Neurodevelopmental Outcomes Following Prenatal Exposure to Serotonin Reuptake Inhibitor Antidepressants: A “Social Teratogen” or Moderator of Developmental Risk?

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Understanding how prenatal serotonin reuptake inhibitors (SRIs) influence early brain development can provide critical clues to how early life experience programs developing neural systems that might contribute to risks for illness across the life span. To date, no gross SRI-related neuroteratogenic effects have been identified, but evidence of subtle functional behavioral disturbances associated with fetal SRI exposure are emerging. Although some outcomes reflect a “main effect” for the SRI exposure, childhood development beyond infancy appears typical or continues to be influenced by life with a mother with a mood disturbance. Research shows that not all infants and children are equally affected; thus appreciating the effects of prenatal and postnatal maternal mental illness and of genetic variations that influence early serotonin signaling offers critical new insights into factors that contribute to developmental risk, plasticity, and resiliency in children with prenatal SRI exposure. Such a developmental perspective should lead us to understand what heightens or lessens neurodevelopmental vulnerability, thereby optimizing maternal pharmacotherapy and identifying who benefits and is least likely to experience neurobehavioral disturbances. Birth Defects Research (Part A) 94:651–659, 2012. © 2012 Wiley Periodicals, Inc.

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INTRODUCTION

Serotonin reuptake inhibitor (SRI) antidepressants are commonly used to manage perinatal mood disturbances. Between 15 and 20% of women experience mood disorders (e.g., depression) during their pregnancy and 5 to 13% are treated with an antidepressant (Oberlander et al., 2006; Cooper et al., 2007). Soon after the introduction of SRIs in the late 1980s, reports of neonatal withdrawal symptoms appeared, suggesting neurobehavioral effects associated with prenatal drug exposure (Oberlander et al., 2002) prompting public (Jetter, 2009) and scientific (Croen et al., 2011) concern about the long-term neurodevelopmental consequences of in utero SRI exposure. Importantly, some (Zeskind and Stephens, 2004; Croen et al., 2011) but not all (Nulman et al., 1997; Pedersen et al., 2009) studies reported neurobehavioral disturbances, leaving critical unanswered questions about G.E.H. is supported by the Canadian Institutes for Health Research, Michael Smith Foundation for Health Research, B.C. Women’s Health Research Institute, and NeuroDevNet. T.F.O. is the R. Howard Webster Professor in Early Child Development at University of British Columbia, and his work is supported by the Child and Family Research Institute and the Canadian Institutes for Health Research.

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whether SRI exposure-related outcomes reflect a transient pharmacological effect, suppressed neurotransmitters, or sustained alterations in brain development.

SRIs primarily act by blocking the serotonin transporter (5-HTT), which increases extracellular serotonin levels. Because SRIs readily cross the placenta and the blood-brain barrier (Kim et al., 2006), maternal prenatal SRI treatment alters central fetal serotonin (5-HT) levels. Serotonin is a phylogenetically ancient neurotransmitter widely distributed throughout the brain and already functional by mid-gestation (Lebrant et al., 2006; Homberg et al., 2010). Serotonin plays two critical roles: during early developmental periods, 5-HT acts as a growth factor, regulating the development of its own and related neural systems (Whitaker-Azmitia et al., 1996). As a trophic factor, 5-HT regulates diverse and developmentally critical processes such as cell division, differentiation, migration, myelination, synaptogenesis, and dendritic pruning (Gaspar et al., 2003). In the mature brain, 5-HT acts as a modulatory neurotransmitter influencing cognition, attention, emotion, learning, sleep, arousal, and stress response. Importantly, as a mediator between early life experience and subsequent behavior (Way and Taylor, 2010), 5-HT has a critical part in shaping individual differences in mental health across the early life span. Given these diverse roles, it is conceivable that altering early 5-HT signaling during development affects neurobehavioral outcomes (Homberg et al., 2010).

