Maternal and Fetal Factors That Influence Prenatal Exposure to Selective Serotonin Reuptake Inhibitor Antidepressants

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Abstract

Prenatal serotonin reuptake inhibitor (SRI) exposure is common and neonatal outcomes vary greatly, often leading to confusion about whether to use or even continue antenatal use of these antidepressants. Importantly, some but not all infants are affected, which raises questions about how maternal drug metabolism contributes to fetal drug exposure. To address this question, this chapter reviews the role of key maternal, fetal, and placental pharmacokinetic, metabolic, and genetic factors that affect the extent of fetal drug exposure. Considering the role of these factors may further our understanding of variables that might assist in optimizing maternal psychopharmacotherapy during pregnancy and neonatal outcomes.

Keywords

Antidepressants • Pharmacodynamics • Pregnancy • Depression • Fetus

4.1 Introduction/Background

Up to one-third of neonates exhibit neonatal neurobehavioral disturbances following prenatal exposure to a serotonin reuptake inhibitor (SRI) antidepressant (Moses-Kolko et al. 2005). While this has been assumed to be an effect of an acute drug exposure, these behavioral disturbances may not be related to maternal

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drug dose, length of gestational exposure, or timing of gestational exposure (Oberlander et al. 2009). These considerations subsequently raise critical questions about what factors affect fetal drug exposure and predict these neonatal outcomes. Determining why some infants and not others are affected by perinatal SRI use remains challenging. Central to addressing this question is our ability to consider the impact of physiological factors of the pregnancy itself and SRI-related pharmacological factors that influence maternal drug metabolism and by extension, fetal exposure. Neonatal outcomes following in utero SRI exposure depend largely on the degree of fetal drug exposure. As such, understanding factors that affect fetal drug pharmacology may offer important clues to any associated developmental risks. Importantly, SRI treatment occurs in the context of antenatal maternal mood disturbances which themselves have a critical impact on fetal and neonatal health (Hanley and Oberlander 2012). However, this chapter will focus on reviewing the key maternal, placental, fetal metabolic, and genetic factors that influence SRI pharmacology and fetal drug exposure. Both selective serotonin reuptake inhibitors (SSRIs, e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and serotonin norepinephrine reuptake inhibitors (SNRIs, e.g., desvenlafaxine, duloxetine, venlafaxine) are increasingly used to manage antenatal mood disturbances (Cooper et al. 2007) and will be referred to as SRIs (serotonin reuptake inhibitors). This chapter is offered as a review to highlight key maternal and fetal variables that account for the variations in maternal perinatal SRI pharmacology, fetal drug exposure, and neonatal outcomes that should serve as a guide to the clinician regarding the benefits and risks associated with SRI use in this setting.

4.2 Fetal Drug Exposure During Pregnancy

The management and treatment of antenatal mood disturbances present an important public health concern. Each year, 15–20 % of women experience mood and anxiety disorders (e.g., major depression, generalized anxiety disorder) during their pregnancy (Cooper et al. 2007). Approximately one-third of these women will be treated with a serotonin reuptake inhibitor (SRI) antidepressant (Oberlander et al. 2006). Importantly, up to 50 % of women discontinue their medication within the first 60 days of their pregnancy (Vesga-Lopez et al. 2008; Oberlander et al. 2006; Bennett et al. 2004; Warburton et al. 2010). This highlights the need to recognize and manage perinatal mood disturbances and to establish evidence to guide SRI medication use in conjunction with non-pharmacological treatments that may be less effective (Yonkers et al. 2009). Discontinuation of pharmacological treatment leads to increased risk for relapse in these patients (Cohen et al. 2006). 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).

Soon after the advent of SRI pharmacological treatment in 1988, reports of use during pregnancy cited a shortening of gestational age, lower birth weights, and

neonatal neurobehavioral disturbances (irritability, weak or absent cry, increased motor activity) suggesting a neonatal "withdrawal" condition (Moses-Kolko et al. 2005). While shortening gestational age at birth (Kallen and Olausson 2008) might explain some of these findings, the severity of behavioral disturbances has been linked to increased maternal and cord SRI drug levels (Oberlander et al. 2004) as well as with altered neonatal monoamine neurotransmitter levels (Laine et al. 2004), suggesting a direct role for pharmacological factors. During gestation, disrupted fetal nonrapid eye movement sleep (Zeskind and Stephens 2004; Mulder et al. 2011) and reduced cerebral blood flow indices and fetal heart rate variability (Rurak et al. 2011) have been associated with SRI exposure, which suggests that neurobehavioral changes may be present even before the prenatal period ends. Importantly, not all neonates are affected (Moses-Kolko et al. 2005), suggesting that genetic variations may moderate such associations (Oberlander et al. 2008; Davidson et al. 2009). The heterogeneity of outcomes following SRI exposure raises critical questions about fetal and maternal factors that affect the extent of drug metabolism and fetal drug exposure.

