Selective Serotonin Reuptake Inhibitors in Pregnancy

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Abstract: The use of antidepressant drugs, such as selective serotonin reuptake inhibitors (SSRIs), during pregnancy is rapidly increasing. To date, the effects of SSRIs on pregnant women and fetuses are controversial and still a matter of debate. Although a number of studies have shown that these antidepressants are not teratogenic, some of them have reported an increase of congenital malformations after antenatal exposure to SSRIs. Moreover, fetal behavior is affected by these drugs, 30% of infants suffer from neonatal withdrawal symptoms and long term sequelae have not yet been excluded. Since there are no clear guidelines for SSRI treatment in pregnancy, potential risks must be balanced against the effects of untreated maternal depression. Treatment with SSRIs before and during pregnancy should only be considered in case of real necessity. Milder forms of depression should be treated with alternative methods. In this paper we have reviewed the literature on effects of SSRIs on embryonic, fetal and infant development.

Keywords: SSRI, depression, pregnancy, fetus, newborn, teratogenic effect.

DEPRESSION OR SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs) IN PREGNANCY?

Depression is a major illness with associated long-term morbidity and social impact. Epidemiological data have shown that women have a predisposition to depression and about 20% have a lifetime chance of being diagnosed with a depressive disorder [1]. Pregnancy seems a risk factor since during and directly after pregnancy 10% of women will develop a major depressive disorder [2]. The use of antidepressant drugs during pregnancy is increasing up to 2-3% of pregnant women in Europe and 8-10% in the USA [3]. This has occurred without solid evidence on safety or efficacy. When managing depression and anxiety with antidepressant medication, the expected benefits must outweigh the risks. Pharmacological therapy is needed when non-pharmacological treatment is insufficient. Suicide attempts and relapse of depression have been described when antidepressant treatment during pregnancy had been stopped [4]. Pregnant women diagnosed with severe depression should therefore be treated. Treatment of maternal depression is uniformly recommended, despite the potential side effects on fetus and newborn [5]. In fact, untreated depression has a negative impact on fetal behavior and on central brain processes related to recognition, memory and habituation [6, 7]. These effects are mediated, in part, by the maternal–placental–fetal neuroendocrine axis [8]. In this regard, the serotonin transporter (SLC6A4), norepinephrine transporter (SLC6A2), and 11b-hydroxysteroid dehydrogenase type 2 (11b-HSD2) genes have been implicated in perturbations of the hypothalamic pituitary adrenocortical axis [9] and in the development and treatment of mood disorders [10]. This includes major depressive disorder, generalized anxiety disorder, and panic disorder [11].

Depression is associated with elevated circulating levels of cortisol and norepinephrine, and with decreased levels of antidepressants [12]. Field et al. have shown that altered neonatal levels of cortisol, norepinephrine, and serotonin reflect maternal biochemistry [13]. In parallel, urinary cortisol is elevated and the 5-HIAA serotonin metabolite is decreased, both in depressed mothers as compared to non-depressed mothers and in newborns of depressed mothers as compared to newborns of healthy mothers [14]. It has been reported that fetuses of high anxious women were more active and more often small-for-dates at birth [15]. At birth, newborns of high anxious mothers had a greater right frontal EEG activation and lower vagal tone and they spent more time in deep sleep, less time in quiet and activity states showing more state changes and a less optimal performance on the Brazelton test [15]. Conversely, in animal model, Rayen et al. have demonstrated that maternal exposure to fluoxetine reversed the effects of prenatal stress on depressive-like behaviour and neurogenesis in adolescence [16].

Children of depressed parents are at increased risk for depression, and both genetic and environmental factors are implicated in this association [17]. Exposure to maternal depression in utero, independent of postnatal exposure, has been linked to adverse neurobehavioral development and temperament [18]. Adverse effects of in utero exposure to maternal depression are further supported by the finding of altered fetal neurobehavior. In addition, prenatal exposure to stress has been linked to disturbances in behavioral and emotional regulation in animal studies, independently from postnatal conditions [19]. The physiological correlates of elevated maternal cortisol levels late in pregnancy have been associated with dys-regulated infant behavior and temperament [20]. Such findings suggest that prenatal conditions may have a long-term impact on stress regulation and the risk for later development of mood disorders in the offspring.