Despite the biologic plausibility of developmental changes, evidence of a main effect of SRI exposure in humans has been inconsistent, leading us to ask why some children are affected by prenatal SRI exposure and others are not. 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 effect of SRIs from underlying prenatal maternal mood disturbances is essential to appreciating the developmental effects of SRI exposure.

This article reviews current evidence of the neurobehavioral effects of prenatal SRI exposure and considers developmental outcomes in the context of how early changes in 5-HT signaling shape neurodevelopment. With this in mind, in utero SRI exposure offers us a developmental model, which reflects how maternal mood disorders (prenatal and postnatal) and the effects of early alterations of serotonergic tone interacting with genetic and social contexts together influence neurodevelopment. Beyond regarding prenatal SRI exposure as a developmental teratogen associated with abnormal physiologic development, this perspective offers us an opportunity to understand how prenatal SRI exposure is associated with developmental risk, plasticity, and resiliency.

**Prenatal Maternal Mood Disturbances**

A key challenge to understanding the developmental consequences of SRI exposure is appreciating how maternal mental health that leads to SRI treatment also affects neurodevelopment (Glover, 2011) and fetal serotonergic signaling (Field et al., 2004, 2008). Each year, 15 to 20% of women experience mood disorders (e.g., depression) during their pregnancy, leading to one third of these women being treated with an SRI antidepressant. However, up to 50% stop medication within the first 60 days of pregnancy (Bennett et al., 2004; Oberlander et al., 2006; Vespa-Lopez et al., 2008; Warburton et al., 2009). Women who discontinue antidepressant medication early in gestation have a higher risk for relapse (68%) compared with those who maintain treatment (26%; Cohen et al., 2006). Even in the presence of prenatal SRI treatment, maternal mood disturbances continue for some women, and there are ongoing developmental risks. Antenatal maternal stress disrupts fetal neurobehavioral development (DiPietro et al., 1996; Tronick and Weinberg, 1997), alters behavioral reactivity in utero (Monk et al., 2000; Allister et al., 2001), reduces birth weight, and increases risks for prematurity (Talge et al., 2007; Glover, 2011). Antenatal depression in newborns has been associated with irritability, atypical frontal electroencephalogram patterns, reduced vagal tone, elevated cortisol and noradrenaline, and lower dopamine and serotonin 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 et al., 2005; Davis et al., 2007; Talge et al., 2007; Pluess et al., 2011), even when accounting for postnatal maternal psychological state. Even 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). The exact mechanisms by which antenatal anxiety or stress influences fetal brain development remain unclear, but the magnitude of the effect is clinically significant, with approximately 15% of emotional and behavioral problems in childhood attributable to antenatal stress or anxiety (Talge et al., 2007). Importantly, not all outcomes reflect adverse early life events. Antenatal exposure to mild to moderate levels of psychological distress may actually advance motor development in a healthy population (DiPietro et al., 2006). Although it is beyond the scope of this article to review developmental outcomes associated with antenatal maternal mental health, it is critical to recognize that substantial animal or human evidence points to how early life experience shapes mental health and stress adaptation across the life span (Charney, 2004; Charney and Manji, 2004).

**Effects of Early Serotonin Transporter Blockade**

The effects of early changes in serotonin signaling have been studied in animal models using pharmacological blockade of 5-HTT using SRI antidepressants (Maciag et al., 2006a, 2006b) or where the serotonin transporter (5-HTT) is genetically absent, a condition resembling complete blockade of 5-HTT reuptake (Ansorge et al., 2004). Regardless, 5-HTT blockade that increases 5-HT levels lead to lasting behavioral, neurophysiologic, and neuroanatomic alterations (Oberlander et al., 2009; Homberg et al., 2010; Simpson et al., 2011; see Olivier et al. [in press] for details). At a neuroanatomic level, high central 5-HT levels during early mouse development (akin to a human third trimester) causes permanent axonal connections deficits in the somatosensory cortex (Homberg et al., 2010), the lateral geniculate nucleus (Gaspar et al., 2003), and altered neuronal dendritic branching, elongation, and pruning (Liao and Lee, 2011; Zheng et al., 2011).

