

# Safety of Selective Serotonin Reuptake Inhibitors in Pregnancy

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**Abstract:** Psychiatric treatment with selective serotonin reuptake inhibitors (SSRIs) may be desirable or necessary during pregnancy; however, the benefit of these treatments must balance the benefits to the mother with any risk to the developing foetus. At the present time, the role of serotonin in normal central nervous system development, as well as the effects of altering serotonin transmission at critical periods of embryo development, remains to be further clarified.

Depression has a high prevalence in pregnant women (around 10%) and approximately one-half of the pregnancies are unplanned, making necessary that physicians have to know the risks associated with the decision to use this kind of antidepressants during pregnancy.

The effects of antidepressants in pregnancy could be classified in several main categories: the teratogenic possible effects; the effects on the normal development of the brain and neuropsychological functions; the effects on birth weight and/or early delivery; the risk of increased bleeding on the mother during delivery; the neuropsychological behaviour and adaptation after delivery, including not only neonatal withdrawal syndromes but also pain reactivity and increased parasympathetic cardiac modulation during recovery after an acute noxious event and in a wide range of neurobehavioural outcomes; and medium- to long-term effects in neurocognitive functions in those children.

These areas are reviewed according to the most recent published cohort-controlled studies and prospective surveys regarding SSRIs use in pregnancy. The review tries to clarify the blurred aspects of the use of SSRI during pregnancy and to give sensible and up-to-dated guidelines for the treatment of psychiatric disorders with SSRI during pregnancy.

## INTRODUCTION

The selective serotonin reuptake inhibitors (SSRIs), fluoxetine, fluvoxamine, paroxetine, sertraline and citalopram, are the result of rational research to find drugs that were as effective as the tricyclic antidepressants but with fewer safety and tolerability problems [1]. SSRIs block the reuptake of serotonin (5-HT<sub>1A</sub>, 5-HT<sub>2C</sub>, and 5-HT<sub>3C</sub>) into the presynaptic nerve terminal, thereby enhancing serotonin neurotransmission, which presumably results in their antidepressant effects. Although this is the predominant mechanism of action of this class of drugs, each SSRI has a slightly different pharmacological profile that leads to its distinct clinical activity, side effects, and drug interactions [2].

SSRIs are extensively used in nowadays clinical practice. Since their introduction in the late 1980s, SSRIs have occupied a prominent place in psychiatry and they have been the mainstay of pharmacotherapy for major depression. At the present time, these versatile medications are becoming the gold standard of treatment for a wide spectrum of other mood and behavioural disorders. SSRIs have approved indications in a number of different disorders, apart from depression, that include: treatment of social phobia, post-traumatic stress disorder (PTSD), and panic disorder, the treatment of obsessive-compulsive disorder (OCD) and the eating disorder bulimia, and the treatment of premenstrual dysphoric disorder (PMDD), a severe form of premenstrual

syndrome. Table 1 shows the indications approved by United States Food and Drug Administration for the different SSRIs.

**Table 1. U.S. Food and Drug Administration (FDA) Approved Indications for SSRIs**

Medication (Brand Name)	Indication
Fluoxetine (Prozac®)	Depression OCD Bulimia PMDD
Paroxetine (Paxil®)	Depression OCD Panic disorder Social anxiety disorder
Sertraline (Zoloft®)	Depression OCD Panic Disorder PTSD
Fluvoxamine (Luvox®)	OCD
Citalopram (Celexa™)	Depression

Although pregnancy has typically been considered a time of emotional well-being, recent studies show that pregnancy is a relatively high risk time for psychiatric disorders in women, particularly for those with pre-existing psychiatric illnesses [3, 4]. Recent epidemiological studies [5-7] report that psychiatric disorders were present in 15-25% of

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pregnant women, with affective disorders being the more prevalent. Table 2 shows the prevalence of the different psychiatric disorders in pregnancy subsidiary to be treated under SSRIs. In addition, since approximately one-half of pregnancies are unplanned [13], women and their physicians often face impromptu decisions regarding the initiation or continuation of antidepressant therapy during pregnancy [14].