Despite the associations between prenatal exposure to anxiety and major depressive disorder with long term emotional, behavioral, and social problems in offspring [21], little is known about the mechanisms of these disturbances such as dysregulation of key neurotransmitter systems in utero.

However, it is clear that alterations in maternal neurotransmitters are reflected in the fetus, with a key regulatory role of the placenta in maintaining fetal homeostasis. In this context SLC6A4, SLC6A2, and 11b-HSD2 genes mediate placental uptake of serotonin, norepinephrine, and cortisol. SLC6A4 is down-regulated in the placenta in response to cocaine [22] or amphetamine exposure [23]. Because of their ability to cross the placenta [24], antidepressants like selective serotonin reuptake inhibitors (SSRIs) have the potential to alter SLC6A4 regulation in the placenta. SSRIs bind to SLC6A4 and induce internalization of the transporter from the neuronal surface, thereby blocking serotonin reuptake from the extracellular space into the pre-synaptic neuron and subsequently enhancing synaptic serotonin levels [25]. In this regard, it is noteworthy that chronic in utero stress, including maternal exposure to cocaine, amphetamine, in utero growth retardation (IUGR) and pregnancy induced hypertension associated with fetal hypoxia, may trigger down-regulation of human placental SLC6A2 expression [26] with an elevation in umbilical arterial plasma of norepinephrine levels [27].

The 11b-HSD2 enzyme oxidizes cortisol to its inactive cortisone form. The abundant expression of this gene in the placenta protects the fetus from circulating maternal cortisol levels [28]. Cortisol exposure increases 11b-HSD2 mRNA levels in human placental trophoblast cells [29]. In contrast, norepinephrine

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inhibits placental 11b-HSD2 expression [30], increasing fetal exposure to maternal cortisol.

Prenatal SSRI exposure is linked to both fetal and newborn neurobehavioral changes, including up to 30% of exposed neonates who have symptoms of a ‘neonatal abstinence syndrome’, resembling that seen in infants withdrawing from (mostly opioid) drugs [31]. One study suggests a smaller head circumference as a consequence of SSRIs [32]. SSRI-exposed infants have decreased basal cortisol levels in the early evening compared with non-exposed infants at 3 months of age, controlling for maternal depression symptoms, and this effect was not related to prenatal or current SSRI exposure level measured in infant plasma [33]. During their first year of life these infants need more medication related to the gastro intestinal system and lungs, which suggests an impact of SSRI on organ development. Follow-up studies demonstrate minor neurological dysfunction and may be an excess of autism [31-34]. Finally, teratogenic effect of SSRI may include cardiovascular anomalies and pulmonary hypertension [35]. So there continues to be a dilemma, to treat or not treat (minor) depression in pregnancy.

It was the aim of this review to present an overview on pharmacokinetics, fetal and neonatal risks associated with antenatal exposure to SSRI administration.

**BASIC PHARMACOKINETICS OF SSRIs**

SSRIs are the most frequently used drugs during pregnancy to treat affective and other psychiatric disorders because of their low side-effect profiles and presumed relatively low risk to the fetus and thanks to their tolerability and safety profile if taken in overdose [36]. Depression exhibits significant co-morbidity with anxiety disorders, for which SSRIs are also first-line pharmacologic treatments. SSRI use during pregnancy has increased from 1.5% in 1996 to 6.2% of all pregnant women in 2005 [37].

SSRIs cross the placenta equilibrating between maternal and fetal plasma and enter the fetal brain where serotonin and its neurons and receptors are present from early embryonic life onwards (5-10 weeks’ gestation) [38]. Serotonin acts as a trophic factor, neuromodulator and transmitter, and serves various roles in neurodevelopment [39]. Modulation of fetal serotonin by SSRI exposure at different stages of pregnancy may affect structural and functional processes resulting in several behavioral effects [40]. The fetus’ inability to metabolize SSRIs and their second pass through re-uptake from the amniotic fluid render the fetus also indirectly but continually exposed to raised drug levels [41].

SSRIs promote an increase in serotonin in the neuronal synapse by inhibiting pre-synaptic reuptake. The serotonin system is involved in the modulation of many important physiologic functions such as: i) thermoregulation; ii) cardiovascular and bowel functions; iii) mood, appetite, sleep-wake cycle; iv) growth and development of various organs such as heart and craniofacial structures [42].

