Persistent Pulmonary Hypertension of the Newborn and Selective Serotonin Reuptake Inhibitors: Lessons From Clinical and Translational Studies

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Two recent studies linking in utero exposure to selective serotonin reuptake inhibitors (SSRIs) with persistent pulmonary hypertension of the newborn (PPHN), a potentially serious but rare respiratory illness, have made clinicians and patients more reluctant to use SSRIs during pregnancy. However, additional clinical studies have associated maternal depression rather than SSRI exposure as a risk factor for PPHN. This review summarizes the current knowledge regarding PPHN pathophysiology, including the role of serotonin and genetic risk factors; the effects of SSRIs on pulmonary vasculature; the possible link between SSRIs and PPHN; and the diagnosis, clinical management, and prognosis of PPHN.

(Am J Psychiatry 2012; 169:134–140)

Despite conflicting clinical evidence regarding the risk of persistent pulmonary hypertension of the newborn (PPHN) in infants exposed to selective serotonin reuptake inhibitors (SSRIs) during pregnancy, many articles in the medical literature and in the popular press present SSRIs as an established risk factor. While some sources urge outright discontinuation of SSRIs in pregnancy and the U.S. Food and Drug Administration (FDA) in 2006 issued a public health advisory on it (1), a set of 2009 guidelines issued jointly by APA and the American College of Obstetrics and Gynecology recommended continued judicious use of SSRIs if no alternative treatments are effective (2).

An estimated 92,000 women received an SSRI prescription during pregnancy in 2006 (3). Discontinuation of antidepressant medication during or before pregnancy is associated with high rates of depression relapse during pregnancy and the postpartum period (4). A mother who is depressed during pregnancy and the postpartum period is at risk of premature delivery and impaired ability to care for herself and her infant, and her infant is at risk of impaired cognitive, social, and emotional development (5, 6).

PPHN is a rare illness that affects an estimated 1.9 infants per 1,000 live births (7). It is a heterogeneous condition with multiple etiologies, the most common being meconium aspiration and other forms of lung injury. Although there is a high mortality rate associated with some forms of PPHN, none of the published studies linking SSRIs and PPHN report any cases of associated infant death or describe the short- or long-term morbidity or typical course of infants with PPHN after in utero exposure.

Recent animal and clinical studies have illuminated the role of serotonin in the development of pulmonary hypertension and the possible differential effects of SSRIs on pulmonary vasculature in adults and fetuses. In this article, we review the relevant clinical and translational findings in order to more critically evaluate the potential effects of in utero SSRI exposure on pulmonary vascular development and risk for PPHN. Informed clinical judgment is needed to balance the risk of this rare condition against the risk of untreated or undertreated depression.

Pulmonary Adaptation at Birth

In the fetus, systemic vascular resistance is low, primarily because of the low-resistance/high-flow placental vessels, and pulmonary vascular resistance is high. Only 8%–10% of venous return enters the lung vasculature; the organ of respiration is the placenta. Deoxygenated fetal blood is carried to the placenta via the umbilical artery, reoxygenated, and then carried back into the fetal circulation via the umbilical vein to the inferior vena cava. Oxygenated blood is shunted right to left via the foramen ovale between the right and left atrium and via the ductus arteriosus between the pulmonary artery and the aorta. Toward the end of pregnancy, the fetal lungs mature to enable gas exchange after birth. Pulmonary fluid production decreases, membrane transporters for clearance of pulmonary fluid increase, and synthesis of surfactant and vasodilator enzymes rises.

At birth, systemic vascular resistance rises (as a result of removal of the placenta) and pulmonary vascular resistance falls (as a result of lung expansion, increased oxygen levels in the airways, and increased endothelial production of the vasodilators, including nitric oxide, the pros-

This article is an article that provides **Clinical Guidance** (p. 140)

taglandin I_2 [PGI_2], and bradykinin). The pressure in the pulmonary artery falls by 50% in the first 24 hours of life. Within the lung vasculature, the formerly brick-shaped smooth muscle cells elongate, the endothelial cells flatten, and the arterial lumina expand. Outside the lung, the ductus arteriosus constricts, the foramen ovale closes, and left heart pressure rises further with increased pulmonary vein return to the left atrium (8).