4.3 Fetal and Neonatal Effects of SRIs Exposure: Preclinical Evidence

Findings from animal studies suggest that prenatal SRI exposure alters fetal behaviors and physiology well before the gestational exposure ends. For example, sheep fetuses exposed to SRI medication in utero showed an alteration in behavioral state (i.e., increased quiet sleep, decreased REM sleep, and fetal breathing movements) and increased ACTH and cortisol surges (Morrison et al. 2002, 2004).

In newborn lambs exposed to 12 days of fluoxetine in late pregnancy, increased newborn activity during the first 2 weeks after birth has also been observed (Nguyen 2013).

Importantly, findings from this sheep model showed no changes in cardiovascular, metabolic, endocrine, and behavior in the newborn lambs (~4 days old) with acute fluoxetine IV injection. In addition, there were low and undetectable plasma fluoxetine and norfluoxetine concentrations in the postnatal lambs exposed to fluoxetine in utero, who exhibited hyperactivity for 2 weeks after birth. This may suggest that acute toxicity may not be the mechanism underlying poor neonatal adaptation in human infants exposed to these drugs (Nguyen 2013).

The effects of SRIs exposure on brain development have also been studied using a mouse model. Prenatal fluoxetine exposure for 14 days leads to a decreased cell count in the nucleus accumbens and in the raphe nucleus, a key brain region responsible for reward response systems (Forcelli and Heinrichs 2008). Using rodent models akin to the human third trimester, early postnatal SRI exposure reduced novelty exploration, increased immobility, sleep abnormalities, reduced sexual activity and anhedonia (Lee 2009; Ansorge et al. 2004; Maciag et al. 2006; Popa et al. 2008). These effects are associated with alterations in brain structure, including neuronal structure in the somatosensory cortex (Lee 2009), a decreased

synthesis of tryptophan hydroxylase (a key rate-limiting enzyme for serotonin synthesis) in the dorsal raphe, and decreased serotonin transporter expression in the cortex (Maciag et al. 2006). However, not all outcomes associated with early SRI exposure using mouse models reflect developmental disturbances. Increased locomotor activity and increased spatial task ability have been observed in mice exposed to citalopram from postnatal days 8–21, respectively (Maciag et al. 2006).

4.4 Drug Metabolism and Genetic Variations

All SRIs are metabolized by phase 1 and 2 hepatic pathways, with only 0–12 % of the drugs being excreted as intact compounds (Hiemke and Hartter 2000; DeVane 1999) (Table 4.1). Phase 1 reactions, which are dependent on hepatic cytochrome P450 enzymes (CYP), typically, CYPs 1A2, 2C9, 2C19, 2D6, and 3A4, are involved in the metabolism of SSRIs and the SNRI, venlafaxine (Table 4.1) (Fogelman et al. 1999). Genetic variations have been identified for each enzyme and some variants are associated with reduced or no catalytic activity (Martinez et al. 1999). For CYP 2D6 and 2C19, there are alleles with no catalytic activity, whereas for CYP 2C9, there are two alleles with significantly reduced catalytic activity and for CYP 3A4 there are many alleles with varying degrees of activity loss (Martinez et al. 1999). While metabolic capacity varies with genetic and pharmacological factors, a linear relationship has been demonstrated between maternal and fetal fluoxetine levels, suggesting that fetal exposure depends on maternal concentrations (Kim et al. 2006).

