

The selective serotonin re-uptake inhibitors / serotonin and noradrenaline re-uptake inhibitors in pregnancy: possible unfavorable effects on fetal and neurobehavioral development

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Abstract

The estimated prevalence of mood disorders in pregnancy ranges from 9 to 16%. The major dilemma for gynecologists and obstetricians is to treat or not to treat depression in pregnancy. In untreated depression, there is a higher risk of maternal morbidity, including arterial hypertension leading to preeclampsia or eclampsia, suicide attempts and postpartum depression. Depression may be associated with an increased risk of preterm or operative delivery, low birth weight, irritability, prematurity, sleep disorders, admission of the newborn to the neonatal intensive care. Abnormal stimulation of serotonin receptors as a result of increased synaptic availability of serotonin during brain development due to SSRIs/SNRIs represents a risk factor for the developing fetus. Epidemiological studies have shown that most of the antidepressant drugs remain relatively safe in pregnancy, nevertheless some significant areas of concern exist, particularly some evidence of higher risk of preterm birth, neonatal adaptation difficulties

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and congenital cardiac malformations. However, experimental studies in rodents showed that administration of SSRIs during a key developmental window created changes in brain circuitry and maladaptive behaviors that became evident long after the drug discontinuation and persisted into adulthood. Understanding of the role of monoamines in brain development is important to identify the possible adverse effects of SSRIs/SNRIs exposure during pregnancy and lactation.

INTRODUCTION

Expecting a baby brings an enjoyment to life. However, in many cases the course of pregnancy and postpartum period may be full of blue mood and persistent feelings of sadness and worthlessness. Many women, and that also in the reproductive age, suffer from major depression or bipolar disorder and in certain cases pregnancy and/or delivery may release serious affective disorders. The estimated prevalence of depression and other mood disorders in pregnancy ranges from 9 to 16 % (Evans *et al.* 2001; Melville *et al.* 2010).

The major dilemma for gynecologists and obstetricians is to treat or not to treat depression in pregnancy. Consequences of untreated depression during pregnancy may be in some cases so serious that pharmacotherapeutic benefit for the mother can overbalance the risk of fetal maldevelopment. And yet, the biological dysregulation caused by gestational depression has not received appropriate attention: most studies focus on the potential but unproven risks of psychotropic medication (Bonari *et al.* 2004). Untreated depression represents a risk mostly for pregnant women. There is a higher risk of maternal morbidity, including arterial hypertension leading to preeclampsia or eclampsia, suicide attempts and postpartum depression. Depression may be associated with an increased risk of preterm or operative delivery, low birth weight, irritability, prematurity, sleep disorders, admission of the newborn to the neonatal intensive care unit and/or increased level of internalizing behaviors in childhood (Chung *et al.* 2004; Oberlander *et al.* 2010).

About 2 to 3 % of pregnant women are treated with antidepressant drugs during gestation. After delivery the number of treated women increases to 5 to 7 %. Most prescribed antidepressants in pregnancy are selective serotonin re-uptake inhibitors and/or serotonin and noradrenaline re-uptake inhibitors (SSRIs/SNRIs), such as fluoxetine, paroxetine, sertraline, citalopram and venlafaxine (Nonacs & Cohen 2002; Tuccori *et al.* 2009; Freeman 2011).

SSRIs are believed to act mostly by inhibiting the re-uptake of serotonin after being released in synapses. In addition, several other mechanisms are suggested for the desired effect, e.g. neuroprotection and anti-inflammatory and immunomodulatory factors. SSRIs act on signal pathways such as cyclic AMP on the postsynaptic neuronal cell, which leads to the release of the brain derived neurotrophic factor (BDNF). BDNF, in turn, enhances the growth and survival of cortical neurons and synapses (Pilar-Cuéllar *et al.* 2012). SNRIs work by inhibiting the reuptake of both serotonin and noradrenaline. This results in an increase in the extracellular concentrations of serotonin and noradrenaline and thus their increased neurotransmission (Papakostas *et al.* 2007). Some of the SSRI/SNRI drugs, such as venlafaxine (Weikop *et al.* 2007), affect also dopaminergic neurotransmission. As the SSRI/SNRI drugs substantially cross the placenta (Rampono *et al.* 2009) and get into breast milk (Norberg *et al.* 2001; Bellantuono *et al.* 2007), they can enter the developing brain and interfere with monoaminergic neurotransmission, which plays an important role in brain development. This kind of drugs can therefore represent a risk for the developing brain and postnatal neurobehavioral development.