Persistent Pulmonary Hypertension of the Newborn

PPHN is a final common pathway of a variety of risk factors and insults that can cause pulmonary underdevelopment, maldevelopment, or poor postnatal adaptation. It is diagnosed by impaired oxygenation and evidence from ECG of abnormally elevated pulmonary pressure, including tricuspid regurgitation and shunts across the ductus arteriosus or foramen ovale. Some clinicians also use the difference between postductal and preductal oxygenation levels (i.e., the differential between vessels that branch off distally and those that branch off proximally to the insertion of the ductus arteriosus) as a diagnostic criterion. This can be measured by arterial sampling or transcutaneous oxygen monitoring. In PPHN, postductal oxygenation is especially low in contrast to preductal oxygenation. A PaO_2 difference of 10–20 mm Hg or greater measured with arterial blood gas sampling, or an SaO_2 difference of 10% or greater measured with a pulse oximeter, suggests a diagnosis of PPHN.

Symptoms of PPHN include tachypnea, retractions, grunting, and cyanosis. A heart murmur consistent with tricuspid regurgitation may also be present. Affected infants typically show little or no response to increases in inspired oxygen concentration or airway pressure in their arterial oxygenation. The differential diagnosis includes other pulmonary disease, infection, structural heart lesions that increase right heart pressure or decrease oxygenation, and myocardial dysfunction.

Known etiologies and risk factors include prematurity or postmaturity; direct lung injury, including meconium aspiration; other causes of neonatal hypoxia; chronic intrauterine hypoxia; hypoglycemia; cold stress; inflammation; sepsis; space restriction due to diaphragmatic hernia with resultant pulmonary hypoplasia; premature closure of the ductus arteriosus (e.g., in association with exposure to nonsteroidal anti-inflammatory drugs); maternal smoking; male gender; cesarean section delivery; and group B streptococcus infection (7–10). In a cohort study of 385 infants with PPHN between 1993 and 1994, delivery occurred via cesarean section in 51% of cases (7), a figure significantly elevated relative to the population base rate. Additional risk factors associated with less severe difficulties in the neonatal respiratory transition include increased maternal age, diabetes mellitus, hypertension, substance abuse, and a history of fetal loss or stillbirth (11). Several of these obstetric risk factors—prematurity, substance abuse, and cesarean section—are more common in women with depression (6, 12, 13).

Forty percent of PPHN cases occur because of meconium aspiration (7). Meconium aspiration syndrome occurs in an estimated 11% of deliveries with meconium-stained amniotic fluid, a condition found in 2%–25% of all births. SSRIs are known to cause gastrointestinal hypermotility in adults and newborns, but a potential association with meconium aspiration syndrome has not been examined.

Although mortality associated with PPHN is 10%–20%, mortality rates vary based on etiology. The mortality risk of PPHN is greatest in cases of pulmonary hypoplasia, as compensatory mechanisms are limited. Mortality is relatively low (6%) in cases associated with meconium aspiration (7). Infants affected by PPHN who survive are at risk for developmental delay, motor disability, and sensorineural hearing deficits, but these morbidities likely depend on the etiology and severity of PPHN. A study of children ages 5 to 11 with a history of PPHN found an elevated risk of learning difficulties and chronic health problems, including the need for bronchodilator therapy (14). Mortality rates in cases of SSRI-associated PPHN have been reported for only part of one study; in that report, all 11 affected infants survived (15). To our knowledge, no morbidity data from long-term follow-up of SSRI-exposed infants with PPHN have been reported.

Pathophysiology of PPHN

The onset and perpetuation of PPHN involves multiple interacting physiological mechanisms, most of which play important roles in pulmonary hypertension in adults as well. Established animal models of PPHN include neonatal hypoxia, antenatal ductus arteriosus ligation, meconium aspiration, and sepsis (8). There is a single report of an animal model of SSRI-induced PPHN (16).

In the endothelial cells of infants with PPHN, production of endothelin-1, a vasoconstrictor, is increased, and production of nitric oxide, a potent vasodilator, is low (17). Endothelin-1 acts on the underlying smooth muscle cells to cause vasoconstriction and smooth muscle cell proliferation (8). Synthesis of nitric oxide by endothelial cells begins during lung embryogenesis and increases during the transition to air breathing at birth. Nitric oxide suppresses some of the negative sequelae of hypoxic injury, including increased production of endothelin-1 (18). Another important contributory factor to endothelial cell dysfunction is disruption of vascular endothelial growth factor (VEGF) signaling. VEGF is critical for normal blood vessel genesis, survival, and functioning, and impairments in VEGF signaling have been demonstrated in both experimental and clinical studies of PPHN (19). Lastly, another important contributing factor to the endothelial dysfunction in PPHN is impairments in prostaglandin functioning, associated with decreased production of PGI_2 (20).