For example, the gene for the CYP2D6 enzyme has more than 80 genetic variants characterized to date (http://cypalleles.ki.se). However, not all are active and some variants encode an inactive protein or no enzyme product, reflecting an autosomal recessive polymorphism. When two nonfunctional alleles occur, the carrier is referred to as a "poor metabolizer" (PM), versus those heterozygous for the defect allele, "intermediate metabolizers" (IMs). Those carrying two functional alleles are classified as "extensive metabolizers" (EMs), while those with >2 functional copies are "ultrarapid metabolizers" (UMs), which may require higher than average doses of medication. Approximately 5–10 % of the Caucasian population is classified as PM, which is relevant to treatment during pregnancy as it leads to higher plasma concentrations of SRIs, particularly since most SRIs depend on the CYP 2D6 enzyme (Bradford 2002). Differences in SRI metabolism accompanying such allelic variants have been demonstrated by several studies (Bijl et al. 2008; Tsai et al. 2010). For the SRIs that depend on multiple CYP enzymes for metabolism, such as fluoxetine, citalopram, and sertraline, the individual genetic variation of one enzyme appears to be less critical. Alternately, desvenlafaxine metabolism and measured serum levels are not dependent on 2D6 variability (Preskorn et al. 2008).

Table 4.1 The cytochrome P450 enzymes utilized during SRI metabolism (Shea et al. 2012)

SRI	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Citalopram	–	–	+	+	+
Desvenlafaxine	–	–	–	–	+
Duloxetine	+	–	–	+	–
Escitalopram	–	–	–	+	+
Fluoxetine	–	+	+	+	–
Paroxetine	–	–	–	+	+
Sertraline	–	+	+	+	+
Venlafaxine	–	–	–	+	+

4.5 Maternal Adaptations to Pregnancy and Their Impact on SSRI/SNRI Disposition

Pregnancy itself alters key drug metabolic enzyme activities, leading to changes in SRIs disposition. Increased maternal blood volume, decreased plasma protein concentrations, increased cardiac output and renal function (GFR), and decreased intestinal mobility all potentially alter drug disposition and SRI dosing (Anderson 2005; Jeong 2010) during pregnancy. This may be reflected in decreased plasma concentrations of fluoxetine, citalopram, and sertraline during pregnancy (Wadelius et al. 1997). While the decrease in maternal antidepressant concentrations reduces fetal drug exposure, it often leads to the need to increase the maternal drug dose to maintain maternal euthymia (Anderson 2005).

Induced CYP2D6 activity during pregnancy has been linked to increased SRI levels (Wadelius et al. 1997). Comparing CYP2D6 activity in late pregnancy with 7–11 weeks postpartum, Wadelius et al. (1997) reported that CYP2D6 activity increased progressively during pregnancy and in the third trimester was ~48 % higher than in the postpartum period. Similarly, Anderson (2005) reported that CYP3A4 increased 35–38 % during all stages of pregnancy, whereas CYP1A2 activity decreased progressively across gestation. Further, increased CYP2C9 and increased uridine diphosphate glucuronosyltransferase activities and decreased CYP2C19 activity have been reported during pregnancy (Jeong 2010). Of note, declining sertraline levels have been reported by Freeman et al. (2008) from the second to the third trimester for most but not all women, reflecting individual variations in enzyme activity. Another prospective investigation found decreasing paroxetine levels from 16 to 40 weeks gestation in ultrarapid and extensive metabolizers of 2D6 (Ververs et al. 2009), while drug levels in the intermediate and poor metabolizers increased with gestational age. In the same study, maternal depression scores also increased as pregnancy progressed in the extensive metabolizers, suggesting a gene x environment (pregnancy) effect (Ververs et al. 2009). Given the differences in CYP metabolic capacities and CYP inhibitory potencies of the drug themselves, further study of links between an individual

antidepressant used in pregnancy and CYP genotypes is needed to characterize the alterations in the disposition of these drugs during pregnancy.

4.6 Interactions with SRIs

SRIs influence their metabolism by inducing and inhibiting the action of CYP enzymes (Tables 4.2 and 4.3). The use of other drugs that are substrates for the same CYPs may lead to competitive inhibition when co-administered with SRIs. Notably, CYP2D6 is inhibited by some, but not all SRIs (Preskorn et al. 2006; Pelkonen et al. 2008). Fluoxetine inhibits 2D6 after only 8 days of treatment (Alfaro et al. 1999). Further, antidepressant–drug interactions have been extensively investigated and impacts of the antidepressants on the pharmacokinetics of a large number of drugs have been identified. It has been argued that, on the basis of the existing in vitro, in vivo, and epidemiologic evidence, antidepressant–drug interactions are rarely clinically significant (DeVane et al. 2006). However, an increased risk for poor neonatal adaptation in neonates with higher levels of paroxetine following combined prenatal exposure to paroxetine and clonazepam—both CYP3A4 substrates—might illustrate the impact of a fetal drug–drug interaction (Oberlander et al. 2004).