MONOAMINES AND BRAIN DEVELOPMENT

Serotonin

In the adult organism, serotonin regulates a variety of physiological functions, such as mood, appetite, memory and learning, sleep-wake cycle, circadian rhythms and hypothalamus-pituitary-adrenal axis functioning. In the developing brain, serotonin acts as a “differentiation signal”, which generally regulates the timing of neuronal genesis and formation of the construction of monoamine circuitry. Serotonergic neurons are present in various brain regions, such as middle brain, epiphysis, hypothalamus or raphae nuclei of the brain stem. Serotonin neurons appear in rats on days 10–12 and in humans on weeks 5–12 of gestation. The first serotonin neurons appear in the raphae nuclei with their neuronal fibers leading to the spinal cord and cortex (Herlenius & Lagercrantz 2004). Serotonin regulates both the development of serotonergic neurons (autoregulation of development) and the development of target tissues (Whitaker-Azmitia 2001). Serotonin acts as a growth factor during embryogenesis and serotonin receptor activity forms a crucial part of the cascade of events leading to changes in brain structure. The serotonergic system interacts with BDNF, S100 β protein and other chemical messengers. Moreover, the system communicates with the GABAergic, glutamergic and dopaminergic systems (Sodhi & Sanders-Bush 2004). Serotonin affects signifi-

cant developmental processes, such as proliferation, migration, differentiation and synaptogenesis, regulates neurogenesis, differentiation and maturation of the hippocampus. At early stages of development, high levels of serotonin in the blood may enter the brain of a developing fetus, causing a loss of serotonin terminals through negative feedback and thus disrupting subsequent serotonergic functions (McNamara *et al.* 2008). Inadequate activation of serotonin receptors in development can result in mental disorders, such as anxiety, drug abuse or autism (Chiriboga 2003).

Noradrenaline

Noradrenergic neurons are concentrated in the brain stem, mostly in the *locus coeruleus*, and project by five main neuronal tracts to the whole brain. Noradrenergic neurons appear in rats on days 12–14 and in humans in weeks 5–6 of gestation (Herlenius & Lagercrantz 2004). Noradrenaline is involved in processes of arousal, attention, fear, anxiety, learning and memory. It is essential for normal brain development by means of regulation of proliferation, migration as well as maturation of cortical neurons. Noradrenaline also regulates the development of Cajal-Retzius cells which are the first cells on the cortex. They are involved in neuronal migration and creation of individual layers of the cortex (Naqui *et al.* 1999).

Dopamine

Dopaminergic neurons are concentrated mostly in the *substantia nigra* and tegmentum and project to the basal ganglia, olfactory bulbs, limbic region, hippocampus and cortex. Dopamine neurons appear in rats on days 10–15 and in humans in weeks 6–8 of gestation (Herlenius & Lagercrantz 2004). The prefrontal cortex involved in the regulation and coordination of executive functions is extremely rich on dopamine. Dopamine regulates also motor and cognitive functions. Developmental disorders of the dopaminergic system cause dyskinesia, dystonia, jerks, abnormal eye movement or obsessive-compulsive disorder and attention-deficit hyperactivity disorder (ADHD). The D₂ dopamine receptor plays a crucial role in working memory processes which, are seriously injured in ADHD patients (Daré 2003).

EPIDEMIOLOGICAL STUDIES

Different cohort studies (prospective or retrospective), case-control studies as well as meta-analysis studies have reported in many cases conflicting results. In the following section only studies with positive results are mentioned.

