothalamic–pituitary–adrenal; IVH, intraventricular hemorrhage; RD, radial diffusivity; ROIs, regions of interest; SNAP-PE, Score for Neonatal Acute Physiology-Perinatal Extension; SSRI, selective serotonin reuptake inhibitors; WMI, white matter injury.

http://dx.doi.org/10.1016/j.neuroscience.2016.11.025
0306-4522/

2010; Kreis et al., 2002; Barkovich et al., 2001; Chau et al., 2012) and distinguishing the impact of antenatal antidepressant exposure from maternal mood remains a key challenge.

Antidepressants such as SSRIs are used in 6% of pregnancies in the United States for the treatment of depression or anxiety (Andrade et al., 2008). SSRIs cross the placenta and in turn fetuses are directly exposed to the effects of the medication (Kim et al., 2006). Evidence suggests that both acute and chronic exposure to SSRIs is associated with factors that may adversely impact neurodevelopment. For instance, in an experimental model, maternal SSRI therapy was associated with disruptions in normal fetal sleep patterns with reports of suppressed rapid eye movement sleep (Vinall et al., 2011), which is critical for fetal brain development (Kim et al., 2008). Antenatal SSRIs also increase levels of fetal cortisol concentrations that may negatively impact lung and brain development (Morrison et al., 2004). While the risks of preterm delivery associated with antenatal exposure to SSRIs is known, the short- and long-term effects of antidepressant usage on preterm brain maturation is lacking and are needed to better understand the impact of these medications on development.

With enhanced exposure to serotonin *in utero*, white and gray matter development of subcortical tracts and structures may be selectively disrupted in preterm neonates. Gray and white matter microstructure can be examined in neonates *in vivo* with diffusion tensor imaging (DTI) which provides a measure of water molecule diffusion rates. Diffusion tensors are described according to the mean diffusivity (MD), an average of radial diffusivity (RD) and axial diffusivity (AD). AD and RD reflect diffusion rates parallel and perpendicular to fiber pathways, respectively. Fractional anisotropy (FA) is indicative of the coherence of the orientation of water diffusion. During normal brain development AD and RD values will decrease in white matter, while FA values will increase (Kersbergen et al., 2014; Miller et al., 2002). Degeneration of cell membranes, alterations in cell density and cell membrane permeability will result in increased MD (Thayyil et al., 2010; Kreis et al., 2002). In gray matter, losses of tissue microstructure or neuronal numbers/size are associated with higher MD and lower FA values (Chau et al., 2012). Alterations in anisotropy values will vary in a non-uniform pattern in the developing cortex. Patterns will vary considerably between 25- and 40-week gestation due to the increased complexity of the developing cortical architecture that includes refinement of thalamo- and corticocortical projections, dendritic arborization, synaptogenesis and gliogenesis. Therefore, patterns of MD and FA may be increased and decreased or show little change in cortical areas (Kersbergen et al., 2014).

Magnetic resonance spectroscopic imaging (MRSI) provides a measure of compounds such as N-acetylaspartate (NAA) and lactate, which are useful in assessing neonatal brain injury and are predictive of functional outcomes (Miller et al., 2002; Thayyil et al., 2010). NAA is found in high concentrations in neurons and levels increase during normal brain development up term age > 37 weeks and is thought to represent neuronal maturation; even recognizing that NAA is also found in pre-oligodendrocytes (Yelnik, 2002). Lactate levels reflect impairments in cerebral energy substrate delivery and oxidative metabolism (McKinstry et al., 2002). Higher lactate levels have been detected during neonatal MRSI studies with preterm-born neonates (Yelnik, 2002). In turn, MRSI is a sensitive imaging modality in neonates to examine brain metabolic development in gray and white matter. Measures of brain metabolic and microstructural development with MRSI and DTI are associated with neurodevelopmental outcomes, with more robust brain development in the neonatal period predicting more optimal outcomes (Ling et al., 2013; Xu et al., 2011).

Given the association between preterm birth and antenatal SSRI exposure we sought to examine the effects of antidepressants on neonatal brain development in a cohort of very preterm-born neonates. The neonates were followed from birth and underwent serial MRI sessions that included DTI and MRSI at two time points, within a few weeks of birth and again at term-equivalent age. The microstructural and metabolic development of major white matter pathways and subcortical regions was assessed in neonates exposed compared to those not exposed to SSRIs, while controlling for demographic and other clinical variables associated with preterm birth. Infants returned at 18-month corrected age for neurodevelopmental assessment. The impact of antenatal exposure to antidepressants on functional outcomes was also evaluated.

EXPERIMENTAL PROCEDURES

Patients

A prospective cohort of very preterm-born neonates (24- to 32-week gestational age), from the level 3 Neonatal Intensive Care Unit at British Columbia Women's Hospital (BCWH), were enrolled in the present study. The BCWH is a provincial tertiary perinatal care facility. The study was approved by the University of British Columbia/BCWH Research Ethics Board. Written informed consent was collected from all parents.

Procedures

MRI. Studies were conducted on a Siemens (Erlangen, Germany) 1.5T Avanto using VB 13A software. Neonates were scanned inside a magnetic resonance-conditional incubator (Lammers Medical Technology, Luebeck, Germany) using a single-channel neonatal head coil (Advanced Imaging Research, Cleveland, OH, USA). Neonates were scanned at two time-points: within a few weeks of birth (once clinically stable) and again at term-equivalent age. T1-weighted images were acquired using a 3-dimensional coronal volumetric sequence (repetition time [TR] = 36; echo time [TE] = 9.2; field of view [FOV] = 200 mm; slice thickness = 1 mm; gap distance = 0). An axial fast spin echo sequence was used for the T2-weighted images

Please cite this article in press as: Podrebarac SK et al. Antenatal exposure to antidepressants is associated with altered brain development in very preterm-born neonates. Neuroscience (2016), http://dx.doi.org/10.1016/j.neuroscience.2016.11.025