All SSRIs have a great affinity for the 5-hydroxytryptophane (HT) reuptake carrier in the synaptic cleft in the CNS, with much less affinity for the noradrenaline reuptake carrier, and for alpha- and beta-adrenergic, dopamine, histamine, 5-HT and muscarine receptors. Blockade of serotonin uptake is related to antidepressant actions and blockade of neurotransmitter receptors to their side effects [43]. The SSRIs include fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram and escitalopram. They have similar antidepressant efficacy and a similar side effect profile. They differ, however, in their pharmacokinetic properties [44]. All SSRIs are subjected to extensive oxidative metabolism in the liver by the activity of any of the numerous drug-metabolizing enzymes, of which the majority is associated with the cytochrome P450 (CYP) mixed-function oxidases, which play a prominent role in the biotransformation of SSRI [45].

The pharmacokinetic characteristics show high inter-individual variability, due to genetic CYP polymorphism [46, 47]. Pregnancy influences pharmacokinetics by changing CYP activity, plasma volume, hepatic blood flow and plasma protein binding [48]. Plasma protein binding of fluoxetine, paroxetine and sertraline is more than 95%, of fluvoxamine it is 77% and of citalopram 50%. The magnitude and the clinical impact of increased unbound fraction of SSRI’s have not been studied.

**Fluoxetine**

Fluoxetine was the first SSRI that became available for clinical use. It is a racemic mixture of two enantiomers, whereby the S-enantiomer is about 1.5 times more potent in the inhibition of serotonin reuptake than the R-enantiomer. After oral administration, fluoxetine is almost completely absorbed. Due to hepatic first-pass metabolism, the oral bioavailability is below 90%, with a large volume of distribution. Fluoxetine has a long half-life of 1–4 days and it is eliminated by the kidney. It exhibits nonlinear kinetics, indicated by a disproportionate increase in blood concentrations after dose escalation [49]. Generally fluoxetine shows decreased plasma concentrations during pregnancy caused by increased CYP 2D6 activity [50]. Fluoxetine use during the first trimester of pregnancy has been associated with congenital malformations (craniosynostosis) [51] and infantile hypertrophic pyloric stenosis [52].

**Fluvoxamine**

Fluvoxamine facilitates serotonergic transmission by potent and selective inhibition of serotonin reuptake into pre-synaptic neurons. After oral application of fluvoxamine, more than 90% of the drug is absorbed, due to its rapid and extensive hepatic first-pass biotransformation. The amount of unchanged drug reaching the systemic circulation is much lower, reducing the bioavailability to approximately 53%. Almost 100% of an oral dose is recovered in urine. Fluvoxamine has a long half-life about 15 hours and similar to most other SSRI it is eliminated through hepatic metabolism. It includes oxidative demethylation and oxidative deamination [53]. Until now pharmacokinetics of fluvoxamine during pregnancy have not been studied but decreasing plasma concentrations are expected. To date, potential side-effects of fluvoxamine on fetus and newborn are controversial and still matter of debate. There are few studies reporting drug detection in human milk without affecting breast feeding [54].

**Paroxetine**

Paroxetine is the most potent serotonin reuptake blocker clinically available, but has a lower selectivity for the serotonin reuptake site than either fluvoxamine or sertraline. In addition, it blocks muscarinic acetylcholine receptors. Paroxetine is a chiral SSRI that is marketed as a pure enantiomer, this makes the pharmacokinetics more uniform when compared with racemic SSRIs, such as fluoxetine or citalopram. Paroxetine is effectively absorbed from the gastrointestinal tract, but is readily metabolized during its first pass through the liver. Paroxetine is metabolized by oxidation and methylation in the liver to inactive metabolites that are further conjugated with glucuronic or sulfuric acid. At least 2 hepatic CYP isozymes are involved in the oxidation of paroxetine. Nonlinear kinetics has been shown. The paroxetine’s half-life is about 20 hours, but is variable, depending on dose and duration of administration; it is eliminated through hepatic metabolism and by kidney [55]. Plasma concentrations of paroxetine decrease or rise in the course of pregnancy depending on the CYP2D6 genotype. The accumulation of paroxetine in mothers who are CYP2D6 poor metabolisers will result in increased exposure to the unborn child [47].
Paroxetine use during the first trimester of pregnancy has been associated with an increased risk of congenital malformations (omphalocele, gastroschisis) and cardiovascular malformations (ventricular and atrial septal defects). This latter issue is still controversial and a matter of debate [56].

