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Antenatal depression, treatment with selective serotonin reuptake inhibitors, and neonatal brain structure: A propensity-matched cohort study

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ABSTRACT

The aim of this propensity-matched cohort study was to evaluate the impact of prenatal SSRI exposure and a history of maternal depression on neonatal brain volumes and white matter microstructure. SSRI-exposed neonates (n=27) were matched to children of mothers with no history of depression or SSRI use (n=54). Additionally, neonates of mothers with a history of depression, but no prenatal SSRI exposure (n=41), were matched to children of mothers with no history of depression or SSRI use (n=82). Structural magnetic resonance imaging and diffusion weighted imaging scans were acquired with a 3T Siemens Allegra scanner. Global tissue volumes were characterized using an automatic, atlas-moderated expectation maximization segmentation tool. Local differences in gray matter volumes were examined using deformation-based morphometry. Quantitative tractography was performed using an adaptation of the UNC-Utah NA-MIC DTI framework. SSRI-exposed neonates exhibited widespread changes in white matter microstructure compared to matched controls. Children exposed to a history of maternal depression but no SSRIs showed no significant differences in brain development compared to matched controls. No significant differences were found in global or regional tissue volumes. Additional research is needed to clarify whether SSRIs directly alter white matter development or whether this relationship is mediated by depressive symptoms during pregnancy.

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1. Introduction

Approximately 18% of pregnant women in the U. S. suffer from depression (Waters et al., 2014). Untreated antenatal depression is associated with intense emotional distress, low fetal growth, preterm birth, neonatal complications, and conduct problems and antisocial behavior in offspring (Waters et al., 2014; Yonkers et al., 2009). While there is no definitive answer regarding optimal treatment for antenatal depression, the American Psychiatric Association and the American College of Obstetricians and Gynecologists provide algorithms for multiple scenarios that result in the initiation or maintenance of pharmacotherapy. Overall, approximately 13% of pregnant women report antidepressant use (Cooper et al., 2007) with selective serotonin reuptake inhibitors (SSRIs) being the most commonly prescribed class. Despite widespread use of SSRIs during pregnancy, effects on the fetus are not fully understood and are a source of concern for many pregnant women.

SSRIs are diffusible through the placenta and blood brain barrier and could potentially target the developing fetal brain (Velasquez et al., 2013). During this early period of neurodevelopment, serotonin from maternal, placental, and fetal sources is involved in neuronal proliferation, migration, and synaptogenesis (Whitaker-Azmitia, 2005). In rodents, exposure to SSRIs in the prenatal and/or early neonatal period disrupts

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dendritic organization and formation of thalamocortical afferents to the somatosensory cortex and results in aberrant axonal morphology, abnormal raphe circuitry, and altered cortical function (Lee, 2009; Liao and Lee, 2011; Simpson et al., 2011; Xu et al., 2004). These changes are accompanied by behavioral disturbances including decreased exploratory behavior and increased emotional reactivity, altered social behavior, and impaired motor performance (Borue et al., 2007; Glover et al., 2015; Xu et al., 2004).

Research on behavioral outcomes in humans exposed to SSRIs *in utero* has focused almost exclusively on measurements of cognitive development and IQ, where exposed children perform at typically developing levels (Nulman et al., 2012). However, motor development and control issues have been observed in a number of studies (Casper et al., 2003; Casper et al., 2011; Hanley et al., 2013; Pedersen et al., 2010; Rampono et al., 2009; Salisbury et al., 2011; Smith et al., 2013). A possible link between prenatal antidepressant exposure and autism spectrum disorders/symptoms has proved particularly controversial with several large studies reporting significant associations (Boukhris et al., 2016; Croen et al., 2011) and other large studies failing to replicate (Harrington et al., 2014; Hviid et al., 2013). Neuroimaging studies are extremely limited. One study reported benign caudothalamic cysts in 6 of 40 at term infants exposed to SSRIs but no unexposed comparison group was evaluated (Laine et al., 2003). We recently reported that children exposed to SSRIs prenatally exhibit a striking increase in Chiari I malformations, a condition resulting from the underdevelopment of the posterior cranial fossa and overcrowding of the normally developing hindbrain (Knickmeyer et al., 2014). The current study is the first to examine brain tissue volumes and white matter development of SSRI-exposed neonates. Based on the rodent literature and the motor deficits observed in human children exposed in utero to SSRIs, we hypothesized that prenatal SSRI exposure would impact diffusion parameters in corticothalamic and corticofugal white matter tracts originating/terminating in motor and somatosensory cortex, as well as gray matter volumes in these particular brain regions. To test the possibility that a history of maternal depression influences brain development in the absence of prenatal SSRI exposure we also examined a separate cohort of neonates whose mothers had a history of depression but were not treated with SSRIs during pregnancy.