**Table 2. Prevalence of Psychiatric Disorders in Pregnancy that Could be Treated with SSRI**

Author	Disorder	Prevalence
Evans <i>et al.</i> 2001 [8]	Depression	11.8-13.6%
Joseffson <i>et al.</i> 2001 [9]	Depression	17-18%
Smith <i>et al.</i> 2004 [10]	PSTD	3%
	Panic Disorder	2%
Kelly <i>et al.</i> 2001 [11]	Anxiety disorders	5%
	Panic disorder	1.5%
	Other anxiety disorder	4%
	Eating disorders	5%
	Bulimia nervosa	2%
	Binge Eating Disorder	4%
Turton <i>et al.</i> 1999 [12]	Eating Disorders	4.9%

The presence of SSRIs and metabolites in amniotic fluid suggests that foetal exposure to these medications is continual and may occur through a variety of paths that include: circulatory *via* placental passage, gastrointestinal *via* foetal swallowing, and respiratory secondary to foetal lung absorption [15]. This increased foetal exposure makes necessary that when prescribing SSRIs during pregnancy, one must consider the risks associated with prenatal exposure to these drugs.

A computerised Medline/Pubmed search was carried out between January 1993 and 15 May 2005 using the key words "antidepressant in pregnancy" and "Selective Serotonin Reuptake Inhibitors in Pregnancy". The resulting articles were cross-referenced for other relevant articles not identified in the electronic search. This review focuses on the effects of SSRI on the development of the foetus and newborn. Human studies are discussed with an emphasis on risk of teratogenesis, risk of neonatal toxicity, risk of long-term neurobehavioural sequelae, and risk of untreated depression.

### RISK OF TERATOGENESIS

About 84.5% of documented pregnancies result in the birth of a viable infant [16]. Of these, 2% to 4% have major malformations, and up to 12% have minor malformations [17, 18]. The timing of exposure to chemical agents during development affects the risk for malformations [19]. The second through the eighth weeks postfertilisation, during which time the development of major organ systems occurs, is the critical period of risk for structural teratogenesis. A drug is considered as teratogen when foetal exposure during this time interferes with the process of formation of major organ systems, and results in an increased risk of congenital

malformation, structural abnormalities or dysfunction, compared with the baseline incidence of congenital malformation or dysfunction in the absence of drug exposure.

Although some animal experiences showed a disruption in the normal cranial morphogenesis in mouse embryos [20], most of the animal studies have shown no significant detrimental effects in the newborn [21]. The human studies are all concurrent in showing a lack of increased incidence of major malformations in children born of mothers taking SSRIs during pregnancy at recommended doses. Table 3 display eight, mostly prospective studies exploring the teratogenic effects of several SSRIs in different countries and settings. To date, no single study showed an increase in the baseline risk of major malformations in women treated with these compounds.

### RISK OF NEONATAL SYMPTOMS

Neonatal toxicity or perinatal syndromes refer to a spectrum of physical and behavioural symptoms observed in the acute neonatal period that can be attributed to drug exposure at or near the time of delivery. In some cases, these effects are reasonably well established and pharmacologically plausible [30], but in most cases, the evidence is limited to case reports in which nonspecific neonatal effects (e.g., poor feeding and irritability) have been interpreted as possible evidence of exposure to, or withdrawal from, certain antidepressants [31].

The bibliography related to perinatal effects of SSRI is abundant. Few articles refer to a lack of effects [32-34], but more frequently, the authors describe a wide range of clinical effects from full blown neonatal withdrawal syndromes [35, 36] to low birth weight [29]. Table 4 displays the most relevant articles on the topic. The main problems associated with the use of SSRIs during pregnancy are related to poor neonatal adaptation, including low APGAR scores, lethargy, abnormal –or lack- of crying, jitteriness, hypertonia or even convulsions, respiratory difficulties and other symptoms. The clinical picture is usually non-severe and self-limited, and all cases are recovered after 24-48 hours of initiation. The prevalence of these problems has not been fully established, but the relative risk of premature delivery (RR: 4.8), admission to special-care nurseries (RR: 2.6) and poor neonatal adaptation (RR: 8.7) appears to be higher than expected [23]. The pain reactivity also seems to be reduced at birth and even up to two months after delivery, as well as an increased parasympathetic cardiac modulation after pain stimulus [35, 48]. The severity of the serotonergic central nervous system adverse effects have been related to the concentrations of 5-HIAA in cord blood, but the actual significance in clinical settings has to be further evaluated.