Given multiple medical conditions may also be present when the pregnancy begins (e.g., gastroesophageal reflux, chronic hypertension, heart disease) or arise during pregnancy (e.g., preeclampsia, preterm rupture of membranes, preterm labor, cholestasis of pregnancy), the potential for antidepressant–drug interactions is substantial. Drugs used to treat these conditions are administered during pregnancy, and many of them are substrates for the CYPs that are inhibited by fluoxetine, paroxetine, and fluvoxamine (Oberlander et al. 2004), and affecting these enzymes may potentially increase fetal SRI exposure (Garnett 2001) (see http://medicine.iupui.edu/clinpharm/DDIs/clinicalTable.aspx).

Pregnancy-related increased gastroesophageal reflux is often treated with proton-pump inhibitors (PPIs), such as pantoprazole or the H2 antagonist cimetidine, which inhibit P450 enzymes (Li et al. 2004; Martinez et al. 1999). Dexamethasone, used to advance fetal lung maturation in threatened preterm labor, inhibits CYP2C9, but induces CYP3A4 (Zhou et al. 2009; Pascussi et al. 2001). When preterm rupture of membranes occurs, erythromycin (an inhibitor of 3A4) is often used to prolong the pregnancy and decrease maternal and neonatal morbidity (Yudin et al. 2009). Nifedipine, a 2C9 inhibitor, is used extensively to treat high blood pressure during pregnancy and is used also as a tocolytic agent in threatened preterm labor (Magee et al. 2011). Psychotropic medications, such as quetiapine, inhibit several SRI-metabolizing enzymes (Arranz and de Leon 2007). Interactions may also unexpectedly occur among commonly prescribed as well as OTC medications during pregnancy. Yeast infections are treated with fluconazole and miconazole, which inhibit key P450 enzymes involved in SRI metabolism (Niwa et al. 2005). These interactions may increase maternal plasma SRI levels, may affect fetal plasma concentrations, and thus increase the risk of drug-elicited

Table 4.2 List of cytochrome P450 enzyme inhibitors and inducers, relevant for SRI metabolism (Shea et al. 2012)

	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Inhibitors	Cimetidine	PPIs	Fluoxetine	Bupropion	Grape fruit juice
	Olanzapine	Fluconazole	PPIs	Duloxetine	Fluoxetine
	Clozapine	Metronidazole	Amitriptyline	Fluoxetine	Cimetidine
		Miconazole	Cimetidine	Paroxetine	Quetiapine
		Valproic acid nifedipine	Miconazole	Sertraline	Risperidone
			Fluconazole	Methadone	Aripiprazole
				Haldol	Clarithromycin
				Valproic acid	Erythromycin
				Celecoxib	Fluconazole
				Cimetidine	Miconazole
				Risperidone	
				Aripiprazole	
Inducers	Smoking	Dexamethasone	St. John's Wort		Dexamethasone
	Vegetables[a]	St. John's Wort			St. John's Wort
	Grilled meat				

PPI proton-pump inhibitor
[a]Cruciferous vegetables only

Table 4.3 Cytochrome P450 (CYP) isozymes involved in the metabolism of SRIs and the CYPs that they inhibit

Antidepressant	CYPs involved in metabolism	CYPs inhibited[g]
Fluoxetine	2C9, 2C19, 2D6[a]	CYPs 2D6 (strong), 2C9 (moderate), 2C19 (weak to moderate), 3A4 (weak)
Paroxetine	2D6, 3A4[b]	2D6 (strong), 1A2 (weak), 2C9 (weak), 2C19 (weak, 3A4 (weak)
Fluvoxamine	1A2, 2D6[c]	1A2 (strong), 2C9 (moderate), 2C19 (strong) 2D6 (weak), 3A4 (moderate)
Sertraline	2B6, 2C9, 2C19, 2D6, 3A4[d]	1A2 (weak) 2D6 (weak to moderate), 2C9 (weak), 2C19 (weak), 3A4 (weak)
Citalopram	2C19, 3A4[e]	CYPs 2D6 (weak to moderate), 2C9 (weak), 2C19 weak), 3A4 (weak
Venlafaxine	2C9 , 2C19, 2D6, 3A4[f]	CYP2D6 (weak)

[a]Ring et al. (2001); [b]Tang and Helmeste (2008); [c]DeVane (1999); [d]Obach et al. (2005); [e]Kobayashi et al. (1997); [f]Fogelman et al. (1999); [g]Spina et al. (2008)

adverse effects with consequences for fetal cardiovascular, neurologic, endocrine, or metabolic function.

