18 Fetal Effects of In Utero Serotonin Reuptake Inhibitor (SRI) Antidepressant Exposure

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Abstract

In utero serotonin reuptake inhibitor (SRI) exposure is relatively common and neonatal behavioral outcomes vary greatly. Such exposure has led to questions about whether these effects reflect an acute short-lived pharmacological phenomenon that results in a "withdrawal" condition, or sustained neurological changes associated with altered serotonin (5-HT) signaling that begins long before birth. Emerging reports now suggest that certain effects associated with in utero SRI exposure become evident during gestation. For instance, in utero SRI exposure appears to influence fetal brain blood flow and neurobehavior. In this chapter, we summarize current research evidence reporting the fetal effects of in utero SRI exposure. Given the paucity of empiric fetal data in humans, we draw from what we know about three postnatal findings that may reflect fetal developmental sequelae associated with in utero SRI exposure.

Keywords

Antidepressants • Pharmacodynamics • Pregnancy • Depression • Fetus

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N. Reissland, B.S. Kisilevsky (eds.), *Fetal Development*, DOI 10.1007/978-3-319-22023-9_18

Introduction

Serotonin reuptake inhibitor (SRI) antidepressants are the most commonly used psychotropic medicine in pregnancy (Hanley & Mintzes, 2014). Between 15 and 20 % of women experience mood disorders (e.g., depression) during their pregnancy and 5–13 % of women with an antenatal mood disorder will be treated with an SRI antidepressant (Cooper, Willy, Pont, & Ray, 2007; Hanley & Mintzes, 2014; Oberlander, Warburton, Misri, Aghajanian, & Hertzman, 2006). Soon after the introduction of SRIs in the late 1980s, reports of preterm birth, low birth weight, pulmonary hypertension, and a cluster of neonatal "withdrawal" symptoms appeared, suggesting gestational and neurobehavioral disturbances associated with in utero SRI exposure (Oberlander et al., 2002). Importantly, some (Croen, Grether, Yoshida, Odouli, & Hendrick, 2011; Zeskind & Stephens, 2004), but not all (Nulman et al., 1997; Pedersen, Henriksen, Vestergaard, Olsen, & Bech, 2009; Stephansson et al., 2013) studies reported neurobehavioral disturbances, leaving critical unanswered questions about whether fetal SRI exposure-related outcomes reflect a transient pharmacological effect, suppressed neurotransmitters, or sustained alterations in brain development that starts long before birth.

The management of antenatal maternal mood disturbances presents an important public health concern as attempting to minimize risk in the fetus while optimizing maternal benefits makes choice of treatment uniquely challenging. Up to 50 % of women discontinue their medication within the first 60 days of their pregnancy (Bennett, Einarson, Taddio, Koren, & Einarson, 2004; Oberlander et al., 2006; Vesga-López et al., 2008; Warburton, Hertzman, & Oberlander, 2010), highlighting the urgency to recognize and manage perinatal mood disturbances and to establish evidence to guide antenatal SRI use in conjunction with non-pharmacological options (Yonkers et al., 2009). Thus, it is critical to understand the pharmacological and physiological effects when weighing the risks and benefits of SRI medication use in pregnant women—particularly in relation to maternal mental health and infant neurodevelopment (Yonkers et al., 2009).

Emerging findings point to evidence of biological and behavioral effects long before symptoms appear after delivery. While some biobehavioral effects associated with in utero SRI exposure are apparent during fetal periods, other effects emerge in the newborn period and over the first year of life. Given the paucity of fetal studies that provide direct evidence of fetal disturbances, this chapter draws from outcome data across infancy and early childhood to illustrate the potential impact of in utero SRI exposure on fetal development.

The Role of Serotonin

Serotonin (5-HT) is a phylogenetically ancient neurotransmitter widely distributed throughout the brain and already functional by mid-gestation (Kalueff, Olivier, Nonkes, & Homberg, 2010; Lebrand, Gaspar, Nicolas, & Hornung, 2006). Serotonin not only acts as a neurotransmitter in the mature brain regulating mood, appetite, and sleep, but also plays a neurodevelopmental role as a trophic signal long before birth, regulating the development of its own and related neural systems (Whitaker-Azmitia, Druse, Walker, & Lauder, 1996). In this way, 5-HT regulates diverse and developmentally critical processes in the fetal brain such as cell division, differentiation, migration, myelination, synaptogenesis, and dendritic pruning (Gaspar, Cases, & Maroteaux, 2003).

The transmembrane serotonin transporter (5-HTT) is a key regulator of 5-HT concentrations and governs the intrasynaptic reuptake of 5-HT into the presynaptic neuron, where it can be degraded or stored for subsequent release (Homberg & Lesch, 2011). The 5-HTT determines the magnitude and duration of extracellular 5-HT levels and is the initial target for SRI antidepressant medication (Lesch & Gutknecht, 2005). Serotonin reuptake inhibitors consist of two classes of antidepressants: selective serotonin reuptake inhibitors (SSRIs) (including citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), and selective norepinephrine

reuptake inhibitors (SNRIs) (including desvenlafaxine, duloxetine, milnacipran, and venlafaxine). Both classes are used to manage antenatal mood disturbances (Cooper et al., 2007) and will be referred to as SRIs. The mechanism of action is similar in both SSRIs and SNRIs, and to date there is no evidence that SRI type has a variable impact on fetal behavior (Mulder, Ververs, de Heus, & Visser, 2011; Rurak et al., 2011).

