Early Human Development 89 (2013) 519–524

Contents lists available at SciVerse ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Infant developmental outcomes following prenatal exposure to antidepressants, and maternal depressed mood and positive affect

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ARTICLE INFO

Article history:
Received 10 September 2012
Received in revised form 12 December 2012
Accepted 23 December 2012

Keywords:
Serotonin reuptake inhibitors
Neurodevelopment
Infant outcomes

ABSTRACT

Background: Prenatal exposure to serotonin reuptake inhibitor (SRI) antidepressants has been associated with delays in early developmental milestones, but there remains uncertainty. Even among a subset of studies examining the Bayley Scales of Infant Development (BSID), some have reported normal mental and psychomotor development while others have suggested a delay in motor development. Given an increasing number of infants exposed to SRIs, furthering our understanding of the possible developmental implications of SRI exposure in utero is critical.
Aims: To examine the effects of prenatal serotonin reuptake inhibitor exposure and maternal mood on infant developmental outcomes at 10 months of age.
Study design: Prospective study of mothers and their 10-month-old infants.
Subjects: We examined 31 mother–child pairs exposed prenatally to SRIs and 52 mother–child pairs who were nonexposed.
Outcome measure: The Bayley Scales of Infant Development (third edition) scores.
Results: Infants exposed prenatally to SRIs scored significantly lower than nonexposed infants on gross motor ($P=0.03$), social–emotional ($P=0.04$) and adaptive behavior ($P=0.05$) subscales of the BSID-III, controlling for pre- and postnatal maternal depressed mood, smoking and alcohol use during pregnancy. No significant differences in any of the BSID-III subscales were observed between infants exposed and infants nonexposed to pre and postnatal maternal depressed mood ($P>0.05$). Increased levels of maternal positive affect at 10 months predicted increased social–emotional scores ($P=0.03$).
Conclusions: Infants prenatally exposed to SRIs score significantly lower on the gross motor, social–emotional and adaptive behavior subscales of the BSID-III, and this was not explained by underlying maternal depression.

1. Introduction

Prenatal exposure to serotonin reuptake inhibitor (SRI) antidepressants has been associated with delays in early developmental milestones and behavioral disturbances during infancy in some [1–3] but not all studies [4,5]. Soon after the introduction of serotonin reuptake inhibitors (SRIs) in the late 1980's, reports of neonatal "withdrawal" symptoms appeared suggesting possible neurobehavioral effects associated with prenatal drug exposure [6]. Given that between 15% and 20% of women experience depression or anxiety during their pregnancy and 5%–13% are treated with an SRI [7,8], there is a need to better understand whether there are long-term neurodevelopmental consequences of prenatal exposure to SRIs [9].

A key challenge to understanding the neurodevelopmental consequences of SRI exposure is distinguishing between the effects of the SRI exposure and the effects of the underlying indication for the drug treatment, the maternal mood disturbance. Antenatal maternal stress has been reported to disrupt fetal neurobehavioral development [10,11] in utero [12,13], reduce birth weight, and increase risks for prematurity [14,15]. Antenatal depressed mood has been associated with neonatal irritability, atypical frontal EEG patterns, reduced vagal tone, elevated cortisol and norepinephrine, and lower dopamine and serotonin levels [15]. The story is further complicated by evidence that antenatal exposure to mild to moderate levels of psychological distress may advance motor development in a healthy population and not always lead to problematic outcomes [16].

SRIs inhibit the function of the serotonin transporter (5-HTT), the protein responsible for the reuptake of serotonin (5-HT) at the presynaptic neuronal membrane. The inhibition of 5-HTT results in an increase of 5-HT in the extracellular space, which increases the magnitude and

Abbreviations: SSRI, Selective serotonin reuptake inhibitor; SRI, serotonin reuptake inhibitor; BSID III, Bayley Scale of Infant Development Third edition; EPDS, Edinburgh Postnatal Depression Scale; HAMD, Hamilton Rating Scale for Depression; PA, Positive Affect.

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http://dx.doi.org/10.1016/j.earlhumdev.2012.12.012

duration of the activity of postsynaptic 5-HT receptors and downstream neural tone. To date research examining outcomes following prenatal SRI exposure has focused on risks for spontaneous abortions, malformations, small-for-gestational (SGA) age birth, low birth weight, persistent pulmonary hypertension (PPHN), and respiratory distress [17–22]. However, given the key developmental role 5HT plays, it is plausible that prenatal SRI exposure alters serotonin signaling at developmentally sensitive periods potentially affecting long term behavior [9]. While animal studies examining prenatal SRI exposure have reported delayed motor development [23–25], studies of neurodevelopmental outcomes in humans have yielded inconsistent results. Typical mental and psychomotor development has been reported in some [4,26,27], but not all studies [1,2,28]. Two studies examining development using the Bayley Scales of Infant Development (BSID) have shown no difference in total BSID score [4,5], while three others have reported lower scores on the motor index of the BSID in exposed children [1,29,30].