The few published studies do not allow to explore a differential pattern or risk between different SSRIs. Most of the studies were focused on fluoxetine, or paroxetine. There are pharmacokinetic differences in SSRIs [49, 50], which could partly explain their different withdrawal effects. Whereas sertraline and citalopram use different enzymes from the microsomal fraction (cytochrome P450 3A3/4 and 2C19, respectively), both paroxetine and fluoxetine are mainly metabolised by cytochrome 2D6. Paroxetine and fluoxetine inhibit the metabolism of this enzyme, presenting

Table 3. Risk of Teratogenesis – Studies

Study	SSRIs	Objective of the Study	Findings
Pasturzac <i>et al.</i> 1993 [22]	Fluoxetine	To compare pregnancy outcome of 128 women following first-trimester fluoxetine exposure with pregnancy outcome in two matched control groups.	The study suggests that the use of fluoxetine during embryogenesis is not associated with an increased risk of major malformations.
Chambers <i>et al.</i> 1996 [23]	Fluoxetine	Prospective study that compared outcomes of 228 pregnant women taking fluoxetine with those of 254 women who were not taking fluoxetine.	Women who take fluoxetine during pregnancy do not have an increased risk of spontaneous pregnancy loss or major fetal anomalies, but women who take fluoxetine in the third trimester are at increased risk for perinatal complications.
Goldstein <i>et al.</i> 1997 [24]	Fluoxetine	Outcomes of all pregnancies identified prospectively with confirmed first-trimester fluoxetine exposure contained in the Eli Lilly and Company worldwide fluoxetine pregnancy registry were compared with historic reports of newborn surveys.	Based on comparison with historic reports of newborn surveys, it is unlikely that maternal fluoxetine use during the first trimester of pregnancy results in increased risk of fetal malformations.
Kulin <i>et al.</i> 1998 [25]	Fluvoxamine Paroxetine Sertraline	To assess fetal safety and risk of fluvoxamine, paroxetine, and sertraline through a prospective, multicenter, controlled cohort study. Controls were randomly selected from women counseled after exposure to nonteratogenic agents.	Fluvoxamine, paroxetine, and sertraline, do not appear to increase the teratogenic risk when used in their recommended doses.
Ericson <i>et al.</i> 1999 [26]	Citalopram	Using an ongoing prospective recording of drug use in early pregnancy, 969 women were identified who reported the use of antidepressants: 531 used only SSRI (selective serotonin re-uptake inhibitor) drugs (mostly citalopram, 375 exposures), 423 used only other antidepressants, and 15 used both. Outcome was compared with all births in the population.	Based on this database, the use of antidepressants in early pregnancy does not seem to carry any significant risk for the infant that is detectable during the newborn period.
Cohen <i>et al.</i> 2000 [27]	Fluoxetine	Obstetric and neonatal records were reviewed for 64 mother-infant pairs where there was documented use of fluoxetine at some point during pregnancy. Differences in several measures of obstetrical outcome and neonatal well-being were examined in early trimester- and late trimester-exposed infants.	No differences in birth weight and acute neonatal outcome were evident across the two groups, though there was a higher frequency of special care nursery admissions for infants with exposure to fluoxetine late in pregnancy. Special care nursery admissions could not be attributed to any specific factor.
Simon <i>et al.</i> 2002 [28]	Fluoxetine Fluvoxamine Paroxetine Sertraline	This study evaluated the effects of prenatal antidepressant exposure on perinatal outcomes, congenital malformations, and early growth and development.	No association was found between tricyclic antidepressant or SSRI exposure and congenital malformations.
Hendrick <i>et al.</i> 2003 [29]	Fluoxetine Paroxetine Sertraline	The purpose of this study was to examine prospectively the incidence of congenital anomalies and neonatal complications after prenatal exposure to antidepressant medication.	After prenatal use of selective serotonin reuptake inhibitor antidepressant medications, neonatal complications and congenital anomalies appear to occur within general population rates.