Maternal SRI treatment during pregnancy is thought to alter central fetal 5-HT levels as SRIs readily cross the placenta and blood–brain barrier (BBB) (Kim et al., 2006; Rampono et al., 2009). However, there is a paucity of comparative data with respect to transplacental SRI drug passage. Given that SRI use in pregnancy involves chronic use, SRIs are likely present at steady-state in terms of drug disposition. Thus, the relationships between fetal and maternal drug concentrations are largely determined by the ability of the fetus to metabolize the drug. For example, evidence for the stereoselective disposition and reduced ability to metabolize fluoxetine compared to paroxetine and other SRIs was shown in both pregnancy and the postpartum period in the mother, infant, and breast milk (Kim et al., 2006). Furthermore, evidence examining 15 human placentas immediately following delivery has suggested that citalopram may result in less fetal exposure than fluoxetine (Heikkinen, Ekblad, & Laine, 2002). A more recent study evaluating drug and metabolite concentrations for citalopram, escitalopram, sertraline, fluoxetine, fluvoxamine, paroxetine (SSRIs), and venlafaxine (SNRI) in the mother and cord at birth reported a linear transfer of both parent drug and active metabolites from the maternal to fetal circulation (Rampono et al., 2009). While this study was limited by a very small sample size, (Rampono et al., 2009) found that sertraline and its metabolite (*N*-desmethylsertraline) had lower cord–maternal ratios (0.33 and 0.4, respectively) than the other SSRIs (cord–maternal ratios of 0.7–0.86).

In terms of crossing the BBB, there are no human studies reporting trans BBB transfer during fetal periods. Using an analogous animal model based on similarities in the ontogenesis of the BBB, an examination of diphenhydramine (a potent histamine H_1 receptor antagonist) concentrations in the cerebral spinal fluid (CSF), extracellular fluid (ECF) and plasma in fetal, newborn and adult sheep found similar concentrations between the CSF and ECF compartments (Au-Yeung, Riggs, Gruber, & Rurak, 2007). In addition, Au-Yeung et al. (2007) reported that the brain–plasma drug ratios were significantly higher in fetal and postnatal lambs compared to adult sheep.

In human studies, brain biomarkers found in blood have been used as proxy measures of what might reflect blood-brain transfer. Neurobehavioral neonatal disturbances have been associated with measures reflecting central serotonergic levels in utero, specifically, levels of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) (Laine, Heikkinen, Ekblad, & Kero, 2003). Laine et al. (2003) reported that SRI-exposed infants had significantly lower cord blood 5-HIAA concentrations compared with a control group. A significant inverse correlation was also seen between the serotonergic symptom score—postnatal adaptation—and umbilical vein 5-HIAA concentrations in the SRI-exposed infants. SRI exposed neonates have lower cord blood levels of a biomarker of early brain maturation and central serotonergic function (i.e., astroglial-specific calcium binding protein, S100B) (Pawluski, Galea, Brain, Papsdorf, & Oberlander, 2009). Furthermore, SRI exposure has been correlated with increased norepinephrine metabolite (dihydroxyphenylglycol), increased thyroid stimulating hormone and reduced IGF-I cord blood levels (Davidson et al., 2009; Hilli et al., 2009), findings that might underlie impaired intrauterine growth in exposed neonates.

To date there is very limited evidence regarding how differences in breast milk drug levels vary with the type of SRI. Although breast milk as a route of postnatal exposure is much less significant than placental transfer in the fetus (Oberlander et al., 2005), a detailed review and pooled analysis including lactating mothers, breast milk and nursing infants revealed that SRI levels are present in breast milk (Weissman et al., 2004). These data revealed that breastfed infants

exposed to paroxetine and sertraline were unlikely to develop detectable serum drug levels, while infants exposed to fluoxetine through breast milk were more likely to develop elevated levels of the drug. The data on citalopram were limited but suggested that some infants developed quantifiable serum levels of the drug. More recent research has suggested that sertraline and paroxetine have the best safety profiles for use during breastfeeding (Davanzo, Copertino, De Cunto, Minen, & Amaddeo, 2011; Lanza di Scalea & Wisner, 2009).

In addition to maternal SRI dosage and serum concentrations, fetal drug exposure is determined by other factors such as fetal gene variants associated with placental transporter proteins that may influence the rate of placental drug transfer (Bonnin et al., 2011). Importantly, maternal treatment with SRI antidepressants occurs in the context of antenatal mood disturbances, which also affect levels of 5-HT during critical periods of neurodevelopment. Thus, distinguishing the impact of SRIs from the underlying maternal mood disturbances presents an immense challenge to all observational studies of fetal effects of SRI exposure (Bosco et al., 2010). Whether SRI antidepressant exposure or the underlying maternal mood disorder affect central fetal 5-HT concentrations, given 5-HTs diverse roles in fetal development, it is plausible that early alterations in serotonergic signaling could influence fetal brain development and thus affect neurobehavioral outcomes (Homberg, Schubert, & Gaspar, 2010).