TABLE 1. Clinical Studies of Persistent Pulmonary Hypertension (PPHN) of the Newborn and Selective Serotonin Reuptake Inhibitors (SSRIs)

Study	Description	Women or Infants in Study	Infants With PPHN	SSRI Exposure Estimated Risk
Negative findings				
Andrade et al. (45)	Multicenter retrospective cohort study	2,208 infants; 1:1 ratio of third-trimester SSRI-exposed and nonexposed	N=5; two SSRI-exposed	No association
Wichman et al. (46)	Retrospective cohort study	25,214 infants; 2.3% SSRI-exposed	N=16; 0 SSRI-exposed	No association
Wilson et al. (47)	Case-control study; PPHN identified via echo or difference in pre- and postductal oxygen saturation	11,923 infants; 1:6 ratio of PPHN patients and healthy infants; number of SSRI-exposed not reported	N=20; 0 SSRI-exposed	No association
Positive findings				
Chambers et al. (44)	Multicenter case-control study	1,213 infants; 1:2 ratio of PPHN patients and healthy infants; 3% SSRI-exposed	N=377; 16 SSRI-exposed	Odds ratio=6.1 (95% CI=2.2–16.8)
Källén and Olausson (15)	Population-based retrospective cohort study; same data set as Reis and Källén (43), with a shorter time frame	831,324 infants; 0.9% SSRI-exposed	N=506; 11 SSRI-exposed	Relative risk=3.57 (95% CI=1.2–8.3)
Reis and Källén (43)	Extended version of Källén and Olausson study (15)	1,251,070 infants; 1.2% SSRI-exposed	N=572; 32 SSRI-exposed	In early pregnancy, relative risk=2.4 (95% CI=1.29–3.80); in later exposure, relative risk=2.56 (95% CI=1.17–4.85); in both early and late exposure, relative risk=3.44 (95% CI=1.49–6.79)

Abnormalities in smooth muscle functioning also contribute to PPHN. Inositol triphosphate (IP_3) generation is increased in vascular myocytes, contributing to increased calcium mobilization and calcium sensitivity, thereby potentiating vascular constriction and smooth muscle proliferation. When PPHN is induced by sepsis or inflammation from meconium aspiration, proinflammatory cytokines released by inflammatory cells and injured lung tissue also activate IP_3 (8).

The animal model of premature ductus arteriosus closure increases right heart output to the pulmonary vasculature and activates two opposing mechanical responses in pulmonary vessels: vasodilation resulting from shear stress and vasoconstriction due to strain (21). Shear stress increases nitric oxide synthesis and vasodilation, but strain responses increase calcium sensitization and IP_3 levels, which promote calcium mobilization, leading to an overwhelming rise in constrictor response, smooth muscle proliferation, and smooth muscle hypertrophy. In later stages of PPHN, irreversible fibrotic changes occur in the lung tissue, including hyperplasia and hypertrophy of the vascular smooth muscle layer and increased extracellular matrix (8).

Serotonin in Pulmonary Hypertension

Serotonin is a potent pulmonary vasoconstrictor, and adult pulmonary hypertension is associated with local alterations in serotonin signaling and metabolism. The lung does not have any prominent serotonergic innervation, but serotonin is synthesized in vascular endothelium, and the serotonin transporter is expressed in vascular smooth muscle, which takes up and stores serotonin in vesicles and releases it in response to local stimuli (22). There is very little free serotonin in the bloodstream because of its rapid metabolism by monoamine oxidase enzymes in the liver and lungs; most of the blood content of serotonin is stored in platelets. Since SSRIs block the uptake of serotonin into platelets, whole blood serotonin levels are low during exposure to SSRIs.