Even before birth, the consequences of in utero SRI exposure are evident as reflected by decreased uterine and fetal brain blood flow, decreased oxygen saturation, and...
decreased rapid eye movement during sleep in a sheep model (Morrison et al., 2001, 2002). In the perinatal period, early SRI exposure is associated with increased neonatal mortality and lower birth weight (Vogel et al., 1990). Fluoxetine-exposed mice show reduced novelty investigation, increased anxiety in conflict tasks, and anhedonia (Ansorge et al., 2004; Ansorge et al., 2008; Popa et al., 2008). Poorer motor performance (Lee and Lee, 2011) has been associated with impaired dendritic structure in striatal and cortical neurons in fluoxetine treated rats (Zheng et al., 2011). As offspring age, the effects of early SRI exposure continues to be evident, reflected in learned helplessness, sleep abnormalities, and permanent reductions in sexual activity (Vogel et al., 1990).

SRI exposure during a specific postnatal period (postnatal days 4–21) of development is also associated, paradoxically, with reduced exploratory behavior as well as depressive and anxiety-related behaviors during adulthood. These effects mimic the effects of genetic 5-HTT inactivation (i.e., gene knockout models leading to the absence of the transporter), thus suggesting that increased serotonin signaling during a developmentally critical period predisposes to subsequent affective disturbances (Gobbi et al., 2001; Lira et al., 2003; Ansorge et al., 2004; Ansorge et al., 2008). In the long term, SRI-exposed animals demonstrate decreased 5-HT levels, possibly via activation of inhibitory receptors (i.e., 5-HT1A; Hensler, 2006). Such alterations in 5-HT are evident in abnormal circuitry and cortical network functions, and go on to be expressed as impaired social behavior and response to novel events (Simpson et al., 2011).

Importantly, not all changes in early serotonergic signaling lead to problematic outcomes. Rodents with genetically absent 5-HTT protein show increased memory and decision making when faced with ambiguity (Kaluweff et al., 2010), similar to the improved spatial (Bairy et al., 2007) learning seen following prenatal SRI exposure. Early SRI exposure appears to also reverse the adverse effects of prenatal stress exposure. Using a rodent model, Ishiwata et al 2005 observed that early postnatal SRI (fluoxetine) treatment (postnatal weeks 13) of prenatally stressed mice normalized corticosterone responses to a subsequent stressor, increased 5HT turnover in the hippocampus and restored the ability to learn spatial information compared with the effects of exposure to prenatal stress alone. Similarly early fluoxetine exposure reverses the reduction in immobility that appears in prenatally stressed adolescent offspring [Rayen et al 2011].

Animal findings highlight three key points regarding early altered 5-HT signaling associated with early SRI exposure. First, physiologic effects are apparent even before in utero exposure ends and persist beyond birth. Second, altered 5-HT signaling, from either genetic variations or pharmacologically induced 5-HT reuptake blockade, at developmentally critical periods, is associated with behavioral changes such as anxiety and depression-like symptoms that appear during adulthood. Third, not all effects of exposure to SRIs are associated with adverse outcomes. Together, these findings suggest that 5-HT autoinhibitory feedback, in the presence of increased serotonergic tone during developmentally sensitive periods, alters the maturation and subsequent function of the 5-HT system (Ansorge et al., 2004). Importantly, early changes in serotonin signaling that lead to altered development might reflect an increased risk for mental and physical illness across the lifespan and as such these findings can serve as a guide to understanding the effects of early SRI exposure in humans.