Animal Models of Altered Early 5-HT Transmission

The effects of early changes in 5-HT signaling have been studied in animal models using pharmacological blockade of 5-HTT using SRI antidepressants (Maciag et al., 2006; Maciag, Williams, Coppinger, & Paul, 2006) or where 5-HTT is genetically absent, a condition resembling complete blockade of 5-HT reuptake (Ansorge, Zhou, Lira, Hen, & Gingrich, 2004). For example, high central 5-HT levels during early postnatal rodent development (akin to a human third trimester) caused permanent axonal connection deficits in the somatosensory cortex and lateral geniculate nucleus (Gaspar et al., 2003; Homberg et al., 2010), and altered neuronal dendritic branching, elongation and pruning (Liao & Lee, 2011; Zheng et al., 2011). Importantly, studies with animal models suggest that a 5-HTT blockade, whether genetically or pharmacologically driven, leads to lasting behavioral, neurophysiological and neuroanatomical alterations (Homberg et al., 2010; Oberlander, Gingrich, & Ansorge, 2009; Olivier, Blom, Arentsen, & Homberg, 2011; Simpson et al., 2011).

Preclinical studies suggest that in utero SRI exposure alters fetal behaviors and physiology well before the gestational exposure ends. Using a sheep model, in utero SRI exposure decreased uterine blood flow and oxygen saturation, and altered the fetus' behavioral state reflected in increased quiet sleep and decreased rapid eye movement (REM) sleep and decreased fetal breathing movements (Morrison et al., 2004; Morrison, Chien, Gruber, Rurak, & Riggs, 2001; Morrison, Chien, Riggs, Gruber, & Rurak, 2002). Increased prenatal fetal plasma adrenocorticotropic hormone (ACTH) and cortisol surges also have been reported (Morrison et al., 2001, 2002, 2004). In newborn lambs exposed to fluoxetine for 12 days in late gestation, increased newborn activity during the first 2 weeks after birth was observed (Nguyen, 2013). However, findings from this sheep model showed no changes in cardiovascular, metabolic, endocrine, or behavioral functions in the newborn lambs (~4 days old) with acute fluoxetine IV injection. In addition, lambs exposed to fluoxetine in utero showed low or undetectable plasma fluoxetine and norfluoxetine concentrations. These findings suggest that acute toxicity or withdrawal effects may not be the mechanisms underlying poor neonatal adaptation in SRI exposed human infants (Nguyen, 2013).

The effects of SRI exposure on brain development have also been studied using a rodent model. Offspring of dams administered fluoxetine for 14 days during pregnancy displayed a significant decline in both the cell count in the nucleus accumbens and serotonin transporter-like immunoreactivity in the raphe nucleus, suggesting that key brain regions responsible for the reward

response systems and serotonergic pathway are impacted by in utero SRI exposure (Forcelli & Heinrichs, 2008). Using rodent models akin to the human third trimester, early postnatal SRI exposure reduced novelty exploration and sexual activity, and increased immobility, sleep abnormalities and anhedonia (Ansorge et al., 2004; Lee, 2009; Maciag, Williams et al., 2006; Popa, Léna, Alexandre, & Adrien, 2008). These effects were associated with alterations in brain structure and function including reduced dendritic span and complexity in the somatosensory cortex (Lee, 2009), decreased synthesis of tryptophan hydroxylase (a key rate limiting enzyme for 5-HT synthesis) in the dorsal raphe, and decreased 5-HTT expression in the cortex (Maciag et al., 2006). However, not all outcomes associated with early SRI exposure using rodent models reflect developmental disturbances. Increased locomotor activity and spatial task ability have been observed in adult rats exposed to citalopram from postnatal days 8–21 (Maciag et al., 2006).

The neuroanatomical and functional consequences of changing 5-HT levels depend on the timing (critical periods) and direction (increased or decreased) of the developmental exposure, which may differ from the impact of an acute exposure in a mature organism (Ansorge, Hen, & Gingrich, 2007; Kalueff et al., 2010). In a rodent model, SRI exposure over a specific early postnatal period (postnatal days 4–21) of development is also associated, paradoxically, with reduced exploratory behavior, and depressive and anxiety-related behaviors in adulthood. These effects mimic the very effects of genetic 5-HTT inactivation (i.e., gene knockout models leading to the absence of the transporter), suggesting that increased serotonergic signaling during a developmentally critical period predisposes to subsequent affective disturbances (Ansorge et al., 2004; Ansorge, Morelli, & Gingrich, 2008; Gobbi, Murphy, Lesch, & Blier, 2001; Lira et al., 2003). Interestingly, in the long term, SRI-exposed animals demonstrate a decrease in 5-HT levels—possibly via activation of inhibitory receptors (i.e., 5-HT_{1a}) (Hensler, 2006). Such alterations in 5-HT signaling are evident at the neurostructural and behavioral levels, and in abnormal circuitry and cortical network functions (Simpson et al., 2011).

