Gestational exposure to antidepressants and the risk of spontaneous abortion: A review.

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Abstract.

Background. Although the relationship between antidepressant use during pregnancy and its adverse effects has been widely investigated, very few studies have evaluated the impact of antidepressant use during pregnancy on the risk of spontaneous abortion. We present an overview of the evidence relating to the association between antidepressant use during gestation and the risk of spontaneous abortion.

Methods. We systematically searched PubMed and the reference lists of all relevant articles, including reviews, published in English or French from 1975 through 2009 for studies that examined the association between adverse pregnancy outcomes and gestational exposure to antidepressants with data on spontaneous abortions. Only etiologic studies were considered.

Results. Fifteen studies met inclusion criteria. The majority of these were prospective cohort studies on tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs) use during pregnancy. Overall, in unadjusted analyses, fluoxetine (OR = 2.0; 95% CI = 1.4 – 3.0) and bupropion (OR = 4.1; 95% CI = 1.5 – 11.1) were significantly associated with the risk of spontaneous abortion. However, in adjusted analyses, only paroxetine (OR = 1.7; 95% CI = 1.3 – 2.3) and venlafaxine (OR = 2.1; 95% CI = 1.3 – 3.3) were significantly associated with the risk of spontaneous abortion.

Conclusions. This review suggests that gestational exposure to antidepressants, especially paroxetine and venlafaxine, can lead to spontaneous abortion.

Keywords: Antidepressants, pregnancy, spontaneous abortion, review
Background

Depression is a common psychiatric disorder during the gestational period, affecting up to 14% of pregnant women [1-3]. The prevalence of depression during pregnancy varies depending on the definition for depression and the depressive symptom measurement scale chosen within studies. In a Northern-Swedish population-based study [4], major and minor depression was present in 3.3% and 6.9% of pregnant women, respectively; “psychiatric disorder” or “depressed mood disorder” have been reported by up to 20% of pregnant women [1, 2, 4, 5]. Finally, a population-based study [6] found that 6.6% of pregnant women in Quebec had a prescription for an antidepressant in the year prior to pregnancy, and that 3.7% of them were using antidepressant during gestation. The hypothesis that pregnancy is a time of emotional well-being, providing protection against psychiatric disorders seems to be weak [7].

The prevalence of antidepressant use during gestation varies between 1 and 8% [6, 8-11]. Although the relationship between antidepressant use during pregnancy and the risk of adverse perinatal events has been investigated widely, very few studies have attempted to evaluate the impact of antidepressant use during gestation on the risk of spontaneous abortion. Spontaneous abortion is the most common pregnancy outcome affecting up to 15% of recognized pregnancies [12, 13]. Spontaneous abortion is defined as the spontaneous loss of a fetus weighing less than 500 grams before 20 weeks gestation counted from the first day of the last menstrual period [14]. The term “spontaneous abortion” is often used synonymously with “miscarriage”, “spontaneous pregnancy loss”, “early pregnancy failure” or “spontaneous termination of pregnancy”. Two etiologies for
spontaneous abortions include congenital uterine malformations and parental balanced chromosomal rearrangements, such as trisomy [12].

Whereas psychological and psychiatric consequences of spontaneous abortions are well documented [15], information regarding the spectrum of attendant risks of prenatal exposure to antidepressant on spontaneous abortion is incomplete. Therefore, we present an overview of the evidence on antidepressant use during gestation and the risk of spontaneous abortion.
Methods

We systematically searched Pubmed for human studies published between 1975 through 2009. Combinations of the following search terms were used: “spontaneous abortion” or “miscarriage” or “termination of pregnancy” or “birth outcome” or “obstetrical outcome” or “anomalies” or “pregnancy” as well as “antidepressant” or “depression” or “selective serotonin reuptake inhibitors (SSRIs)” or “paroxetine” or “serotonin” or “fluoxetine” or “fluvoxamine” or “citalopram” or “venlafaxine”. Additional references were identified from the reference lists of retrieved articles. All relevant articles, including prospective and retrospective studies, reviews and meta-analyses, published in English or in French that examined the association between gestational exposure to antidepressants and the risk of adverse pregnancy outcomes having data on spontaneous abortions were reviewed. Only etiologic studies were considered. The initial selection criteria were broad to ensure that as many studies as possible were assessed for review.

Within each selected study, the following information was retrieved: first author’s name, year of publication, study population, design, exposure definition, data source, confounders considered, results including p-values, relative risks (RR) or odds ratios (OR) when provided.

When the odds ratios for spontaneous abortions had not been reported by authors, we calculated crude odds ratios from the available data in order to compare study results and interpret data. Where this was not reported, we also calculated the prevalence of spontaneous abortion, after excluding ectopic pregnancies and elective abortions, from
the control sample. Analyses were performed using the SAS System for Windows Version 9.1.3 (SAS Institute Inc, North Carolina, USA).
Results

Included studies

We found 15 studies that met inclusion criteria. The majority of these were prospective cohort studies. Spontaneous abortion was the primary outcome for only two studies. However two meta-analyses considered the association between spontaneous abortion and antidepressant use. Characteristics of reviewed articles are presented in table 1.