Impact of Prenatal SRI Exposure in Humans

To date, no gross structural neurotrophic effects following in utero SRI exposure have been identified in humans; however, evidence indicating functional behavioral disturbances is emerging (Oberlander et al., 2009). Fetal SRI exposure varies greatly (Kim et al., 2006; Rampono et al., 2009) and is a reflection of maternal, placental, and fetal metabolic, genetic, and pharmacologic factors (Shea et al., in press). During gestation, well before SRI exposure ends, changes in fetal neurobehavioral development have been observed. These include disrupted non-rapid eye movement sleep (Mulder et al., 2011), reduced brain flow indices, and reduced fetal heart rate variability (Rurak et al., 2011). Using fetal cardiotocography with ultrasound observations, increased motor movements, and reduced fetal breathing have also been reported in SRI exposed fetuses (Salisbury et al., 2009). In late gestation, SRI-exposed fetuses were found to have a reduced middle cerebral artery cross-sectional area before and after a typical daily maternal SRI dose (Rurak et al., 2011), suggesting an early and sustained medication-related effect. Together with these findings, increased cord red blood cell indices suggest that SRI exposure might be associated with altered early blood flow and fetal hypoxia (Rurak et al., 2011). Whether these changes persist and represent the early origins of altered neonatal or childhood neurobehavior remains to be studied.

Neonates with prenatal SRI exposure are at increased risk for neurobehavioral disturbances that include altered motor activity, tremors (Moses-Kolko et al., 2005) and stress/pain regulation (Oberlander et al., 2002). The severity of these symptoms may reflect increased SRI drug levels (Oberlander et al., 2004) and pharmacogenetic metabolic factors (Laine et al., 2004), suggesting potential pharmacological toxicity. Neurobehavioral changes have been associated with measures reflecting central serotonergic levels in utero, specifically levels of the serotonin metabolite 5-HIAA (Laine et al., 2005). 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 et al., 2009). SRI exposure has also 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.

SRI exposure has also been shown to alter early stress regulation. Neonates with prenatal SRI exposure are at increased risk for neurobehavioral disturbances that include altered motor activity, tremors and stress/pain regulation (Oberlander et al., 2002). 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, prenatal SRI exposure affects cortisol levels and its-binding
ing protein, corticosteroid-binding globulin (CBG; Pawluski et al. 2011). Exposed neonates had increased CBG levels, particularly after vaginal delivery, though cord cortisol levels did not vary with prenatal SRI exposure or antenatal maternal mood.

Interestingly, effects of SRI exposure on stress regulation may be evident only in the presence of specific postnatal environments. At 3 months, SRI-exposed infants have a reduced diurnal change in salivary cortisol across the day, possibly via altered serum neonatal CBG levels (Pawluski et al. 2011). This may contribute to altered HPA stress reactivity patterns and lower early evening basal cortisol levels observed at the same age in SRI-exposed infants (Oberlander et al., 2008b). In particular, in response to a nonnoxious challenge SRI-exposed and nonexposed infants exhibited similar salivary cortisol levels, yet only when infant feeding status was considered, differences associated with SRI exposure emerged. Namely, compared with breastfed SRI- and breastfed non SRI-exposed infants, non–SRI-exposed and non-breastfed infants showed a blunted post-stress cortisol pattern (Oberlander et al., 2008b). These findings might suggest an early SRI-related programming effect on the HPA stress system that becomes apparent only in a particular postnatal maternal caregiving context.

Beyond infancy, outcomes continue to reflect the effects of in utero SRI exposure (Hilli et al., 2009), but increasingly environmental and genetic influences emerge. Early life with a depressed mother influences childhood outcomes (Oberlander et al., 2008a), but maternal mood effects can be difficult to disentangle from the effects of prenatal SRI exposure. The duration of maternal depression and the number of depressive episodes predicts lower intelligence quotient and language scores in fluoxetine-related programming effect on the HPA stress system that becomes apparent only in a particular postnatal maternal caregiving context.