Sertraline

Sertraline is the second most potent inhibitor of serotonin reuptake and the second most selective blocker of serotonin over noradrenaline uptake. Like paroxetine, sertraline possesses two chiral centers. Absorption from the gastrointestinal tract is almost complete, but rather slow, with a time to reach the maximum plasma concentrations of 6–8 h. Linear pharmacokinetics is suggested for sertraline. The major metabolic pathway of sertraline is N-demethylation to N-desmethylsertraline in the liver. The sertraline’s half-life is about 26 hours, a relevant portion of oral sertraline is excreted in the faeces (about 50%) [57]. Sertraline plasma concentrations decrease in the course of pregnancy whereas the N-desmethylsertraline plasma concentrations rise. However, this metabolite exhibits only one twentieth of the effect of the parent compound [58].

Sertraline use during the first trimester of pregnancy has been associated with congenital malformations (anencephaly, omphalocele) and cardiovascular malformations (ventricular and atrial septal defects) [59].

Citalopram

Citalopram has by far the highest selectivity for inhibiting serotonin reuptake over noradrenaline reuptake. It is marketed as a racemate, but its pharmacological effects are almost exclusively ascribed to the S-(1) enantiomer. As for other lipophilic drugs, the absorption of citalopram from the gastrointestinal tract is almost complete. In contrast to the other SSRI, the first-pass effect of citalopram seems to be of minor importance. Since only 50% of the dose is excreted in urine, a significant faecal elimination is suggested. The primary metabolic pathway of citalopram is N-demethylation to N-desmethylcitalopram, which is further N-demethylated to didesmethylcitalopram. A linear relationship between citalopram dosage and plasma concentration has been reported under steady-state conditions. Citalopram has a long half-life of 36 hours [60]. Citalopram plasma concentrations do not change significantly during pregnancy [58]. Citalopram use during the first trimester of pregnancy has been associated with septal heart defects [61].

Escitalopram

Escitalopram, the active S-enantiomer of citalopram, is effective and well tolerated. Following oral administration, escitalopram is rapidly absorbed and reaches maximum plasma concentrations in approximately 3–4 hours after either single- or multiple-dose administration. Escitalopram is metabolized in the liver, mainly into desmethylcitalopram and S-didesmethylcitalopram. The elimination half-life is about 27–33 hours. Escitalopram exhibits linear and dose-proportional pharmacokinetics [62]. Escitalopram plasma remain unchanged during pregnancy [58].

To date, potential side-effects of escitalopram on fetus and newborn are controversial and still matter of debate. One study has shown that escitalopram is safe for use during breastfeeding. Because its absolute infant dose has been found to be lower than that for an equivalent antidepressant such as raccitalopram, it may be preferred over racitalopram in treating depression in lactating women [63].

RISKS ASSOCIATED WITH SSRI EXPOSURE IN PREGNANCY

For health care professionals it is difficult to balance the benefits of SSRIs in pregnancy against the risks without incontestable scientific information. Scientific data on the effects of each antidepressant are limited; animal studies have shown that antidepressants have effects on abortion, birth defects and enduring behavioral alterations [64]. Molecular analysis of fluoxetine in utero exposed mice has shown long-term alterations in serotonin transporter levels in the raphe nucleus and in dose dependent depressive and anxiety related behavior during adult life. Such effects were not seen in fluvoxamine exposed mice [65]. Sparse human series have shown similar findings including abortion, neural tube defects, cardiovascular malformations, persistent pulmonary hypertension, preterm birth, low birth weight, neonatal withdrawal syndrome and neurodevelopment abnormalities [66, 67]. Studies showed an increased risk for all congenital malformations with SSRI and particularly with paroxetine [68, 69]. However, these risks are considered low [70] (Table 1).

A recent study has indicated that maternal depression was associated with slower rates of fetal body and head growth. Fetuses of women treated with SSRI had no delay in body growth but had a delayed head growth and were at increased risk for preterm birth [32].