Kállén and Otterblad Olausson (2007) found that women who received paroxetine in early pregnancy had a two-fold increase in risk for delivering an infant with cardiac defects compared to births in the entire population. Bar-Oz *et al.* (2007) reported a significant increase in the risk of cardiac malformations in infants exposed to paroxetine in the first trimester. Moreover, they found that users of paroxetine, other SSRIs and non-SSRI drugs had a significantly higher mean number of diagnostic tests (ultrasound, echocardiography, amniocentesis) during gestation compared to those who did not use antidepressants. Davis *et al.* (2007) performed a retrospective cohort study comparing infants exposed to antidepressants during pregnancy and unexposed controls with a significant risk for congenital abnormalities of the eye in infants exposed to paroxetine.

Chambers *et al.* (2006) found an association between maternal exposure to fluoxetine, paroxetine and sertraline during late pregnancy and occurrence of persistent pulmonary hypertension of the newborn. Higher risk of abortion, preterm birth and low birth weight and admission to a neonatal intensive care unit were also reported in SSRI users (Kulin *et al.* 1998). Women treated with SSRIs late in pregnancy had a higher frequency of delivering small-for-gestational age infants (Toh *et al.* 2009). Recent studies have also documented an increased risk of cerebral hemorrhage (Favreliere *et al.* 2010). A variety of behavioral and neurological symptoms including irritability, persistent crying, shivering, tremor, restlessness, feeding difficulties, sleep disorders, and seizures, has been reported in infants born to women who used SSRIs during pregnancy (Moses-Kolko *et al.* 2005). This clinical picture has been interpreted as representing a neonatal withdrawal syndrome (or direct toxic effect of antidepressants on the newborn) and was designated the neonatal behavioral syndrome. This syndrome includes poor tone, respiratory distress and hypoglycemia as well (Nourrisson *et al.* 2010). Among unwanted effects of SSRIs in pregnancy, Gentile (2005) reported subtle effects on motor development and motor control.

Casper *et al.* (2003) found that SSRIs administration during pregnancy was associated with lower scores on the psychomotor and behavioral development subscales of the Bayley Scales of Infant Development at 6 to 40 months. Prenatal exposure to SSRIs antidepressants was found to be associated with increased internalizing behaviors during early childhood (Oberlander *et al.* 2010). Hadjikhani (2010) hypothesized that increase serotoninemia during pregnancy, due also to SSRI intake, may be one of the causes of the raising prevalence in autism.

Udechuku *et al.* (2010) critically reviewed the literature on adverse effects of antidepressant use during pregnancy. Most results were derived from cohort (prospective and retrospective) and case control studies. Congenital malformations were identified in 35 studies, 12 studies demonstrated significant association. Related to pregnancy and neonatal outcomes, 35 studies identified elevated risk for spontaneous abortion, preterm birth, abnormal birth weight, 17 studies showed neonatal adaptation difficulties, 3 studies showed conflicting results on persistent pulmonary hypertension. As for long-term developmental outcomes, 6 of 7 studies found no significant differences. The review has shown that most of the antidepressant drugs remain relatively safe in pregnancy, though some significant areas of concern do exist, particularly some evidence of higher risk of preterm birth, neonatal adaptation difficulties and congenital cardiac malformations (with paroxetine).

EXPERIMENTAL STUDIES

Early exposure (pre-, peri- and/or neonatal periods) to SSRIs/SNRIs can disrupt the normal maturation of the monoaminergic system and neuronal processes dependent on it. Functional alterations of brain development, in turn, can lead to various neurobehavioral dysfunctions manifested in later postnatal development.

Association between prenatal exposure to SSRIs and persistent pulmonary hypertension of the newborn were reproduced in an animal model where fluoxetine was administered to pregnant rats (Belik 2008). Prenatal exposure to fluoxetine was further found to reduce serotonin content in the frontal cortex of prepubescent male offspring (Cabrera-Vera *et al.* 1997).

Prenatal fluoxetine in pregnant sheep was found to cause an acute increase in plasma serotonin levels, leading to a transient reduction in uterine blood flow. This, in turn, reduced the delivery of oxygen and nutrients to the fetus. Fluoxetine further increased the high-voltage/non-rapid eye movement behavioral state in the fetus, increased the magnitude of the prepartum rise in fetal corticosterone concentrations and altered adult hypothalamic functions (Morrison *et al.* 2005).