Fetal Effects of SRI Exposure: Human Findings

Gross structural neuroteratogenic effects following in utero SRI exposure have not been identified in humans; however, evidence pointing to functional behavioral disturbances is emerging (Oberlander, 2012). Fetal SRI exposure varies greatly (Kim et al., 2006; Rampono et al., 2009) and is a reflection of key maternal, placental, fetal metabolic, genetic, and pharmacological factors (Shea, Oberlander, & Rurak, 2012). During gestation, well before SRI exposure ends, changes in fetal neurobehavioral development have been observed including disrupted non-REM sleep and increased motor activity early in gestation followed by poor inhibitory motor control during non-REM quiet sleep near term (Mulder et al., 2011). Reduced fetal brain flow indices and heart rate variability also have been observed in the third trimester both before and after a typical daily maternal SRI dose (Rurak et al., 2011), even when controlling for maternal mood disturbances. Using fetal actocardiography with ultrasound observations, increased motor movements and reduced fetal breathing have been reported in SRI exposed fetuses (Salisbury, Ponder, Padbury, & Lester, 2009). In late gestation, SRI exposed fetuses were found to have reduced middle cerebral artery cross-sectional area before and following a typical daily maternal SRI dose (Rurak et al., 2011), suggesting an early and sustained medication-related effect. Moreover, altered cord red blood cell indices (increased hemoglobin concentration and increased hematocrit) at birth suggest that SRI exposure might be associated with altered fetal hypoxia and hypoxia-induced altered blood flow (Rurak et al., 2011). Whether these changes persist and represent the early origins of altered neonatal or childhood neurobehavior remains to be studied. Together these findings support the notion that the effects of SRIs on fetal behavior and function are a reflection of early alterations in neurobehavior, in contrast to the view that poor behavioral disturbances are associated with the acute cessation of SRI drug exposure at birth, pharmacological toxicity (Oberlander et al., 2004), or excess of 5-HT (Laine et al., 2003).

Impact of Prenatal Maternal Mood Disturbances

The impact of fetal SRI exposure cannot be effectively determined without considering the effects of the underlying indication for the drug treatment, and the maternal mood disturbance, which has been shown to impact fetal physiology and behavior. Many studies examining outcomes of in utero SRI exposure frequently yield highly conflicting findings showing both increased or no risk to neonatal/infant outcomes (Homberg & Lesch, 2011). This confusion can be explained at least partially as the result of the key challenge of "confounding by indication" (Bosco et al., 2010). Failure to effectively treat maternal depression and/or anxiety can lead to compromised prenatal care, increased risk of obstetrical complications, self-medication and/or substance abuse, as well as exposure to the illness itself. Maternal mental health that leads to SRI treatment also affects neurodevelopment (Glover, 2011) and fetal serotonergic signaling (Field, 2004; Field et al., 2008). Importantly, SRI treatment does not effectively treat maternal mental health disturbances for all women, and many women being treated with SRI antidepressants continue to experience depression and anxiety. Regardless of whether women continue or discontinue their antidepressant during pregnancy, Yonkers et al. (2011) showed that both groups had a similar risk of a major depressive episode in pregnancy (approximately 16 %).

There is evidence that antenatal maternal stress disrupts fetal neurobehavioral development (DiPietro, Hodgson, & Costigan, 1996; Tronick & Reck, 2009) and alters behavioral reactivity in utero (Allister, Lester, Carr, & Liu, 2001; Monk et al., 2000).

Perinatal maternal mood disturbances have been associated with reduced birth weight, and increased risks for prematurity (Glover, 2011; Talge, Neal, & Glover, 2007). Furthermore, antenatal exposure to maternal depressed mood appears to be reflected in newborns and has been associated with neonatal irritability, atypical frontal EEG patterns, reduced vagal tone, elevated cortisol and norepinephrine, and lower dopamine and 5-HT levels (Talge et al., 2007). Beyond the newborn period, antenatal maternal anxiety predicts infant temperament and attention regulation during the first year of life (Austin, Hadzi-Pavlovic, Leader, Saint, & Parker, 2005; Davis et al., 2007; Pluess et al., 2011; Talge et al., 2007), even when accounting for postnatal maternal psychological state. After controlling for obstetric risk, psychosocial disadvantage, and postnatal maternal mood, antenatal maternal anxiety continues to influence cognitive, behavioral, and emotional outcomes well into childhood (Talge et al., 2007). While the exact mechanisms by which antenatal anxiety/stress influence fetal brain development remain unclear, there is sufficient animal or human evidence to suggest that early life adversity predisposes to poor mental health and stress adaptation across the life span (Charney, 2004; Charney & Manji, 2004).