SSRIs have been shown to cross the placenta entering in the fetal brain where serotonin and its neurons and receptors are present from early life [38, 71]. Serotonin acts various roles in neurodevelopment and its modulation due to SSRI exposure all along pregnancy may affect structural and functional processes leading to varied behavioral effects [40, 41]. In this regard Mulder et al. [34] recently reported that fetuses exposed to standard or high SSRI dosages compared with control, un-medicated, or low-medicated fetuses showed significantly increased motor activity at the beginning and end of the second trimester. They particularly exhibited disrupted emergence of non-rapid eye movement (non-REM) quiet sleep during the third trimester, characterized by continual bodily activity and, thus, poor inhibitory motor control during this sleep state near term (‘fetal sleep-walking’) [72]. The SSRI effects on the fetus were dose-related, but independent of SSRI type. These results demonstrate that changes in fetal neurobehavioral development associated with standard and high SSRI dosages are observable all along pregnancy. A first-choice SSRI type was not apparent from this study. Bodily activity at high rate during non-REM sleep in SSRI-exposed fetuses was an abnormal phenomenon, but its significance for postnatal development needs further investigations on neurological short/long-term follow-up [64-74].

NEONATAL OUTCOME

It has been reported that neonatal effects observed after exposure to antidepressants are mostly mild and transient, including tremors and excessive crying, but also more severe symptoms have been reported [73].

Exposure to SSRIs in late pregnancy has been associated with a three-fold increased risk of neonatal behavioral syndrome, characterized by mild and major symptoms, occurring in 30% of cases requiring specialized medical care [74]. The following mild symptoms are not persistent: increased motor activity, irritability and disturbed sleep regulation. However, in some of the cases there are severe symptoms such as: feeding problems, neonatal convulsions, hypotonia, respiratory distress and persistent pulmonary hypertension [75-79]. Poor neonatal adaptation can occur immediately or within few hours or days after birth. It is unknown whether these symptoms result from: i) acute cessation of SSRI exposure at birth (withdrawal), ii) alterations in
neurodevelopment or neuroregulatory systems to sustained prenatal exposure (in-utero effect), and, iii) a combination of these effects [3, 78]. The duration of gestational exposure has been found to be indicative for the risk of neonatal respiratory distress and for low birth weight [80], although no association has been found with dose, pharmacokinetic properties of specific antidepressants (more side effects for paroxetine) [81].

SSRIs may also affect other organ systems. During the first year of life infants of women who were treated by SSRIs in pregnancy use among others more laxatives and oromucosal and pulmonary medication [82]. The increase in laxative use has recently been confirmed in a second publication, together with an increase in with infantile hypertrophic pyloric stenosis [52]. SSRIs may influence the development of the enteric nervous system in two ways. Blockage of the serotonin re-uptake transporter during fetal development could influence migration, differentiation and survival of cells leading to abnormal development in the first trimester of pregnancy. The second way relates to 5-HT that acts as a growth factor in the primitive enteric nervous system through the Blockage of the serotonin re-uptake transporter during the first trimester of pregnancy. The second way relates to 5-HT that acts as a growth factor in the primitive enteric nervous system through the a growth factor in the primitive enteric nervous system through the fetal side effects of SSRI use in pregnancy. Women who want to become pregnant in the near future should only be treated with medication if this is really necessary and alternative therapies are not applicable. Patients should be counseled accordingly.

Further studies are necessary to address the risks and mechanism of action of the SSRI to prevent and treat the neonatal consequences of maternal antidepressant treatment during pregnancy. Children of women at risk may benefit from close monitoring and from early intervention when problems are timely acknowledged, risk identification is indispensable for development of efficient policies on neonatal management of newborns prenatally exposed to antidepressants. In this regard, the following general suggestions may be of some help for physicians:

a) Drugs are not safe until proven unsafe. Treatment advantages/risks change with time according to scientific progresses;

b) One of the largest groups of antidepressant users are women in their child bearing years. Thus, physicians should anticipate on a future pregnancy when prescribing antidepressant to women;

c) When treatment is unavoidable, the first choice is fluoxetine, citalopram, sertraline and fluvoxamine that, to date, there is the most evidence for a safe use in pregnancy. Conversely, paroxetine has been associated with a increased risk for congenital heart disease [76];

d) The lowest effective dose is recommended. Therefore genotyping or measurement of SSRI concentration during pregnancy is recommended. Standard ultrasound and brain biochemical monitoring in different biological fluids may be of help in monitoring whole organ development, especially CNS, all along pregnancy;

e) Newborns of mothers antenatally treated by antidepressant drugs should be monitored during the first 48 hours after birth.