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**Other Susceptibilities: Genetic Factors and the Postnatal Environment**

The serotonin system is regulated by a complex network of genes, gene receptors and their subtypes, neurochemicals, and metabolic enzymes (Homberg et al., 2010). Thus incorporating information about interactions between genetic variations and the postnatal environment may help to explain individual heterogeneity in developmental outcomes (Boyce and Ellis, 2005; Moffitt et al., 2005). Importantly, not all allelic variations carry the same risk, and experiential variables continue to influence susceptibility to environmental factors long after gestation. (i.e., gene and environment interactions; Moffitt et al., 2005; Caspi and Moffitt, 2006). Variations in the gene (5-HTTLPR, SLC6A4) encoding the serotonin transporter protein, critical for reuptake of serotonin, influences 5-HT levels available at the presynaptic site (Homberg and Lesch, 2011). The serotonin transporter protein (5-HTT) is often regarded as a “master controller” of intrasynaptic serotonin signaling and plays a critical role in modulating environmental influences and developmental risk (Homberg and Lesch, 2011). Allelic variations have been shown to influence risks for cognitive and emotional disturbances (Lesch et al., 1996) and the efficacy of SRIs (Wellsberg and Seckl, 2001; Van den Bergh et al., 2008). Variations for SLC6A4 may shape sensitivity to negative as well as positive environments (Way and Taylor, 2010), offering a way to understand how some, but not all, factors that shape serotonin signaling affect individuals in the same way. In this way allelic variations in this gene offers critical insights into how altered early 5-HT signaling might have lasting developmental consequences.

Two key alleles, a long (l) (16 repeats of 2023 base pair sequence) and a short (s) (14 repeats) have been identified (Heils et al., 1996). The short allele is associated with reduced 5-HTT binding in the limbic region of the brain, lower 5-HTT expression, and decreased 5-HT reuptake into presynaptic neurons (Collier et al., 1996). Compared with the long form, the short allele is associated with reduced serotonin transporter (5-HTT) protein availability and function (Talge et al., 2007), indicating a higher effective intrasynaptic serotonin dose. Considerable evidence indicates associations between the short allele and an increased stress sensitivity, emotional disturbances, risks for cognitive, mood and personality disorders (Schinka et al., 2004; Sen et al., 2004; Karg et al., 2011), although not all studies have replicated such relationships (Willis-Owen et al., 2005).

Even early in life, allelic variations in SLC6A4 already appear to influence neonatal behavior. Neonates with two short alleles undergoing a heel lance pain event have significantly higher cortisol responses than those with two long alleles (Mueller et al., 2010). Interactions with context also count. At 6 months of age, infant SLC6A4 genotype moderates the effects of antenatal maternal anxiety on infant temperament and emotionality (Pluess et al., 2011). Greater antenatal maternal anxiety and higher levels of infant negative emotionality were observed in infants with two short alleles, whereas genotype did not have an effect under conditions of low maternal stress, highlighting how infant genotype only matters in a particular maternal context. Across the life span allelic variations for SLC6A4 may confer differential vulnerability to depressive disorders associated with stressful events in early life (Caspi et al. 2003, Kendler et al., 2005; Lesch, 2007), for some but not all individuals (Risch et al 2008). While adults with two short alleles may be at increased risk for depression following early adversity, those raised in a nurturing environment may have a lower risk for depressive symptoms (Taylor et al., 2006), suggesting heightened susceptibility to the environmental conditions, whether positive or negative. In this way, increased central 5-HT associated with the SLC6A4 short allele may contribute to an increased sensitivity to environmental stimuli or hyper-vigilance, leading to adaptation on one hand or increased
risk for mental health disorders on the other. In other words, in a low reward or low adversity setting, such hypervigilance may confer an actual benefit that increases processing of relevant stimuli that improves learning and social cognition (Homberg and Lesch, 2011).