Even small changes in maternal disposition among euthymic mothers may be associated with differences in blood flow, fetal heart rate variability, and diurnal fetal patterns. We examined whether mothers positive and negative affect were associated with fetal vascular and heart rate changes at 36 weeks of gestation in euthymic mothers (Hanley, Rurak, Lim, Brain, & Oberlander, 2014). Negative affect reflects an individual's tendencies to express feelings like anger, contempt, shame, fear, and depression in response to life's stressors (Watson & Pennebaker, 1989). On the other hand, individuals' with high positive affect (which reflects an individual's enthusiasm, activity, control, and commitment) seem able to maintain a positive outlook both over time and in various situations (Bood, Archer, & Norlander, 2004). We found that mothers who reported high levels of negative affect showed reduced uterine artery flow, decreased fetal heart rate variability, an altered diurnal pattern, and decreased uterine artery cross-sectional area compared to mothers who reported low levels of negative affect. In contrast, mothers with low positive affect had a steeper diurnal pattern in fetal heart rate accelerations and decreased uterine artery mean velocity flow than mothers with high positive affect. While this was a small cohort study and these results need further investigation,

it suggests the possibility that even in the absence of an Axis I Major Depressive Disorder (MDD), maternal affect may have an impact on fetal and uterine physiology.

The Impact of Fetal SRI Exposure: Postnatal Findings in Humans

Neonatal Neurobehavioral disturbances: A postnatal adaptation syndrome (PNAS) or "withdrawal-like condition" has been widely reported and could be regarded as an extension of in utero behavioral changes (Moses-Kolko et al., 2005). PNAS typically includes some combination of the following symptoms: respiratory distress (Chambers, Johnson, Dick, Felix, & Jones, 1996; Davis, Rubanowice, et al., 2007; Diav-Citrin et al., 2008; Hemels, Einarson, Koren, Lanctôt, & Einarson, 2005), feeding difficulty (Ansorge et al., 2004; Oberlander, 2012), jitteriness (Oberlander, 2012), temperature instability (Oberlander, 2012; Tronick & Reck, 2009), sleep problems (Hensler, 2006), tremors (Laine et al., 2003), shivering (Laine et al., 2003), restlessness (Laine et al., 2003), convulsions (Davis et al., 2007; Kallen et al., 2004), jaundice (Costei, Kozer, Ho, Ito, & Koren, 2002; Oberlander et al., 2006), rigidity (Laine et al., 2003), and hypoglycemia (Chambers et al., 1996; Costei et al., 2002; Davis et al., 2007; Kallen et al., 2004). PNAS occurs in about 30 % of SRI exposed newborns (Levinson-Castiel, Merlob, Linder, Sirota, & Klinger, 2006; Oberlander et al., 2004) with a particular risk associated with SRI exposure during the last trimester of pregnancy (Moses-Kolko et al., 2005).

Studies on the impact of timing of exposure are few and logistically challenging (i.e., sample size, infrequent outcomes, and controlling for confounders that influence timing). Women treated with SSRIs late in pregnancy had a higher frequency of delivering SGA (small for gestational age) infants, and women receiving non-SSRI antidepressants were more likely to deliver premature and SGA offspring (Toh et al., 2009). Further, neonates with third trimester SRI exposure (often referred to as "late exposure" in the literature) have been reported to be at an increased risk for a special care nursery admission (Chambers et al., 1996; Cohen et al., 2000) and respiratory difficulty (Costei et al., 2002; Kallen et al., 2004; Oberlander et al., 2004) compared to neonates with first or second trimester or no SRI exposure. Importantly, for the most part, PNAS symptoms are mild and self-limited. The average time of onset for PNAS symptoms ranges between birth and 3 days of age and lasts for up to 2 weeks (Austin, 2006).

PNAS symptoms resemble a neonatal SRI drug withdrawal associated with an acute cessation of drug exposure, a pharmacological condition well recognized in adults, yet the underling etiology and clinical significance remains unclear (Warner, Bobo, Warner, Reid, & Rachal, 2006). Moreover, these behaviors also could be a continuation of fetal behavioral disturbances secondary to an acute fetal drug exposure or a reflection of sustained altered brain development that spans gestation. The severity of increased motor activity and tremors (Moses-Kolko et al., 2005), and altered stress regulation (Oberlander et al., 2002) has been associated with increased SRI drug levels (Oberlander et al., 2004) and pharmacogenetic metabolic factors (Laine et al., 2003), suggesting a potential pharmacologic toxicity. Further supporting this hypothesis, fluoxetine has the longest half-life of the commonly used SRIs and the lowest risk of withdrawal among adult patients (Coupland, Bell, & Potokar, 1996), yet maternal treatment in late pregnancy is associated with PNAS (Moses-Kolko et al., 2005). A dose dependent relationship with the severity of PNAS symptoms has been observed (Levinson-Castiel et al., 2006).

PNAS symptoms also are thought to reflect neurobehavioral changes associated with measures reflecting sustained central serotonergic levels in utero, specifically, levels of 5-HIAA (5-HT metabolite) (Laine et al., 2003). In this sense, PNAS symptoms could reflect fetal disturbances that predate birth. How these findings play out in terms of infant and child health risk over the first few years of life remains unclear; however, emerging evidence points to links between PNAS and development in early childhood. In SRI

exposed children, externalizing behaviors were associated with increased cord drug levels, particularly in children with a history of neonatal withdrawal symptoms (Oberlander et al., 2007). Further, in a recent study, Klinger et al. (2011) reported increased social behavioral disturbances in 2–6 year olds with a history of PNAS. Determining why some, but not all neonates are at risk for these neurobehavioral disturbances is a key question.