a non-linear kinetic, which produces a rise in the half-life with high doses or after long-term treatments. Apart from the 2D6 enzyme, other cytochrome P450 enzymes are also included in fluoxetine's metabolism (especially 3A3/4, 2C19, 2C9/10), and its metabolites, being less potent than the parent compound, still have a pharmacological effect and a long half-life. In the case of paroxetine, the existence of another enzyme of low-affinity and high capacity has been proposed, but not yet identified, and the metabolites have no pharmacological effect [51]. As a result, despite the increased half-life of paroxetine after continuous treatment or high doses, it has the shortest half-life of the SSRIs, and its metabolites do not contribute to the maintenance of the pharmacological effect. Furthermore, when dosing is stopped, plasma concentrations begin to fall slowly because of the continued inhibition of the main metabolic enzyme. However, as concentrations continue to fall, the enzyme becomes more active as it becomes unblocked with an accelerated process of clearance. These metabolic characteristics associated with a relative lower NA/5HT selectivity of paroxetine and fluoxetine might be related to

the fact that paroxetine has been associated with neonatal withdrawal syndrome in a frequency that might be superior to other SSRI [36].

Another perinatal complication that must be taken into account is the increased risk of haemorrhagic complications, both for the child and the mother. SSRIs have been reported to inhibit serotonin uptake into platelets, resulting in decreased platelet function [52]. The role of serotonin in SSRIs-induced haemorrhage is not completely understood, but at least a case of a large intraventricular haemorrhage in a newborn baby has been associated with maternal use of paroxetine [42]. Despite that there are not yet published reports exploring the risks of high bleeding around delivery in mothers, clinical experience shows that an increase in bleeding complications during delivery might be associated with the last trimester use of SSRIs.

#### RISK OF LONG-TERM EFFECTS

Since the development of the central nervous system continues not only after the first trimester but for years after birth, the central nervous system remains particularly

vulnerable to toxic agents throughout pregnancy, and even after birth. Exposures that occur after neural tube closure, at 32 days of gestation [53], may produce more subtle changes in behaviour and functioning. Behavioural teratogenesis refers to the potential of a psychotropic drug administered during pregnancy to have long-term neurobehavioural effects (cognitive or behavioural problems, as well as neuropsychiatric symptoms, at a later point during their development). The fields of behavioural teratology and neurobehavioural toxicology have arisen during the past 30 years to allow researchers to examine with well defined methodologies the more subtle and more long-lasting effects of such exposure [54]. Behavioural teratology studies have been applied in some scarce instances to human populations, but they have not yet become a required component of premarket testing of new pharmaceuticals. Given the vulnerability of the pregnant human population, it is difficult to conceive how premarket testing could be realised, but nevertheless it is exactly the potential vulnerability of this population that needs to be addressed in the future [54]. The types of behavioural effects to study after a prenatal exposure to SSRIs should include short- or long-term cognitive impairment, alterations in diurnal rhythms,

emotional reactivity, and alterations of normal motor development.

To date, the evidences of this type of long-term effects are weak and controversial (Table 5). The few published studies failed to show long-term effects on global IQ, language development or behavioural development in preschool children [55]. Nevertheless, there is a lack of comparative studies of general population against exposed children, and the differences seem to be subtle enough as to require enormous sample sizes that prevent more in-detail studies. Another problematic issue is the long-term effects of untreated depression of the mother during pregnancy in children, that has been associated with less cognitive and language achievements by their children [56]. Of course, the deleterious effects of drugs in the developing brain have to be balanced against the environmental effect of a child in a family with a depressed mother during early-school years.