Lifestyle-related factors may also influence SRI-metabolizing enzymes. For example, cigarette smoking and intake of cruciferous vegetables (such as broccoli) and grilled meat induce CYP1A2, which also metabolizes duloxetine (Lampe et al. 2000; Kall and Clausen 1995). Serum levels of duloxetine were found to be

significantly lower among smokers possibly due to CYP1A2 induction by the polycylic hydrocarbons found in cigarettes (Fric et al. 2008). See Table 4.2 for a summary of CYP enzyme inducers and inhibitors, relevant to pregnancy.

Together, an awareness of key pharmacological and environmental factors could decrease (via induction of enzymes, EM, UM) or increase (enzyme inhibition, PM) drug levels in the mother and her fetus. Individualized therapeutic drug monitoring has been suggested by DeVane et al. (2006). Although it may offer a way to optimize pharmacotherapy and reduce side effects for women and their fetuses, it also raises questions about the ethics, cost, and complexity of care inherent to genotyping. At the very least, understanding the metabolic implications of multiple co-administered drugs, OTC mediations, and environmental influences, as well as prescribing SRIs that utilize more than one enzyme, increases the likelihood that metabolism will be less affected by drug–drug interactions or enzyme genetic variability.

4.7 Placental Contributions to Fetal SRI Exposure

While the role the placenta plays in determining fetal SRI exposure remains unclear, fetal levels are comparable to maternal levels (Kim et al. 2006). Maternal–fetal exchange of drugs occurs via the chorioallantoic placenta, which in humans is of the villous hemochorial type (Carter and Enders 2004). As with other epithelial structures, the extent of placental transfer of a molecule depends in large part upon its physicochemical properties, with placental permeability being inversely related to molecular size, polarity, and charge and directly related to lipophilicity (Faber and Thornburg 1983). All SRIs are lipophilic (Wishart et al. 2006), leading to high placental permeability and extensive maternal to fetal SRI transfer in humans (Kim et al. 2006; Rampono et al. 2009), although the fetal/maternal concentrations vary substantially. Associations between cord SRI levels and risk for neonatal behavioral disturbances remain inconsistent (Rampono et al. 2009; Oberlander et al. 2004; Laine et al. 2004), suggesting that other factors such as fetal metabolism, variations in drug potency that influence the inhibition of serotonin reuptake, or the presence of psychoactive metabolites may also be important predictors of neonatal outcomes.

4.8 Fetal Contributions to SRI Metabolism

For lipophilic drugs, two factors are important in determining fetal to maternal concentration ratios and hence the extent of fetal drug exposure. First, maternal and fetal differences in plasma protein drug binding are a key determinant of drug availability (Hill and Abramson 1988) and this is particularly important for SRIs that are highly protein bound (Hiemke and Hartter 2000; DeVane 1999). Second is the magnitude of drug clearance in the fetus, which is important in a setting with chronic drug dosing that results in steady-state plasma drug concentrations, as is

Table 4.4 Summary of ontogenesis of the hepatic CYPs involved in the metabolism of SRIs in the human

	Fetus		New born	Infants	Children	Adults
Genes and proteins	<20 weeks	>20 weeks	<1 month	<1 year	<12 years	>12 years
CYP2C9	−	+				+++
CYP2C9	−/+	+	++	+++	+++/++++	++++
CYP2C19	−	−/+				+++
CYP2C19	−	−/+	+	+	++	+++
CYP2D6	+	+	++	+++	+++	+++
CYP2D6	−/+	+	++	+++	+++	++++
CYP3A4	+	+				++++
CYP3A4	−	+	++	+++	+++/++++	++++
CYP3A7	++++	+++				+
CYP3A7	++++	++++/+++	++/++++	++	+/−	−

Data from Hines et al. 2002

+++++ very high expression, ++++ high expression, +++ moderate expression, ++ low expression; + very low expression; − no or negligible expression

typical for SRI drug therapy. Further, fetal drug clearance can be divided into placental (i.e., fetal to maternal drug transfer) and non-placental clearance, including hepatic drug metabolism and renal drug excretion (Szeto et al. 1982). The main route of non-placental clearance of drugs appears to be via metabolism in the liver (Kumar et al. 1997). Renal drug excretion does not serve as a route of drug elimination in the fetus. Fetal urine is excreted into the amniotic cavity, and from there can be returned to the fetus via fetal swallowing of amniotic fluid and reuptake by the intra-membranous pathway into the vasculature in the fetal membranes overlying the placenta (Brace 1997; Rurak et al. 1991), then metabolized in the fetal liver, or transferred back to the mother across the placenta when fetal/maternal drug concentration ratios permit.