Risk for congenital malformations and cardiac defects using a case control study design (Louik, Lin, Werler, Hernández-Díaz, & Mitchell, 2007) were increased with first trimester paroxetine exposure (Jimenez-Solem et al., 2012; Knudsen, Hansen, Garne, & Andersen, 2014), while in other studies no association with increased first trimester exposure have been reported (Oberlander et al., 2008; Wichman et al., 2009). Importantly, confounding by indications associated with the use of SSRIs during pregnancy, such as socioeconomic status and maternal mood disturbances, may have an impact on risk (Jimenez-Solem et al., 2012; Oberlander et al., 2006). Further, rather than a particular point in time, length of prenatal SSRI use appears to affect neonatal and infant behavior (Casper et al., 2011; Oberlander, Warburton, Misri, Aghajanian, & Hertzman, 2008).

Genetic variations have been considered to play a role in moderating the impact of in utero SRI exposure, similar to differences in clinical effects of SRIs in adults (Pollock et al., 2000). Allelic variations for 5-HTT may influence the risk for PNAS, suggesting a gene-environment interaction. A 44 base pair insertion/deletion in the 5-HTT gene-linked polymorphic region (*5-HTTLPR*) produces a long (l) or short (s) allelic variant, with the long variant transcriptionally more efficient, resulting in higher 5-HTT expression and function (Homberg & Lesch, 2011). In SRI exposed neonates, two short alleles (ss) for the transporter were found to be associated with reduced 5-min Apgar scores, increased jitteriness, and increased muscular tone (Oberlander et al., 2008). In addition, compared to non-exposed infants, birth weight was lower in SRI exposed infants with an ls allele, and risk for respiratory symptoms (respiratory distress and tachypnea) was higher in SRI exposed infants with an ll allele (Oberlander et al., 2008).

Stress Regulation

In utero SRI exposure has also been shown to alter early stress regulation. Preclinical and human findings point to an in utero SRI-related "programming" effect on both sympathetic adrenal medullary (SAM) and hypothalamic pituitary adrenal (HPA) stress systems. However, some of these effects only become apparent in a particular postnatal maternal care-giving context. In response to an acute painful event, the duration of facial action and cardiac responses—particularly parasympathetic cardiac activity—are shorter and less intense in exposed neonates (Oberlander et al., 2002). Altered pain reactivity persists at 2 months of age, after controlling for drug levels and maternal mood (Oberlander et al., 2005).

In early infancy in utero SRI exposure affects cortisol levels and its binding protein, corticosteroid-binding globulin (CBG) (Pawluski, Brain, Underhill, Hammond, & Oberlander, 2011). Exposed neonates had increased CBG levels, particularly after vaginal delivery, though cord cortisol levels did not vary with in utero SRI exposure or antenatal maternal mood. These findings are not surprising given that serotonergic neurons projecting from the raphe nuclei to brain regions that affect motor development also affect sleep-awake function (Fuller, Gooley, & Saper, 2006) and regulate autonomic control (Bairy, Madhyastha, Ashok, Bairy, & Malini, 2007). Thus, changes in fetal 5-HT signaling may alter developmental processes that influence sleep, motor, and stress regulation.

Interestingly, the effects of prenatal SRI exposure on stress regulation may be apparent only in the presence of specific postnatal challenges long after delivery. At 3 months, SRI exposed infants had a reduced diurnal change in salivary cortisol, possibly suggesting that prenatal SRI exposure affects the developing HPA system via altered serum neonatal CBG levels (Pawluski et al., 2011). This also may be reflected in altered HPA

stress patterns and lower early evening basal cortisol levels in SRI exposed infants (Oberlander et al., 2008). In response to a non-noxious challenge at 3 months of age, SRI exposed and non-exposed infants exhibited similar salivary cortisol levels. However, when infant feeding status was considered, differences associated with SRI exposure emerged. Specifically, compared with breastfed SRI and breastfed non-SRI exposed infants, non-SRI exposed/non-breastfed infants showed a blunted post-stress cortisol pattern (Oberlander et al., 2008), possibly reflecting a self regulatory capacity that might heighten a senstivity to maternal caregiving.

Child Development and In Utero SRI Exposure

Motor Development

Recently research has begun to report differences in child development following in utero SRI exposure that might reflect long-term consequences of altered fetal neurodevelopment. These results appear to be consistent with animal studies reporting delayed motor development in SRI exposed mice (Bairy et al., 2007). The findings are not all together unexpected given the common neurodevelopmental role of 5-HT (Kalueff et al., 2010). Research using animal models has suggested that the links between in utero SRI exposure and motor control might reflect an early effect of muscle tone development under serotonergic control (Jacobs & Fornal, 1999). Poorer motor performance has been associated with impaired neurodevelopment in fluoxetine treated rats (Zheng et al., 2011), and alterations in muscle tone control have been reported as effects of SRIs in human infants (Laine et al., 2003). Human studies on motor development have presented conflicted findings. Typical mental and psychomotor development has been reported in some (Misri et al., 2006; Nulman et al., 1997, 2002), but not all studies (Casper et al., 2003; Hanley, Brain, & Oberlander, 2013; Mortensen et al., 2003; Pedersen, Henriksen, & Olsen, 2010). Two studies examining development using the Bayley Scales of Infant Development (BSID) have shown no difference in total BSID score (Nulman et al., 1997, 2002), while four others have reported lower scores on the motor index of the BSID in exposed children (Casper et al., 2003, 2011; Galbally, Lewis, & Buist, 2011; Hanley et al., 2013). Further research is needed in this area. We recommend that specific measures designed to assess motor development need to be collected in a longitudinal cohort of children in order to add to our understanding of the impact of prenatal SRI exposure on long-term motor development. Importantly, while differences in motor development were statistically significant, the clinical and long-term developmental consequences remain to be determined.