There are more clear evidences that pain reactivity is modified after birth, possibly related to serotonin mediated pain inhibition [45]. The same author has found that behavioural responses to acute procedural pain might be disturbed in children up to two months of age, after only prenatal exposure to SSRI [48]. Nevertheless, the time pattern of this outcome remains to be fully established.

**Table 4a. Risk of Neonatal Symptoms – Case Report Studies**

Study	SSRIs	Objective of the Study	Findings
Spencer, 1993 [37]	Fluoxetine	Case Report	A case of fluoxetine toxicity in a newborn of 38 weeks' gestation is presented. Central nervous system symptoms were most prominent in this newborn. He also had an increased heart rate. The neonate in this case was asymptomatic at 96 hours of age, indicating that the parent compound, fluoxetine, may be the active part of the drug and side effects may be caused by the parent compound.
Dahl <i>et al.</i> 1997 [38]	Paroxetine	Case Report	Letter to the editor describing a Paroxetine withdrawal syndrome in a neonate.
Nordeng <i>et al.</i> 2001 [39]	Citalopram, Paroxetine and Fluoxetine	The study report five cases of neonatal withdrawal syndrome after third trimester in utero SSRI exposure. In three cases the mother used paroxetine in doses from 10 to 40 mg, one mother used citalopram 30 mg, and one mother fluoxetine 20 mg	Neonatal withdrawal syndrome can occur after third trimester in utero SSRI exposure. All neonates exposed to SSRIs during the last trimester should be followed-up closely for withdrawal symptoms after birth.
Nijhuis <i>et al.</i> 2001 [40]	Paroxetine	Case Report	Withdrawal reactions of a premature neonate after maternal use of paroxetine.
Stiskal <i>et al.</i> 2001 [41]	Paroxetine	Case Reports	Four term neonates presented with symptoms such as jitteriness and necrotising enterocolitis after paroxetine exposure <i>in utero</i> .
Duijvestijn <i>et al.</i> 2003 [42]	Paroxetine	Case Report	A case of a large intraventricular haemorrhage in a 6-h-old boy, whose mother used paroxetine during pregnancy is reported.
Jaiswal <i>et al.</i> 2003 [43]	Paroxetine	Case Report	A term neonate born to a mother who stopped paroxetine intake 48 h prior to birth, who had features suggestive of paroxetine withdrawal and supported by paroxetine not being detected in plasma and cerebrospinal fluid showing no change in serotonin metabolites.
Morag <i>et al.</i> 2004 [35]	Paroxetine	Case Report	A newborn of a SSRI-treated mother presented with lethargy, no crying, and no response to tactile stimulation. EEG findings were abnormal. Laboratory and clinical evaluations were normal. He recovered at the age of two weeks. We suspect these symptoms are attributed to the intrauterine exposure to paroxetine, through modulation of pain signals.