In animal models of PPHN, hypoxic insults and pulmonary arterial distension increase the activity of tryptophan hydroxylase, the rate-limiting enzyme for serotonin synthesis in pulmonary vasculature endothelial cells. Increased serotonin from the endothelial cells then activates the underlying smooth muscles cells, leading to proliferation and contraction of the smooth muscle. Evidence suggests that serotonin-induced contraction of smooth muscle cells occurs primarily through activation of 5-hydroxytryptamine receptor 1B ($5\text{-}HT_{1B}$) and that smooth muscle cell proliferation occurs through both activation of $5\text{-}HT_{1B}$ and the internalization of serotonin via the serotonin transporter (23). In clinical studies, adults with idiopathic pulmonary hypertension have increased production of tryptophan hydroxylase in the pulmonary vascular endothelium (24). In addition, some medical conditions

Strengths	Weaknesses
Prospectively collected exposure data	Underpowered to detect small effects
Prospectively collected information	Small SSRI-exposed sample; underpowered to detect small effects
Explicit diagnostic criteria for PPHN; prospectively captured prescription information	Incidence of SSRI use in population unreported; no control for length of gestation beyond exclusion of <34 weeks
Large number of PPHN cases; required exposure after 20 weeks	Exposures based on telephone interviews with only 70% participation (potential recall bias); no control for mode of delivery or gestational age beyond 34-week exclusion; overly sensitive criteria for PPHN (required PaO_2 gradient of only 5 mm Hg between pre- and postductal circulation); not all PPHN cases confirmed via echocardiography
Large data set; prospectively obtained SSRI usage	Cases defined by ICD-9 coding alone; no control for mode of delivery or for gestational age beyond exclusion of infants <34 weeks
See Källén and Olausson (15)	

that impair platelet storage of serotonin are associated with greater circulating serotonin levels and a higher risk of adult pulmonary hypertension (22). Similarly, a rat strain with an inherited form of platelet serotonin storage dysfunction has elevated serum serotonin and develops pulmonary hypertension (25).

In adult animal models, SSRIs have a protective effect against the development of pulmonary hypertension (26, 27). A cross-sectional clinical study (28) suggested that SSRIs may slow progression of pulmonary hypertension in adults, but a longitudinal study did not show any benefit of SSRI treatment (29). SSRIs are not currently a recommended treatment for pulmonary hypertension in adults, but neither are they contraindicated in patients with pulmonary hypertension.

Notoriously, three anorexigens (fenfluramine, *d*-fenfluramine, and aminorex) have been associated with the development of pulmonary hypertension in adults. These drugs differ from SSRIs in that they are structurally amphetamine-like and they trigger serotonin efflux via the serotonin transporter. However, they are similar to SSRIs in that they also inhibit serotonin reuptake.

Differential Effect of SSRIs on Fetal Pulmonary Vasculature

Fornaro et al. (16) studied pregnant rats that were treated with fluoxetine on days 11 through 21 of gestation. Exposed fetuses showed signs of pulmonary hypertension with an increase in the weight ratio of the right ventricle to the left ventricle plus septum and an increase in pulmonary arterial medial thickness. They also observed lower oxygenation and higher mortality in exposed pups. In vitro, fluoxetine caused pulmonary arterial muscle contraction in fetal, but not adult, tissue. Lastly, the fetal but not the adult pulmonary smooth muscle cell proliferation rate increased in response to fluoxetine exposure.

Another observation of differential effects of SSRI exposure in neonates (30) involved blood levels of S100B, a calcium-binding protein produced in astroglia that mediates outgrowth and survival of neurons and is commonly used as a biomarker of neuronal injury. S100B release is triggered by the stimulation of $5\text{-}HT_{1A}$ receptors on astroglia. Serum S100B levels were higher in mothers treated with SSRIs compared with unexposed mothers, but the levels were lower in SSRI-exposed neonates compared with unexposed neonates.