Results on all antidepressants combined

Crude odds ratios are presented in table 2 and illustrated in (fig. 1) for all antidepressants use combined. In 1993, Pastuszak et al. [16] were the first authors to associate spontaneous abortion and antidepressant use in a prospective cohort study with 128 pregnant women who contacted four Teratogen Information Services (TIS) in Canada and the United States requesting information about the teratogenic potential of fluoxetine. Pastuszak et al. compared pregnant women exposed to fluoxetine with two age-matched non-exposed groups of women. The first non-exposed group included 74 women exposed
to tricyclic antidepressants (TCAs) during pregnancy, and the second included 128 women exposed to nonteratogenic agents. All exposed women used either TCAs or fluoxetine during the first trimester of pregnancy. Hence, Pastuszak et al. noted an increase in spontaneous abortions in exposed women, compared with the non-exposed group, but this did not reach statistical significance. In 2001, Einarson et al. [17] published the first prospective cohort study on the effects of venlafaxine use during pregnancy on adverse fetal outcomes by identifying 150 women treated with venlafaxine between the 4th and 14th week of gestation. These women were compared to SSRI users and women not exposed to known teratogens. The use of both venlafaxine and SSRIs during pregnancy was not associated with a statistically significant increase in the prevalence of spontaneous abortions. Therefore, Einarson et al. combined their findings with the results of two previous studies [16, 18] using a meta-analytical approach. They found a summary OR of 1.68 (95% CI = 1.12-2.51). We chose not to show it in our forest plots because exposed and non-exposed groups were not well defined. In 2003, Einarson et al. [19] published the first prospective cohort study of the use of trazodone and nefazodone during pregnancy. The primary objective was to ascertain whether trazodone or nefazodone increased the baseline risk for major malformations. Birth outcomes of women who took these agents during the gestational period were compared with those of women who used either TCAs, SSRIs or venlafaxine or nonteratogens. The prevalence of spontaneous abortions was higher in the exposed and the “other antidepressants” group but the study did not have enough statistical power. In a 2005 meta-analysis, Hemels et al. [20] combined results from studies by Pastuszak et al. [16], Chambers et al. [21], McElhatton et al. [22], Kulin et al. [18] and Einarson et al. (one on venlafaxine [17] and
the other on trazodone and nefazodone [19]). Hemels et al. concluded that maternal exposure to antidepressants was associated with a significant increase in the risk of spontaneous abortion (RR = 1.45; 95% CI = 1.19-1.77). No differences were found among antidepressant classes in spite of their different mechanisms so underlying depression could not be ruled out as a cause. In 2005, Chun-Fai-Chan et al. [23] published the first prospective cohort study on bupropion use during pregnancy. The objective was to determine whether bupropion increased the risk of major malformations above the baseline populational risk. Pregnancy outcomes of 136 women who took bupropion in the first trimester, for either depression or smoking cessation, were compared with a) those with depression who were taking other antidepressants and b) non-depressed women who took drugs with no known teratogenic potential. When all women taking bupropion were compared with women who took nonteratogens, the only statistically significant difference was an increase in the number of spontaneous abortion in the bupropion group. Djulus et al. [24] published in 2006 a prospective, multicenter, observational study of mirtazapine use during the gestational period. The objective was to determine whether mirtazapine used by pregnant women increased the risk for major malformations in newborns, but the number of spontaneous abortion was also reported. Pregnancies in which the fetus was exposed to mirtazapine were compared with a group of pregnant women who took other antidepressants and to a group of pregnant women who took nonteratogens. Both antidepressant groups had higher prevalence of spontaneous abortions compared with the nonteratogen group, but the difference was not statistically significant (crude OR = 1.97; 95% CI = 0.96 – 4.05). Recently our research team conducted a nested case-control study [25] using the Quebec Pregnancy Registry
database, to quantify the association between antidepressants use during pregnancy and the risk of spontaneous abortion. We found that gestational use of antidepressant medications significantly increased the risk of spontaneous abortion. A recent prospective cohort study from Einarson et al. [26] quantified the impact of prenatal antidepressant use on the risk of spontaneous abortion, without adjusting for depression or distinguishing different types of antidepressants. They found a small but statistically significant increased risk of spontaneous abortion (RR: = 1.63; 95% CI = 1.24 – 2.14).

**Tricyclic antidepressants (TCAs)**

TCAs were the first antidepressant to be marketed [22]. These agents act by inhibiting the reuptake of norepinephrine and 5-HT into neuronal synapses, thus leading to sustained facilitation of noradrenergic and serotonergic transmission. TCAs have a wide range of other neuropharmacological effects [27]. Today, TCAs are used less frequently because of their side effects profile. However, these agents continue to have a place in the treatment of depression, particularly among patients who fail to respond to or tolerate newer antidepressants [28]. Amitriptyline, imipramine, doxepin, nortriptyline and desipramine are the most prescribed TCAs in the US [29]. TCAs were used by 12% of pregnant women who took antidepressants during the gestational period in Quebec between 1998 and 2003 [6]. Nortriptyline is the only antidepressant listed as category D by the FDA [30]. This means that nortriptyline showed positive evidence of fetal risk, but the benefits may be acceptable despite this [30].