Table 4b. Risk of Neonatal Symptoms – Clinical Studies

Study	SSRIs	Objective of the Study	Findings
McElhatton <i>et al.</i> 1996 [32]	Tricyclic Fluvoxamine	Data were collected prospectively from the time of in utero exposure and all the cases were followed up to the first few weeks of postnatal life using standardized procedures. In most cases, no longer term follow-up data were available. Approximately two-thirds of the mothers were on multidrug therapy, and of those, half took a benzodiazepine. About 95% of the patients were exposed during the first trimester.	No causal relationship could be established between in utero exposure to antidepressants and adverse pregnancy outcome.
Chambers <i>et al.</i> 1996 [23]	Fluoxetine	Prospective study that compared outcomes of 228 pregnant women taking fluoxetine with those of 254 women who were not taking fluoxetine.	Premature delivery (relative risk 4.8) Admission to special-care nurseries (relative risk 2.6) Poor neonatal adaptation (relative risk 8.7).
Nordeng <i>et al.</i> 2001 [39]	Citalopram, Paroxetine and Fluoxetine	The study report five cases of neonatal withdrawal syndrome after third trimester in utero SSRI exposure. In three cases the mother used paroxetine in doses from 10 to 40 mg, one mother used citalopram 30 mg, and one mother fluoxetine 20 mg.	Neonatal withdrawal syndrome can occur after third trimester in utero SSRI exposure. All neonates exposed to SSRIs during the last trimester should be followed-up closely for withdrawal symptoms after birth.
Costei <i>et al.</i> 2002 [44]	Paroxetine	Prospective, controlled cohort study of fifty-five pregnant women counseled prospectively by the Motherisk program in Toronto, Ontario, regarding third-trimester exposure to paroxetine and their infants were included in the study group.	Paroxetine is associated with a high rate of neonatal complications, possibly caused by its common discontinuation syndrome.
Simon <i>et al.</i> 2002 [28]	Fluoxetine, Fluvoxamine, Paroxetine, Sertraline	This study evaluated the effects of prenatal antidepressant exposure on perinatal outcomes, congenital malformations, and early growth and development.	No association was found between tricyclic antidepressant or SSRI exposure and developmental delay. SSRI exposure during pregnancy was associated with earlier delivery and consequent lower birth weight. Third-trimester SSRI exposure was also associated with lower Apgar scores.
Heikinen <i>et al.</i> 2002 [33]	Citalopram	Eleven mothers taking citalopram and their infants were enrolled in the study, and a control group of 10 women who were not taking medication were prospectively matched for confounding obstetric characteristics at the time of delivery.	Results from this prospective clinical trial suggest uncomplicated pregnancy outcome in mothers using citalopram during pregnancy and minimal exposure of the infants to citalopram during lactation.
Oberlander <i>et al.</i> 2002 [45]	Fluoxetine Paroxetine Sertraline	To examine biologic and behavioral effects of prenatal exposure, neonatal responses to acute pain (phenylketonuria heel lance) in infants with prolonged prenatal exposure were examined.	Prolonged prenatal SSRI exposure appears to be associated with reduced behavioral pain responses and increased parasympathetic cardiac modulation in recovery following an acute neonatal noxious event. Possible 5HT-mediated pain inhibition.
Hendrick <i>et al.</i> 2003 [29]	Fluoxetine Paroxetine Sertraline	The purpose of this study was to examine prospectively the incidence of congenital anomalies and neonatal complications after prenatal exposure to antidepressant medication.	Maternal use of high doses of fluoxetine throughout pregnancy may be associated with a risk for low birth weight.
Laine <i>et al.</i> 2003 [46]	Citalopram Fluoxetine	A prospective, controlled, follow-up study with 20 mothers taking 20 to 40 mg/d of either citalopram or fluoxetine for depression (n = 10) or panic disorder (n = 10) and their infants and 20 matched controls not receiving psychotropic medication for confounding obstetric characteristics.	Infants exposed to SSRIs during late pregnancy are at increased risk for serotonergic central nervous system adverse effects, and the severity of these symptoms is significantly related to cord blood 5-HIAA levels.
Suri <i>et al.</i> 2004 [34]	Fluoxetine	Sixty-four outpatient women with an Axis I diagnosis of major depressive disorder or no psychiatric history were followed in each trimester of pregnancy with administration of the CES-D. A subset of the women with depression received treatment with fluoxetine during pregnancy.	In contrast to other studies, this study did not demonstrate an adverse effect of fluoxetine exposure per se on obstetrical outcome. In addition, this study did not find a significant impact of depression during pregnancy on obstetrical outcome.
Zeskin & Stephens, 2004 [47]	Fluoxetine Paroxetine Sertraline	This is a prospective study of the effects of maternal use of selective serotonin reuptake inhibitors during pregnancy on newborn neurobehavioral integrity, including systematic measures of behavioral state, sleep organization, motor activity, heart rate variability (HRV), tremulousness, and startles.	Women who use SSRIs during pregnancy have healthy, full-birth weight newborn infants who show disruptions in a wide range of neurobehavioral outcomes. Effects on motor activity, startles, and HRV may be mediated through the effects of SSRI exposure on gestational age. Future research can lead to a better understanding of the effects of SSRI use during pregnancy and an improved public health outcome.
Sanz <i>et al.</i> 2005 [36]	Paroxetine Fluoxetine Sertraline Citalopram Fluvoxamine	An association between paroxetine and neonatal convulsions was identified in December, 2001, by the data mining method routinely used to screen the WHO database of adverse drug reactions. An information component (IC) measure was used to screen for unexpected adverse reactions relative to the information in the database.	By November, 2003, a total of 93 suspected cases of SSRI-induced neonatal withdrawal syndrome had been reported, and were regarded as enough information to confirm a possible causal relation. 64 of the cases were associated with paroxetine, 14 with fluoxetine, nine with sertraline, and seven with citalopram. SSRIs, especially paroxetine, should be cautiously managed in the treatment of pregnant women with a psychiatric disorder.