Genetic Factors

Functional polymorphisms in the serotonin transporter gene (SLC6A4) that may modulate the risk for developing pulmonary hypertension have been identified in humans (22, 31). The long (l) allele of the 5HTTLPR polymorphism in the promoter region of SLC6A4 is associated with increased transcription of the transporter gene and with an approximately 50% increase in serotonin reuptake in pulmonary vascular cell cultures. In a study of adults with pulmonary hypertension, the l/l genotype of the 5HTTLPR polymorphism was found in 60% of study subjects relative to 28% of healthy comparison adults and was associated with higher levels of serotonin transporter mRNA and protein in lung tissue (32). The l/l genotype has also been associated with increased pulmonary artery pressure in patients with left ventricular dysfunction (33). Similarly, in a study of newborns, the risk for neonatal respiratory distress was elevated in SSRI-exposed neonates with the 5HTTLPR l/l genotype relative to nonexposed neonates with the same genotype (34). Overexpression of the serotonin transporter gene in mice resulted in elevated pulmonary pressure and more severe hypoxia-induced pulmonary hypertension, whereas serotonin transporter-deficient mice were less susceptible to hypoxia-induced pulmonary hypertension, vascular remodeling, and right ventricular hypertrophy (35).

Abnormalities in bone morphogenetic protein receptor 2 (BMPR2), a member of the transforming growth factor-β (TGF-β) superfamily of receptors that is expressed in pulmonary vascular endothelium and smooth muscle cells, are the genetic factor most clearly linked to pulmonary hypertension in adults. Loss-of-function BMPR2 mutations have been linked to more than 60% of cases of familial pulmonary hypertension and 25% of cases of sporadic pulmonary hypertension (36, 37), but penetrance is low (38), indicating that other contributing factors are im-

portant in the development of the illness. Loss of BMPR2 function promotes the proliferation of vascular smooth muscle (39) and increased expression of inflammatory cytokines (40). Both BMPR2 and the serotonin transporter regulate the calcium-binding protein S100A4, which induces pulmonary artery smooth muscle cell migration and proliferation (41).

Treatment of PPHN

The management of PPHN is largely supportive, consisting of adjunctive oxygen therapy, assisted ventilation, surfactant administration, and sedation as needed. Fluid and vasopressor support, as well as correction of acidosis, may also be indicated. The most commonly used drug treatment is inhaled nitric oxide, which is effective for up to 70% of infants with PPHN (42). Administration of inhaled nitric oxide rapidly decreases pulmonary artery pressure and improves oxygenation in responsive infants without causing a concomitant drop in systemic blood pressure, and it is generally well tolerated. Extracorporeal membrane oxygenation is another therapy used in PPHN, albeit less frequently. It is reserved for those infants with severe PPHN who do not adequately respond to inhaled nitric oxide. Small studies support treatment with sildenafil, milrinone, and other phosphodiesterase inhibitors, which can prolong the intracellular effects of nitric oxide.

Clinical Studies of SSRI-Associated PPHN

It is difficult to study SSRI-associated PPHN because the condition is so rare. The existing clinical literature, consisting of six studies, identified a total of 50 infants with PPHN among an estimated 25,000 who were exposed to SSRIs. Two of the studies examined the same population database, the second study including additional, more recent births, and found overall relative risks of 3.44 and 3.57 (15, 43). A third study found an increased risk only if exposure occurred in the second half of pregnancy (odds ratio=6.1) (44). The other three studies found no increased risk of PPHN related to SSRI exposure. Details of these six studies and their strengths and weaknesses are summarized in Table 1.

One major limitation of the clinical studies published to date is that the severity of pulmonary hypertension and clinical course of infants is not described. The Källén and Olausson study (15) reported an overall mortality rate of 9% for PPHN, but all 11 SSRI-exposed infants survived. Another problem is that diagnostic criteria for pulmonary hypertension vary among studies. In the largest studies, cases of PPHN were identified only with medical record ICD-9 codes. In the retrospective study with the highest SSRI-associated risk (44), the initial case screening identified infants who needed mechanical ventilation, then charts were reviewed in more detail. Several infants diagnosed with pulmonary hypertension did not have echocardiograms, and the cutoff for the gradient between preductal and postductal oxygen saturation was 5% rather than the standard 10% or 20%, which may have inflated the observed incidence of PPHN. In addition, mothers were interviewed by telephone to determine SSRI use during that pregnancy, potentially introducing recall bias.

Discussion

It is a challenge to distinguish the impact of SSRIs from the impact of depression on risk for PPHN. First, obesity and smoking, established behavioral risk factors for PPHN, occur more commonly in depressed women (43). Second, both unmedicated depression and treatment with SSRIs during pregnancy have been linked to reduced length of gestation and increased risk of premature birth (6). Risk of PPHN is increased fourfold in babies born at 34–36 weeks' gestation compared with 37–41 weeks' gestation (15, 48). All of the positive studies excluded infants younger than 34 weeks, but two studies (15, 44) noted that the risk of PPHN associated with SSRIs was reduced if length of gestation was entered in the analysis. Third, depression is associated with increased rates of cesarean section (13), another known risk factor for PPHN. None of the three positive studies controlled for mode of delivery. A group that analyzed the same data set that was used as the basis for one of the positive studies (44) demonstrated a link in that infant group between cesarean delivery and higher risk of PPHN (49).