Individuals with two short alleles may be more affected by both negative and positive environments (Taylor et al. 2006, Belsky and Pluess 2009a). In the face of early life adversity such genetic variants may increase risks for depression (Caspi et al. 2003, Kendler et al., 2005; Lesch, 2007), for some but not all individuals (Risch et al. 2008). Such variations may also be associated with improved cognitive functions and an enhanced sensitivity to relevant environmental stimuli (Homberg and Lesch 2011). Hypervigilance may be adaptive and enhance emotional response to environmental demands, drawing attention away from stimuli predicting adversity (or towards reward). Alternatively, in a non-threatening environment, such responses may be maladaptive and become antecedent to psychopathology. The short alleles may reflect an increased sensitivity to negative social contexts, they also confer sensitivity to positive life circumstances. In this sense, allelic variations function less like factors predicting ‘vulnerability’, but rather like a ‘plasticity factor’ (Belsky J, Pluess M. 2009b).

In combination with prenatal SRI exposure, allelic variations in SLC6A4 may compound risks associated with altered serotonin levels. Among SRI-exposed neonates, neonatal health risk (as reflected by lower 5-minute Apgar scores and risk for neuromotor symptoms) is more prevalent among those with the short allele (Oberlander et al., 2008a). In contrast, risk for respiratory distress was higher in SRI-exposed neonates with two copies of the long allele (Oberlander et al., 2008a). By 3 years of age, in children with reduced 5-HTT expression (two short alleles), antenatal exposure to maternal mood predicted increased anxious and depressed behavior, regardless of prenatal SRI exposure (Oberlander et al., 2010). In contrast, 3 year olds with two copies of the long allele, presumably leading to increased serotonin reuptake, coupled with late gestational maternal mood disturbance, were more likely to exhibit externalizing behaviors. The effects of antenatal maternal mood on child behavior was moderated by child SLC6A4 genotype, reflecting early changes in central 5-HT signaling via either genetic variations or SRI exposure.

Future Considerations

While pharmacology, genetics and maternal mental illness, clearly affect outcomes, we still face pressing questions about how and why prenatal SRI exposure influences early human neurodevelopment. Human research is constrained by ethical, medical, and logistical factors limiting randomized control studies that enable examination of age-dependent timing of exposures (i.e., prenatal and postnatal, mood, and medication). Although considerable attention has been focused on SRI effects on serotonergic neural transmission, a number of key, neurodevelopmental, pharmacological and contextual variables need to be considered. For example SRIs are also known for their off-target effects, such as on neurosteroid synthesis and gaba-aminobutyric acid (GABA\textsubscript{A}) receptor function (Robinson et al., 2003; Bianchi, 2008), suggesting that novel targets are needed for downstream developmental and behavioral studies.

Changes in SRI pharmacokinetics during pregnancy that might alter drug disposition and metabolism could influence the efficacy of antenatal treatment (Freeman et al., 2008) and fetal drug exposure. Studies examining the maternal gestational and fetal developmental metabolic (i.e., CYP450 metabolism) and pharmacologic variables (drug-drug interactions, physiologic adaptations associated with pregnancy) are needed. Future research should include studies of the role of the placenta in drug metabolism and transplacental transfer (Shea et al., in press).

Beyond allelic variations, epigenetic changes that influence gene expression are now increasingly recognized as critical factors that influence relationships between genetic variations, early life experience, and risk for psychopathology (Weaver et al., 2004; Whitelaw and White- law, 2006; Roth and Sweatt, 2011). Epigenetic modifications of DNA in response to environmental exposures (toxins, diet, and stress) have been widely documented (Zhang and Meaney, 2010) and offer critical new directions for research examining neurodevelopmental effects of SRIs. To date human evidence of prenatal SRI epigenetic changes have not been reported, however animal studies suggesting potential SRI-related epigenetic effects are emerging (Branchi et al, 2011). In adult mice early postnatal fluoxetine exposure was associated with behavioral inhibition and upregulation of hippocampal brain-derived neurotrophic factor messenger RNA levels. Interestingly, these effects were reversed with fluoxetine treatment in adulthood.