**Table 5. Risk of Long-Term Effects – Studies**

Study	SSRIs	Objective of the Study	Findings
Nulman <i>et al.</i> 1997 [55]	Tricyclic fluoxetine	Children of 80 mothers who had received a tricyclic antidepressant drug during pregnancy, 55 children whose mothers had received fluoxetine during pregnancy, and 84 children whose mothers had not been exposed during pregnancy to any agent known to affect the fetus adversely are studied.	In utero exposure to either tricyclic antidepressant drugs or fluoxetine does not affect global IQ, language development, or behavioral development in preschool children.
Nulman <i>et al.</i> 2002 [56]	Tricyclic Fluoxetine	In a prospective study, motherchild pairs exposed throughout gestation to tricyclic antidepressants (N=46) or fluoxetine (N=40) and an unexposed, not depressed comparison group (N=36) were blindly assessed. The three groups were compared in terms of the children's IQ, language, behavior, and temperament between ages 15 and 71 months.	Exposure to tricyclic antidepressants or fluoxetine throughout gestation does not appear to adversely affect cognition, language development, or the temperament of preschool and early-school children. In contrast, mothers' depression is associated with less cognitive and language achievement by their children.
Casper <i>et al.</i> 2003 [57]	SSRIs	To compare the structural growth and developmental outcome of children born to mothers diagnosed with major depressive disorder during pregnancy who were exposed or not exposed to selective serotonin reuptake inhibitors (SSRIs) in utero. Children whose mothers were diagnosed with major depressive disorder in pregnancy and elected not to take medication (n = 13) were compared with children of depressed mothers treated with SSRIs (n = 31) on birth outcomes and postnatal neurodevelopmental functioning between ages 6 and 40 months. Children underwent blinded standardized pediatric and dysmorphology examinations and evaluations of their mental and psychomotor development with the use of the Bayley Scales of Infant Development (BSID II).	The Bayley mental developmental indexes were similar in both groups. Children exposed to SSRIs during pregnancy had lower APGAR scores and scored lower on the Bayley psychomotor development indexes and the motor quality factor of the Bayley Behavioral Rating Scale than unexposed children. The findings that SSRIs during fetal development might have subtle effects on motor development and motor control are consistent with the pharmacologic properties of the drugs.
Oberlander <i>et al.</i> 2005 [48]	Fluoxetine Paroxetine Sertraline	Prospective study that examine biobehavioral responses to acute procedural pain at 2 months of age in infants with prenatal and postnatal selective serotonin reuptake inhibitor medication exposure.	Blunted facial-action responses were observed among infants with prenatal SSRI exposure alone, whereas both prenatal and postnatal exposure was associated with reduced parasympathetic withdrawal and increased parasympathetic cardiac modulation during recovery after an acute noxious event. These findings are consistent with patterns of pain reactivity observed in the newborn period in the same cohort. Given that postnatal exposure <i>via</i> breast milk was extremely low and altered biobehavioral pain reactivity was not associated with levels of maternal reports of depression, these data suggest possible sustained neurobehavioral outcomes beyond the newborn period.