Meconium aspiration is the most common cause of PPHN. Although there is evidence that autonomic nervous system development is altered in fetuses of depressed and anxious mothers relative to healthy comparison subjects (5), and SSRIs are associated with gastrointestinal hypermotility, no data exist as to whether meconium aspiration is more common in children of depressed mothers. It has not been determined whether there may be shared genetic risk factors for PPHN and depression.

Another understudied question is to what degree delayed pulmonary vascular relaxation may be related to the neonatal neurobehavioral syndrome that is commonly observed in SSRI-exposed infants in the first postpartum week. While PPHN is quite rare, 25%–30% of infants exposed to SSRIs in utero will experience a transient "neonatal adaptation syndrome." This syndrome consists of a mix of symptoms consistent with either SSRI withdrawal or toxicity, including jitteriness, fussiness, gastrointestinal distress, feeding difficulties, and poor temperature regulation (50). It also includes tachypnea and other symptoms of respiratory distress, which may present earlier than the gastrointestinal and irritability symptoms (51). More research is needed to determine whether the respiratory symptoms seen in SSRI-exposed neonates represent a subclinical form of PPHN.

At this point, the data supporting a link between SSRI exposure and pulmonary hypertension is weak. Many factors

associated with depression itself may account for the association, and there has been no examination of a potential association between depression and PPHN. Few people treated with SSRIs are in full remission from their illness, so physiological and behavioral effects of depression are likely to still affect the fetuses of SSRI-treated women.

It is important to balance the risk of PPHN against the risk of untreated depression. Women who stop taking their antidepressant medications in the peripartum period have an estimated 68% chance of having a major depressive episode, compared with 26% for those who stay on their medication (4). While suicide in the peripartum period is rare, it is the leading cause of death in the first postpartum year (52). A less quantifiable risk is that of termination of pregnancy, which, in our clinical experience, is not infrequently contemplated by severely depressed pregnant women.

In summary, the unknown risks to pulmonary vasculature development associated with SSRI exposure in utero must be balanced against the known risks of untreated maternal depression during pregnancy. More translational research is needed to clarify the effects of SSRIs and depression on pulmonary vasculature in the fetus and the neonate. Future clinical studies should include more detailed characterization and follow-up of affected infants and better controls for mode of delivery, gestational age, severity of maternal depression, smoking, substance abuse, body mass index, and genetic risk factors for PPHN. If SSRIs are associated with increased risk of PPHN or other milder difficulties with the respiratory transition, clarification of mediating mechanisms will enable better prevention, diagnosis, and treatment of these conditions.

Received Apr. 6, 2011; revision received Aug. 25, 2011; accepted Sept. 6, 2011 (doi: 10.1176/appi.ajp.2011.11040553). From the Department of Psychiatry at Weill Cornell Medical College in New York. Address correspondence to Dr. Occhiogrosso (mbc2003@med.cornell.edu).

The authors report no financial relationships with commercial interests.

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Clinical Guidance: Pulmonary Hypertension of the Newborn and Maternal Antidepressant Treatment

Occhiogrosso et al. review the incidence of persistent pulmonary hypertension in newborns of women treated with SSRIs. Three of six studies showed elevated risk, but all these studies failed to control fully for the possible effects of depression itself, including shorter fetal gestation periods. While persistent pulmonary hypertension is rare, about one-fourth of infants exposed to SSRIs experience a short-lived neonatal adaptation syndrome, including jitteriness, fussiness, gastrointestinal distress, feeding difficulties, and poor temperature regulation. Tachypnea and other symptoms of transient respiratory distress may present earlier. Spinelli (p. 121) concurs that the effect of depression on pregnancy outcome far exceeds the effect of antidepressant treatment. She further points out that many studies of effects associated with SSRIs fail to include confounders such as family history of illness and maternal alcoholism when claiming association with fetal abnormalities or risk for autism.