### CONCLUSIONS

In summary, SSRI administration during pregnancy, although of clinical benefit to the mother, presents risks for the infant. It is obvious that severe maternal depression needs to be treated. However, the current increase in SSRI use in pregnant women, suggests that indications have become more loose. A positive effect of SSRIs has never been proven in minor forms of depression. Moreover, there are alternative ways to improve maternal psychological wellbeing. In many countries SSRIs are prescribed by general practitioners. It is of importance that they are aware of...
are limited at clinical patterns description stage [77-84]. This holds CNS and multiorgan diseases. More recently, both in experimental model and in humans, CNS development, function and damage monitoring trough the assessment of brain constituents in different biological fluids has been proposed. This could be especially useful in the perinatal period at a stage when CNS development is at its higher peak. Advantages also reside in the possibility of pregnancy/postnatal longitudinal monitoring at low risk and stress for fetus, newborn and mother.

Among brain constituents currently investigated for high risk pregnancies and newborns, S100B protein has been demonstrated to constitute a well-established marker of CNS function and damage. S100B is an acidic calcium-binding protein located in the CNS mainly in the glial cells, astrocyte, Schwann cells, and in neurons [91]. Elevated (micromolar) S100B concentrations are a consolidated marker of brain damage and/or hypoxia in adults, in neurons [91]. Elevated (micromolar) S100B concentrations are a consolidated marker of brain damage and/or hypoxia in adults, in children and in animal models. At nanomolar concentrations S100B acts as a cytokine with a neurotrophic effect [92]. The protein is thought to be involved in the regulation of several cellular functions (cell–cell communication, cell growth, cell structure, energy metabolism, contraction, and intracellular signal transduction) and in the pathophysiological steps leading to neuronal necrosis and apoptosis [93-96].

In different biological fluids (i.e., cerebrospinal, blood, urine, and amniotic), elevated S100B concentrations have been found after CNS injury [96-99]. More recently, in pregnancies complicated by IUGR and postnatal cerebral hemorrhage elevated protein’s concentrations have been detected in maternal blood complicated by IUGR and postnatal cerebral hemorrhage elevated after CNS injury [96-99]. More recently, in pregnancies and amniotic), elevated S100B concentrations have been found apoptotic [93-96].

In the pathophysiological steps leading to neuronal necrosis and apoptosis [93-96].

The present data are consistent to those previously reported by van den Hove et al. [110] in a rat model where they investigated the effects of prenatal stress on S100B concentrations in the hippocampus. Prenatal stress resulted in a 25% reduction in hippocampal S100B content. Further, male hippocampal S100B content was negatively correlated with plasma corticosterone levels. Positive correlations were found between female S100B levels and fetal growth, and hippocampal brain-derived neurotrophic factor content. These authors suggested that the reduction in neonatal hippocampal S100B levels, as a consequence of prenatal stress, may be involved in affecting postnatal brain development [16]. Of note, Tramontina et al. [111] showed in a rat model, that fluoxetine, independently of serotonin and serotonin receptors, exerted a transitory and early increase in S100B concentrations in astrocyte hippocampal cultures (1-6 hours) via protein kinase A activation. Authors supported a role of S100B in depressive disorders and suggested that other molecular targets may be relevant for antidepressant activity.

Taken together, the present preliminary observations in the human and in experimental models have shown that biochemical perinatal monitoring is becoming feasible and may open-up a new cue on further studies aimed at investigating CNS and multiorgan development/damage in fetuses and newborns in mothers treated by SSRIs.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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ABBREVIATION

5HIAA = 5-Hydroxyindoleacetic Acid
5-HT = 5- Hydrossitriptophane
SSRI = Selective Serotonin Reuptake Inhibitors
CYP = Cytochrome P450
IUGR = Intrauterine Growth Retardation
CNS = Central Nervous System

REFERENCES


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Eriksen, J.L.; Gillespie, R.A.; Druse, M.J. Effects of in utero ethanol exposure and maternal treatment with a 5-HT1A agonist on S100Bcontaining glial cells. Dev Brain Res. 2000, 121, 133-143.