### RISK OF UNTREATED DEPRESSION

While there is wide variability in reported effects, untreated depression during pregnancy appears to carry substantial perinatal risks [58]. Most researchers have found that untreated depression may have associated obstetric complications and puerperal pathologies [58-64]. The perinatal risks may be direct risks to the foetus and infant or risks secondary to unhealthy maternal behaviours arising from the depression that could include suicide attempts [65]. Because untreated depression presents risks to the mother and can increase the risk of prematurity, low birth weight, and neonatal complications in the infant, the benefits of initiating or continuing antidepressant therapy during pregnancy need to be weighed against any potential risks. Pregnancy is often unplanned and assessment of these risks prior to initiating antidepressant treatment in women of child-bearing potential is prudent.

Because randomised, placebo-controlled studies of pregnancy outcome following drug exposure are unobtainable, data gathered *via* cohort-controlled or case-

controlled studies, patient surveys, anecdotal case reports, and retrospective evaluations are used to assess the effects of medication on human pregnancy outcome. Unfortunately, many reviews seem to give equal weight to each of these methods, preventing proper interpretation of the risks of treatment and leading to assumption of higher risks than actually exist [14].

### DISCUSSION

The use of drugs, and especially antidepressants in pregnancy, and their possible effects in the new-born, and even more if related to withdrawal syndromes, convulsions of poor neonatal adaptation, is a hot topic that elicits sensitive and visceral reactions that must be reduced to their proper magnitude.

According to the present knowledge, the use of antidepressants and especially SSRIs during pregnancy is safe in an overall evaluation. There are evidences of the lack of an increase in the risk of neonatal malformations and teratogenesis. In the same way, although the long-term

effects on the brain and the cognitive and behavioural functioning in childhood associated with pre-natal exposure to SSRIs remains to be fully studied, but the current data suggest that the risk is limited or non-existent. Nevertheless, the perinatal risks are more clearly defined. The symptoms associated with prenatal exposure to SSRIs are mild and self-limited in most cases, despite that in particular occasions, the clinical picture might appear with neonatal convulsions, respiratory failures or a full neonatal withdrawal syndrome. The published series to date does not allow to know a concrete figure of the prevalence of such symptoms and signs, but most children are born with a clinical situation entirely similar to other healthy babies not exposed to SSRIs. With the current evidences, mothers using SSRI during pregnancy should be followed with care during the last period of pregnancy and delivery, and obstetrics and neonatologist must be aware of possible complications that usually only require symptomatic and support treatments.

The management of women with an affective disorder during pregnancy is based on balancing the potential risk of the symptoms against the potential risks of pharmacotherapy. It is necessary to consider the use of nonpharmacological therapies that may eliminate or reduce the need for antidepressants, including cognitive behaviour therapy for anxiety and interpersonal therapy for depression. Meta-analysis showed that psychotherapy is effective in enhancing psychological well-being, regardless of the way it is measured by researchers [66]. The efficacy of inter-personal therapy has proved to be superior to placebo, similar to medication and did not increase when combined with medication. Overall, inter-personal therapy was more efficacious than cognitive behavioural therapy. Current evidence indicates that inter-personal therapy is an efficacious psychotherapy for depressive spectrum disorders and may be superior to some other manualised psychotherapies. [67]. In the same way, cognitive behavioural therapy has shown to be an effective method of treatment for generalised anxiety disorder. Differences between control and treatment group are comparable to or larger than those reported in studies on antidepressant drugs [68].

In the light of the available data, one of the main risks of SSRIs in pregnancy could be the lack of efficacious and needed treatment of a depressive pregnant woman when treatment is really needed and no other treatment alternatives are indicated, based on a mislead conception of the risks of these drugs.

At the present time, there is a considerable clinical experience with the use of SSRIs in pregnant women and although the data available are reassuring, additional clinical experience, especially long-term neurobehavioural neuropsychiatric follow-up studies are needed.

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