Risks for Autism Spectrum Disorder

Beyond motor development, increasing attention is being paid to the association between 5-HT during fetal brain development and autism spectrum disorder (ASD) in the child. Altering 5-HT levels during critical periods of development may affect brain areas in which serotonergic innervation is involved in regulating communication and social behavior—two key components that characterize ASD. As such, these alterations could underlie psychiatric and/or developmental conditions such as ASD (Jørgensen, Kjaer, Knigge, Møller, & Warberg, 2003).

The serotonin hypothesis of autism proposes that autism may in part have its origins in early dysfunctional 5-HT signaling. The developmental hyperserotonemia (DHS) model was proposed following a report that higher levels of 5-HT were detected in a third of patients with ASD (Whitaker-Azmitia, 2005). The DHS model hypothesizes that before the BBB is fully formed, high levels of 5-HT in maternal blood could enter the fetal developing brain and lead to a loss of serotonergic nerve terminals through negative feedback, blunting long term 5-HT signaling. Hyperserotonemia is the most consistent neurochemical change associated with ASD (Anderson, Horne, Chatterjee, & Cohen, 1990; Cook et al., 1993); it has been observed in first-degree relatives (Cross

et al., 2008) and is associated with risk of ASD within families (Abramson et al., 1989; Piven et al., 1991). Considering the DHS model and the fact that SRI antidepressants increase how much and how long extracellular 5-HT remains active and available, altering fetal central 5-HT levels (Weikum, Oberlander, Hensch, & Werker, 2012), concerns have been raised about how such early altered 5-HT signaling contributes to ASD risk.

Using animal models, manipulating prenatal 5-HT levels induce numerous neurological and behavioral abnormalities similar to those observed in ASD patients (Green et al., 2001; Modahl et al., 1998; Nelson et al., 2001). To model DHS in animals, rodents exposed to a 5-HT agonist during a gestational period analogous to the third trimester in humans, were observed to have changes in serotonergic receptors and columnar development in the cortex (Casanova, Buxhoeveden, Switala, & Roy, 2002; Whitaker-Azmitia, 2005). Changes in the amygdala and hypothalamus, brain regions that regulate mood, stress, emotion, and social responsiveness (all of which are dysregulated in ASD patients) showed higher levels of calcitonin gene-related peptide (Nelson et al., 2001) and lower levels of oxytocin (a peptide involved in bonding and social behavior), two key findings observed in humans with ASD (Green et al., 2001; Modahl et al., 1998). At a behavioral level, rodents exhibited behaviors similar to the clinical presentation of autism such as decreased social bonding, social interactions (McNamara, Borella, Bialowas, & Whitaker-Azmitia, 2008), sensory hyper-responsiveness, seizures, and motor impairment (Whitaker-Azmitia, 2005).

Direct evidence that links altered serotonergic signaling with an increased ASD risk in humans remains limited. Two recent epidemiological studies offer new lines of evidence suggesting that in utero SRI exposure may be one of the contributing factors. Researchers at Kaiser Permanente (California) used nested case-control methods to determine if exposure to SRIs in utero was more common among children aged 0–2 years with a diagnosis of ASDs than in typically developing comparison children (Croen et al., 2011; Rai et al., 2012). The researchers reported a twofold increase in exposure to SRIs among case children (6.7 % vs. 3.3 % in controls), even when controlling for maternal psychiatric history, demographics and co-morbidities. However, it is not clear if diagnostic codes for autism available in administrative datasets are valid indicators of autism, and the authors did not refer to any validation studies done on these data, suggesting possible diagnostic uncertainty. A second epidemiological study from Sweden used valid diagnoses of ASD. Rai et al. (2012) reported that maternal depression during pregnancy, and/or exposure to either SRIs or a non-selective monoamine reuptake inhibitor antidepressant (i.e., tricyclic antidepressants) was associated with an increased risk of an ASD. However, as with all observational research examining the effects of SRI use during pregnancy, these findings are susceptible to "confounding by indication" whereby distinguishing the impact of maternal mood disturbances and the medication used to treat it, remains a significant methodological challenge. This concern is increased by the fact that an increased risk of ASD also has been reported among children born to mothers who were depressed during pregnancy (Daniels et al., 2008; Piven & Palmer, 1999). Two recent studies have suggested that the association between SRI exposure in utero and ASD can be entirely explained as confounding by indication. Both Clements et al. (2014) and Hviid, Melbye, and Pasternak (2013) failed to identify a statistically significant increased risk of ASD among children who were exposed to SRIs in utero, but they did identify increased risk in children whose mothers used SRIs prior to pregnancy, suggesting that the risk was the underlying maternal psychopathology rather than the medicine. While these may be intriguing outcomes, the lack of follow-up beyond early childhood, the ongoing difficulty distinguishing maternal mood from medication effects, and the paucity of directly validated individual specific ASD diagnoses in these studies means that this area warrants further study.