Fetal drug metabolic capacity is limited by the low expression of phase I and II enzymes in the liver. With the exception of the high expression of CYP3A7, which is involved in the metabolism of endogenous steroids and declines progressively after birth, the expression of most of CYPs is low or absent in the fetus, with more or less progressive increases after birth (Hines and McCarver 2002; McCarver and Hines 2002). This is summarized in Table 4.4, which gives the CYP enzyme mRNA and protein levels in the human fetus, newborn, child, and adult (Hines and McCarver 2002; McCarver and Hines 2002). It is likely that the differences in the fetal/maternal drug ratios (Table 4.3) reflect the degree of CYP expression in the fetus and the extent of inhibition of these CYPs by the various SSRIs and SNRIs.

4.9 Considerations for Perinatal Mental Health Clinicians

Prenatal SRI exposure is common and neonatal outcomes vary greatly. Identification of 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, neonatal SRI syndrome) in maternal–infant pairs must be prioritized as critical research topics to improve the benefits to both mother and her infant following SRI use in pregnancy. By considering the role of key maternal, fetal, and placental pharmacokinetic, metabolic, and genetic factors that affect the extent of fetal drug exposure we may develop evidence to guide optimal treatment with SRIs in pregnancy. Knowledge to inform pharmacologic care for pregnant women and their offspring is a critical investment in the health of the next generation. Overall, a key clinical approach should recognize the role of both fetal and maternal factors that influence pharmacological efficacy, a history of previous SRI treatment and related effects that might offer clues to pharmacological and genetic barriers to drug efficacy, the influence of environmental exposure that might influence drug effects (i.e., reduce drug–drug interactions), and efforts to minimize drug exposure where possible. The value of therapeutic drug monitoring and pharmacogenetic CYP testing for SRIs is unclear, given the limited evidence for clear drug concentration–effect relationships with the reported adverse fetal and neonatal consequences of antenatal drug exposure.

In providing antenatal care 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 considering all treatment options (cognitive/behavioral therapy, social support, diet, housing, etc.), remembering that medications may just be one of many options available. Recognizing interrelated risks of both antenatal maternal mood disorders and SRI exposure is critical for developing empirical, evidence-based approaches that identify the best fit between a pharmacological agent, non-pharmacological therapy, and maternal and neonatal factors so as to balance risks and benefits for both mothers and their children. Given increased risks associated with both untreated maternal depression and in utero SRI exposure, the clinical application of these findings may be challenging. This is not a setting where neonatal outcomes can be easily attributed to one causal factor—either maternal depression or SRI antidepressants. Rather, for most infants, the health risk is the result of an interplay between psychological, pharmacological, genetic, and social factors related to both the mother and the child. SRIs are prescribed with the expectation of treating the underlying maternal mood disorders to improve both maternal and infant health; however, such pharmacologic treatment during pregnancy does not guarantee remission of the underlying maternal mental illness. Identifying mothers who are likely to benefit from SRI treatment is a pressing issue. Clinicians may guide their management approaches by identifying patients who have a previous history of remission of depression/or anxiety with an SRI; however, this is not possible in all situations. Algorithms are available to guide

clinical decision making regarding treatment for maternal mental illness for mothers who are planning to conceive and for those who are already pregnant (Yonkers et al. 2009). The decision to initiate SRI treatment during pregnancy rests with the mother and her physician carefully weighing the risks and benefits, understanding that the implications—both for better and worse—may last far longer than the pregnancy. Risks to infant health do not end in the newborn period and are not confined to neonatal behavior or heart and lung development. Given ongoing life with a depressed mother, our challenge is to find ways to "stack the deck" in favor of optimal neonatal health in the context of family well-being, extending well into childhood. Recognition of multiple and ongoing "environmental pathogens" requires ongoing surveillance and timely interventions that reduce risk exposures and maximize the benefits of treatment.

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