There is substantial evidence pointing to associations between low socioeconomic status (SES) and poor health of mothers and their infants, though little is known about how SES influences maternal depression, the likelihood of being prescribed SRIs or other psychotropic medications, and child developmental risks. Given that low SES is one of the key predictors of risk for both physical and mental illness and disability (Evans et al., 1994), increasing our understanding of relationships between SES, perinatal mental health, antidepressant treatment and developmental effects should open opportunities for population public health interventions that optimize maternal and child health.

Beyond gestational SRI exposure infant and child neurobehavior may continue to be at risk, because of ongoing maternal mood disturbances. While SRIs are often considered for antenatal therapy with the goal of improving maternal mental health during pregnancy (Gentile, 2005), such treatment has been shown to result in remission of a major depressive disorder in only 37% of patients and an overall cumulative remission rate of 67% (Rush et al., 2006). With a substantial number of pregnant women remaining partially or fully symptomatic after treatment (Suri et al., 2007; Wisner et al., 2009), poor maternal mental health continues to have an effect on early childhood behavior (Oberlander et al., 2007; Oberlander et al., 2010) long after birth. Continued work is needed to study longitudinal outcomes and attempt to distinguish the effects of maternal mood (prenatal and postnatal) from the effects of SRI exposure and identify how nurturing or supportive postnatal care giving “buffer” developmental risk. Finally, studies of non-pharmacologic therapies are needed to identify which therapies are effective and who can benefit from them.
Concluding Thoughts and Recommendations

Why some individuals and not others are affected by prenatal SRI exposure remains a central pressing and unanswered question. Two key findings might help guide our thinking. First, using animal models, early alterations in serotonergic tone have molecular, neuroanatomic, and functional consequences, reflecting processes that are dependent on the timing (critical periods) and direction (increased or decreased) of changes in signaling (Ansorge et al., 2004; Oberlander et al., 2009). Second, neurodevelopmental main effects following prenatal SRI exposure in humans are limited to relatively few studies and findings of long-term effects are frequently confounded by the difficulty in separating the effects of the antidepressants from the disease itself. Still, findings from animal models support a hypothesis that during brain development, autoinhibitory feedback shapes the maturation of the 5-HT system. With increased feedback signaling in the presence of high serotonergic tone (secondary to SRI exposure), 5-HT system maturation may be blunted thereby influencing neurodevelopment. Fetal 5-HT signaling sets pathways for health and disease across the life span. Higher serotonergic tone can be set by a combination of factors such as functional polymorphisms in the serotonin system, the prenatal and postnatal care giving environmental or pharmacologic factors. In contrast, low serotonergic tone during development may also contribute to neurobehavioral disturbances, such as reduced birth weight, prematurity, and irritability (Oberlander et al., 2002; Ansorge et al., 2008). In this context of setting optimal levels of SHT during development, SRI exposure during pregnancy could conceivably under some circumstances also have beneficial effects on fetal development, thereby counteracting factors that reduce fetal serotonergic tone. A next generation of research is needed to identify which factors influence developmental 5-HT signaling and understand how they contribute to setting fetal serotonergic tone, for better or worse.