2. Methods

2.1. Recruitment

Participants were drawn from three prospective longitudinal neuroimaging studies being carried out at UNC (Gilmore et al., 2010; Gilmore et al., 2012; Knickmeyer et al., 2014). Recruitment occurred through community physicians, relevant clinics at UNC, including the perinatal psychiatry clinic and general obstetrics clinics, and mass emails to the UNC community. Participants were recruited between November 2003 and December 2010.

Exclusion criteria in mothers were major medical illness or substance abuse during pregnancy. Exclusion criteria for neonates were gestational age at birth less than 32 weeks, major postnatal complications, major congenital anomalies, and metal in the body. After complete description of the study to subjects' parent(s), written informed consent was obtained. Study protocols were in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the Institutional Review Board of the UNC School of Medicine and the National Institutes of Health as well as Uniform Requirements for manuscripts submitted to Biomedical journals (http://www.icmje.org/).

2.2. Cohort 1Participants (SSRI exposed)

This analysis included 27 SSRI-exposed (7 males; 21 singletons; 6 twins) and 54 matched control (20 males; 42 singletons; 12 twins) neonates. Diagnosis of a mood disorder and SSRI use in all three trimesters was confirmed through self-reports (oral interview) and review of medical records (primarily prenatal and labor & delivery). Nineteen mothers reported that they received a diagnosis of depression prior to study entry; medical records provided corroborating information in all cases. Twelve of these women reported active depression at entry and one additional woman reported active depression without a past history. Additionally, four women did not report active depression or a past diagnosis of depression at study entry, but review of medical records indicated such a diagnosis was made prior to or during pregnancy. Medical records were not sufficiently detailed to determine the exact date of diagnosis. The most common diagnoses were major depression and depressive disorder not elsewhere classified, one woman reported bipolar disorder, and seven were diagnosed with an anxiety disorder in addition to a mood disorder. Medical record review indicated fifteen mothers took SSRIs at the time of conception and six mothers began SSRI treatment during the first trimester. For three women, we could not determine whether treatment began before or after conception (data on SSRI type and dosage can be found in Supplementary Fig. 1). Use of a psychiatric drug other than an SSRI was an exclusion criterion for the current analysis with the exception of trazodone (N=1 SSRI-exposed), low dose benzodiazepines (N=3 SSRI-exposed), and psychostimulants (N=1 SSRI-exposed). For data on non-SSRI medications during pregnancy see Supplementary Table 1.

Each exposed neonate was matched to two control neonates (offspring of pregnant women with no known history of mood disorders, anxiety, or antidepressant use) based on gender, gestational age at birth and MRI, maternal age, ethnicity, and education using propensity scores. Singletons were matched to singletons and twins to twins. See Table 1 for demographic information. Infants were considered positive for perinatal problems if there was a presence of a nuchal cord or if they experienced meconium aspiration, asphyxia or RH incompatibility. Infants were considered positive for postnatal problems if they experienced jaundice, seizures, sepsis, pneumonia, necrotizing enterocolitis, or respiratory distress syndrome.

2.3. Cohort 2 Participants (history of maternal depression)

We identified 41 neonates (21 males, 16 singletons, 25 twins) of mothers who received a diagnosis of depression prior to or during pregnancy but did not receive antidepressants in any trimester. This cohort may potentially share with the SSRI-exposed cohort a generally higher risk of un-identified behaviors (e.g. unreported smoking, substance misuse, exposure to other teratogens) as well as genetic factors associated with depression. Twenty-five mothers reported that they received a diagnosis of depression prior to study entry; medical records provided corroborating information in all cases. Three of these women reported active depression at entry. The other seven women did not report active depression or a past diagnosis of depression at study entry, but review of medical records indicated such a diagnosis was made prior to or during pregnancy. Medical records were not sufficiently detailed to determine the exact date of diagnosis. The most common diagnoses were major depression and depressive disorder not elsewhere classified. Additionally, one woman reported a lifetime history of bipolar disorder, and two women reported a lifetime history of anxiety disorder in addition to a mood disorder. One mother was also diagnosed with ADHD in addition to having a lifetime history of depression.

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