Movement disorders and neurochemical changes were found in zebra fish larvae. Developing larvae exposed to fluoxetine had decreased spontaneous swimming activity and decreased concentration of SERT and 5-HT(1A) receptor transcripts in spinal cord (Airhart *et al.* 2007).

Fluoxetine during the gestational period decreased the number of neurons and 5-HT receptor sites in the frontal cortex of rat fetuses (Swerts *et al.* 2009). In a postnatal developmental study, both fluoxetine and venlafaxine reduced the body weight of litters, however by the time of weaning the body weight of litters from treated dams was equal to the weight of control litters (da-Silva *et al.* 1999). Administration of venlafaxine from day 15 to 20 of gestation resulted in mild signs of maternal toxicity manifested by decreased body weight gain of pregnant rats (Dubovicky *et al.* 2011). Neonatal fluoxetine exposure affected tactile and thermal perceptions as well as locomotor activity in adolescent rats. At the morphological level, the number of branch tips of thalamocortical afferents to the somatosensory cortex was reduced (Lee 2009). An *in vitro* study showed that fluoxetine dose-dependently modulated apoptotic processes in maturing neuronal cells (Schaz *et al.* 2011).

Chronic neonatal (postnatal days 8–12) exposure to citalopram resulted in increased locomotor activity and decreased sexual behavior. Adult sexual deficit in neonatally exposed rats to citalopram may be the consequence of abnormal stimulation of 5-HT_{1A} and/or 5-HT_{1B} receptors as a result of increased synaptic availability of serotonin during critical periods of development (Maciag *et al.* 2006).

Further experimental studies in rodents showed that administration of SSRIs during a key developmental window created changes in brain circuitry and maladaptive behaviors that were evident long after drug discontinuation and persisted into adulthood (Borue *et al.* 2007). These behavioral changes described as the „neonatal antidepressant exposure syndrome“ (NADES) in rats include alteration in locomotor activity, reduced male sexual activity and competence, increased ethanol consumption, dysregulation of the hypothalamus-pituitary-adrenal axis, sleep disorders and increased immobility in the forced swim test (Mirmaran *et al.* 1981; Hilakivi & Hilakivi 1987; Hansen *et al.* 1997). Similarly, serotonin transporter (SERT) knock out mice were found to display increased anxiety- and depression-like behaviors, reduced aggressive behavior, and exaggerated responses to environmental stress (Lira *et al.* 2003; Ansorge *et al.* 2004). These studies indicate that disruption of SERT due to SSRIs/SNRI may be accompanied by changes in aggressive and conflict-related behaviors.

CONCLUSIONS

The SSRIs/SNRIs are the most common antidepressant drugs used in treatment of mood disorders in pregnancy and the postpartum period. The serotonergic system plays an important role in brain development. Thus abnormal stimulation of serotonin receptors as a result of increased synaptic availability of serotonin and disruption of SERT activity during brain development due to SSRIs/SNRIs can lead to functional alterations followed by postnatal neurobehavioral dysfunctions. Delayed and/or late neurobehavioral consequences of action of prenatal and perinatal insults, including antidepressants, occur mostly in late postnatal development, in adolescence, adulthood or even senescence. Some of these dysfunctions can be hidden or masked. They can be stress-related, manifest in response to stressful stimuli.

Effects of preventing re-uptake of presynaptic serotonin on fetal and postnatal development have not been sufficiently elucidated. Moreover, prospective epidemiological studies focused on older children, adolescents and adults exposed *in utero* to antidepressants are not available. Understanding the role of monoamines in brain development is important to identify possible adverse effects of SSRIs/SNRIs exposure during pregnancy and lactation. The potential functional and behavioral consequences of the alterations induced by these drugs remain to be clarified. Scientists should therefore focus on late consequences of prenatal and perinatal exposures with emphasis on various patterns of behavior, including emotions, aggression, sociability, coping and sexual functions.

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