In the context of both early (i.e., prenatal) and ongoing (i.e., postnatal) life experience, allelic variations that alter serotonin signaling illustrate how a serotonergic “differential susceptibility” (Belsky and Pluess, 2009) or “biologic sensitivity to context” (Boyle and Ellis, 2005) contribute to early child development. With such a perspective, the role of SRI exposure can be considered in the context of an individual’s genetic variations, prenatal exposure and postnatal experiences and not all outcomes can be predicted or attributed to one causal factor (e.g., maternal mood, the drug, genetics, placenta, maternal pharmacological variables). Development and behavior in this setting represents an interplay of psychological, pharmacologic, genetic, and social factors inherent to both the mother and her child acting via altered central 5-HT signaling. Importantly, it is not a case of 5-HT that is “too high” or “too low”, but rather a case of what does it take to ‘finely tune’ 5-HT levels during critical periods of development in a particular social context. Timing of exposure also matters. During the first year of life, infant psychomotor and mental development appear to be enhanced when there was a consistent pattern between prenatal and postnatal maternal depressed mood, regardless of whether maternal mood conditions were optimal or adverse (Sandman et al., 2012). Interestingly, postpartum euthymic mothers conferred no additional benefit to their infant who had been exposed to antenatal depressive symptoms. These findings illustrates the effects of the continuity between prenatal and postnatal depressive environments and how such stability confers an adaptive advantage that might prepare the fetus for a postnatal world ahead. To paraphrase Eisenberg (1998), this is indeed a setting in which nature meets nurture and niche.

In summarizing our current knowledge three themes emerge. First, whereas prenatal SRI exposure alters central 5HT levels, developmental outcomes do not necessarily reflect a “main effects” story that can be attributed easily to one causal factor (i.e., maternal mood, genetics, or the drug). Rather, outcomes in this setting represent an interplay of psychological, pharmacologic, genetic, and social factors related to the mother and her child. Second, although SRIs might be prescribed during pregnancy, with the expectation of optimizing infant health coupled with associated improved maternal mood, children may continue to be at risk as maternal pharmacotherapy might not buffer or protect them from antenatal or postnatal maternal mood disturbances. Third, this is a context of developmental vulnerability as well as plasticity. Therefore, identifying children who might benefit from prenatal maternal SRI treatment remains a key and pressing question. Longitudinal study designs that integrate a maternal and child developmental perspective should help us move away from characterizing prenatal SRI exposure, maternal mood, or even genetic variations as bad or harmful and instead 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 maternal mental illness 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 and Wisner, in press). 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 mothers and their exposed children. There is a need to effectively diagnose and address antenatal maternal mental health with pharmacologic and nonpharmacologic (e.g., cognitive, behavioral, social support, diet, housing) options, 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 providing lay community support. Addressing barriers to identifying and treating maternal perinatal mood disturbances should be seen as an urgent public health concern that will benefit mothers and children alike. The needs of mothers and their children in this setting may differ, but the well-being of each is critical to the other. Recognizing interrelated risks associated with both antenatal maternal mood disorders and pharmacotherapy is critical for developing empiric, evidence-based approaches that identify the best fit for both mothers and their children.

Even with current and emerging knowledge about SRI effects, we are still faced with pressing questions about whether we should discourage or support the use of SRIs in pregnancy. To date the evidence suggests that it
depends on balancing maternal and infant interests and risks (Oberlander and Wisner, 2012). In this sense it remains critical to consider what else is being done to "stack the deck" in ways that support the broader social context for mothers and their families (Goodman and Dimidjian, in press). SSRIs are prescribed with the anticipation of improving maternal and neonatal health. However, maternal pharmacotherapy might not result in symptomatic remission and the expected "buffering" of the fetus or neonate from maternal mood disturbances. In this context where developmental vulnerability continues, identifying mothers who benefit from prenatal maternal SRI treatment remains a key and pressing question. Longitudinal study designs that integrate a maternal and child developmental perspective should help us move away from regarding maternal mood, prenatal SRI exposure or even specific genetic variations as either bad or harmful and instead consider these as adversity- or risk-related factors that heighten or lessen neurodevelopmental vulnerability. Ultimately, it might not be possible to distinguish the effects of disease from antidepressant treatment, nor may it be easy to be sure of what is critical is that we recognize that multiple and ongoing environmental pathogens in this setting require ongoing watchful surveillance and timely interventions. Understanding the developmental effects of prenatal SRI exposure is a complex story that has much to teach us about the basic science of early neurodevelopment and offers critical clues that should help to promote healthy child development.

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**REFERENCES**