Even in the presence of prenatal SRI treatment, some women continue to experience depressed mood, presenting an ongoing risk to early human development both during gestation and long after prenatal SRI exposure ends. Importantly, up to 50% of women treated with an SRI during pregnancy stop medication within the first 60 days of pregnancy [31]. A recent study by Yonkers et al. suggested that, regardless of whether women continue their antidepressant treatment or not, approximately 16% of women develop a major depressive episode during pregnancy [32]. Beyond the dimensions of depressed or anxious mood, there is increasing evidence of positive developmental impacts of nurturing environments in early infancy [33–35]. Early care giving environments may contribute to cognitive development later in childhood [36]. Maternal sensitivity and mindfulness when their infants were 1 year of age predicted executive functions a year later [37]. Further, maternal 'positive affect' when infants were 10 months of age predicted increased preschool and post kindergarten early cognitive development [38]. While increasing interest in the potential benefits of positive affect have been widely reported [39], to date there have been no studies reporting the impact of "positive psychology" or positive feelings during and following pregnancy on early infant development and behavior. Thus, even in the presence of prenatal SRI treatment, pre and postnatal maternal mood disturbances continue and potentially contribute an ongoing developmental risk for their infants.

The objectives of the current study were two-fold: first, we sought to determine whether there were developmental effects of prenatal SRI exposure at 10 months of age that were separate and distinct from the potential developmental effects of the underlying prenatal and postpartum maternal depressed mood. Second, beyond the dimension of maternal depressed mood, we sought to examine the developmental impact of maternal feelings that reflect pleasure such as happiness, joy, excitement, enthusiasm, and contentment (i.e. positive affect) [40]. We hypothesized that SRI exposure effects would differ from the impact of perinatal mood disturbances and that maternal positive affect, as a separate maternal psychological dimension, would have an impact distinct from prenatal exposure to SRI antidepressants and maternal depressed mood.

2. Methods

In this cohort study ninety-two mothers were recruited during their second trimester of pregnancy (mean gestational age 27.7 weeks) from community midwife clinics, family physician clinics, and a reproductive mental health clinic in metropolitan Vancouver (34 using SRIs vs. 58 not using SRIs). Of these mother–child pairs, 83 were followed until the infants were 10 months of age (3 exposed and 6 nonexposed mother–child pairs were lost to follow up). Informed consent was obtained from all mothers and the study was approved by the University of British Columbia Research Ethics Board and the BC Women's Hospital Research Review Committee. All SRI exposed mothers had been diagnosed with an Axis I mood disorder and were already on antidepressants at the time of conception.

Inclusion criteria for this study were singleton pregnancy, confirmed gestational age, ability to give informed consent and no fetal anomalies that were detected by ultrasound. Exclusion criteria included bipolar disorder, illicit drug abuse and significant maternal medical, obstetrical, or fetal conditions. History of alcohol and tobacco use was obtained at every visit by interview with the research staff.

2.1. Maternal characteristics and neonatal data

Demographics, reproductive and medical history, and information regarding prescribed medications were obtained at the time of enrollment, 36 weeks gestation, and 10 months postpartum. Data on neonatal outcomes at birth were obtained from the neonatal health records including gestational age at birth, birth weight, length, head circumference, and Apgar scores at 1 and 5 min.

2.2. Maternal depression and mood

Maternal depressed mood was assessed using the self rated Edinburgh Postnatal Depression Scale (EPDS) [41] and the clinician-rated Hamilton Rating Scale for Depression (HAMD) [42] at the time of recruitment (mean 27.7 weeks gestation) and during the 3rd trimester of pregnancy (mean 36.1 weeks gestation) and again at 10 months postpartum (mean infant age 43.9 weeks). A trained research assistant did the clinician rated assessments. The EPDS is a 10-item self-rated questionnaire intended to assess the existence and severity of depression symptoms. It has been reported to have good validity and sensitivity in both pregnant and postpartum women. The HAMD is a 21-item clinician rated scale that measures the severity of depression in adults with a range from 0 to 63.

To address the impact of positive affect on early developmental health, we used the Positive and Negative Affect Scale (PANAS) [43]. It consists of 10 adjectives representing positive affectiveness (PA), such as self-assuredness, joviality, attentiveness, etc. Subjects were asked about each of these adjectives during the last week and response alternatives were presented on a five-grade scale, extending from 1 to 5 with 1 representing not at all and 5 representing very much. To create overall positive affect scores, the positively-charged adjectives were summated to a PA result for positive affect. High PA represents the extent to which an individual experiences pleasurable engagement with their environment, and the extent to which an individual feels enthusiastic, active and alert [44]. The PANAS instrument has been validated across multiple populations [45–47]. Positive affect scores were collected at the same time as the EPDS and HAMD measures and were used as measures of trait affect.

2.3. Child development

At 10 months of age, infant development was assessed using the Bayley Scales of Infant Development third edition (BSID-III) [48]. The BSID-III yielded developmental outcomes across five domains: cognitive, language, motor, social–emotional and adaptive behavior. The cognitive, language and motor domains were assessed by a trained physical or occupational therapist blinded to the antidepressant exposure status of the infant. The measures of social–emotional and adaptive behavior were obtained from maternal report.

2.4. Statistical analysis

Comparisons of descriptive characteristics for mothers and infants were undertaken using univariate analyses of variance. Categorical variables were compared using chi-squared tests. When examining whether there were statistically significant differences in BSID-III scores between exposed and nonexposed infants, we used univariate analyses