Summary

In utero SRI exposure is common and neonatal behavioral outcomes following exposure vary greatly. Emerging findings suggest that SRI effects may be evident during gestation. In utero SRI exposure appears to influence fetal brain blood flow and neurobehavior. Moreover, fetal biobehavioral disturbances associated with such in utero exposure might predict altered developmental processes and subsequent long-term developmental risk. Preclinical findings highlight three key points regarding changes in 5-HT signaling associated with early SRI exposure that have critical implications for our understanding of human fetal development. First, both behavioral and physiological effects are apparent even before acute in utero exposure ends and these effects persist beyond birth. Second, altered 5-HT levels—either from genetic variations or pharmacologically driven following SRI exposure—induces a 5-HT reuptake blockade that appears to have a long-term impact on behavior such as anxiety and depression-like symptoms that extend into adulthood. Third, altered stress regulation has been associated with in utero SRI exposure which may have implications for mental and physical health across the life span. Together these findings suggest that in utero SRI exposure that alters early 5-HT auto-inhibitory feedback, leading to high serotonergic tone during developmentally sensitive periods, alters the maturation and function of the 5-HT system (Ansorge et al., 2004). Emerging findings in humans appear to point to similar in utero biobehavioral effects as well as long-term developmental and behavioral sequelae. Together these findings add to mounting concern about the use of SRI antidepressants during pregnancy and uncertainty for mothers and their clinicians.

While in utero SRI exposure alters central 5-HT levels, developmental outcomes do not necessarily reflect a solitary effect that can be easily attributed to one causal factor (i.e., maternal mood, genetics, or antidepressants). Rather, outcomes in this setting represent an interplay of psychological, pharmacological, genetic and social factors related to both mother and her child. Antidepressants might be prescribed during pregnancy with the expectation of optimizing infant health coupled with associated improved maternal mood; however, current evidence suggests that not all women respond to treatment and infants may continue to be at risk as maternal pharmacotherapy might not "buffer" or protect them from antenatal or postnatal maternal mood disturbances. It is important to recognize that this is a context of developmental vulnerability as well as neuroplasticity. Therefore, identifying mothers and their infants who might benefit from in utero maternal SRI treatment remains a key and pressing question. Longitudinal study designs that integrate both maternal and infant/child developmental perspectives should help us move away from characterizing in utero SRI exposure, maternal mood, or even genetic variations as "bad" or "harmful" and rather look at these as adversity or risk related factors that heighten or lessen vulnerability associated with early development.

From a maternal–child health perspective our task is to recognize risks arising from *both* the maternal disease and its treatment, and find ways to promote optimal child development and behavior in the context of family well-being. The decision to initiate SRI treatment during pregnancy rests with the mother and her physician carefully weighing the risks and benefits (Oberlander & Wisner, 2012). In providing antenatal treatment that requires SRI antidepressants, one needs to recognize risk characteristics that are inherent to an individual mother (and her child), in contrast to seeing them as just part of a population of prenatally treated mothers and their exposed children. There is a need to effectively diagnose and address antenatal maternal mental health with pharmacological and non-pharmacological options (cognitive/behavioral, social support, diet, housing, etc.), remembering that medications may just be one of many options available. This should include addressing the well-being of the entire family and its social context, ensuring access to affordable and appropriate health care, and laying community support. Ultimately, it might not be possible to distinguish the effects of disease from antidepressant treatment, nor may it even be necessary. What is critical is that we

recognize that multiple and ongoing "environmental pathogens" in this setting require ongoing watchful surveillance and timely interventions.

Future research needs to prioritize distinguishing the impact of maternal mood from the SRI exposure as well as working to identify the factors that contribute to both positive (e.g., maternal remission of depression, neonatal health) and negative outcomes (e.g., continued maternal depression and anxiety, PNAS syndrome) in maternal–infant pairs exposed to SRIs during the perinatal period. Improving our understanding of these critical topics will increase our ability to safely and effectively address maternal mental health disturbances during pregnancy.

Acknowledgement We are grateful to Ursula Brain, Leanne Fells, and Meisan Brown-Lum for their editorial assistance in the preparation of this chapter. GEH is supported by the Canadian Institutes for Health Research (CIHR), Michael Smith Foundation for Health Research (MSFHR), BC Women's Health Research Institute and NeuroDevNet. TFO is the R. Howard Webster Professor in Early Child Development (UBC, College of Interdisciplinary Studies). DR was supported by an Investigatorship Award from the Child & Family Research Institute. None of the authors have conflicts of interest, including financial interests that are relevant to the study reported in this chapter.

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