![Fig 2: Risk of spontaneous abortions for TCA class](image)
Crude odds ratios are presented in table 2 and illustrated in (fig. 2) for TCAs use. Pastuszak et al. [16] noted a numeric increase in spontaneous abortions in the TCA-exposed pregnancies, compared with the non-exposed group, but it did not reach statistical significance. McElhatton et al. [22] published in 1996 a large case series, reporting the outcome of 689 pregnant women who took either TCAs or non-TCAs including selective serotonin reuptake inhibitors (SSRIs) and trazodone. McElhatton et al. found prevalence of spontaneous abortion within the 12-15% expected range whether TCAs use was combined with other drugs such as benzodiazepine or not.

*Monoamine oxidase inhibitors (MAOIs)*

MAOIs including phenelzine and tranylcypromine are not recommended during pregnancy due to their side effects and alimentary restrictions [28]. Hence, the use of these agents is minimal (<0.1%) [6, 10] and no studies meeting eligibility criteria were found for this review.

*Selective serotonin reuptake inhibitors (SSRIs)*

Serotonin is the former name for 5-hydroxytryptamine (5-HT) [27]. SSRIs selectively inhibit the neuronal 5-HT reuptake pump at the presynaptic junction, leading to increased concentrations at the synaptic cleft and potentiating serotoninergic neurotransmission, without affecting other neuroreceptors such as histamine, acetylcholine and adrenergic receptors [31, 32]. SSRIs have limited direct action on other neurotransmitter sites such as serotonin but not on norepinephrine site [33], hence patients have an increased tolerance and fewer adverse side effects when compare to TCAs. SSRIs are used not only
for affective disorders such as major depression, anxiety and chronic pain, but also for dysthymia, panic disorder, eating disorders and premenstrual dysphoric disorder [32, 34]. SSRIs are often preferred over TCAs for the following reasons: they usually have fewer side effects; they are well tolerated; an overdose is rarely fatal if no other drugs are taken; and patients tend to be compliant [32, 34].

![Crude odds ratios are presented in table 2 and illustrated in (fig. 3) for “any SSRI” use. McElhatton et al.[22] found prevalence of spontaneous abortion within the expected range of 12-15% whether SSRIs use was combined with other drugs such as benzodiazepine, or not. In 1998, Kulin et al. [18] published the first prospective, multicenter, cohort study of pregnancy outcomes including congenital malformations and spontaneous abortions following fetal exposure to new SSRIs, including fluvoxamine, paroxetine and sertraline. Women who were counselled by the Motherisk Program after exposure to one of these agents were matched to non-exposed women who were randomly selected from the total group of women counselled and followed after exposure to a nonteratogen drug. Women who were exposed to a known human teratogen or drugs...](image)
of uncertain teratogenicity were excluded. Prevalence of spontaneous abortion did not significantly differ between the exposed and non-exposed groups (crude OR = 1.5; 95% CI = 0.9 – 2.7). Einarson et al. [17] found that the use of SSRIs during pregnancy was not associated with a statistically significant increase in the prevalence of spontaneous abortions. A meta-analysis [35] was published in 2005 focusing on SSRIs use. The author combined results from Pastuszak et al. [16], Chambers et al. [21], Kulin et al. [18], Einarson et al. (on venlafaxine) [17] and Diav-Citrin et al. [36], finding that the summary odds ratio for the risk of spontaneous abortion was statistically significant (OR = 1.7; 95% CI = 1.28-2.24). One group, Sivojelezova et al., [37] reported a study on citalopram in which they evaluated 132 women treated with this drug during gestational period. The objective was to determine whether citalopram use during pregnancy was associated with an increased risk of adverse pregnancy outcomes, including spontaneous abortion. Pregnant women administered citalopram were matched to a group of women treated with other SSRIs (eg, fluoxetine, paroxetine, sertraline) and a group of women exposed to nonteratogenic agents, both with the same disease status. The exposed group and the two comparison groups were matched for maternal age at the time of conception as well as gestational stage of pregnancy at the time of recruitment. Sivojelezova et al. failed to demonstrate statistically significant differences in the prevalence of spontaneous abortion between the groups (crude OR = 1.10; 95% CI = 0.50 – 2.45). In 2008, Diav-Citrin et al. [38] evaluated the prevalence of birth outcomes, including spontaneous abortions, after gestational exposure to paroxetine, fluoxetine or nonteratogen drugs in a multicentre, prospective cohort study. On crude analyses, Diav-Citrin et al. found higher prevalence
of spontaneous abortion in the SSRI-exposed groups, but after adjustment these results were not statistically significant.

**Fluoxetine**

Crude odds ratios for the risk of spontaneous abortion following gestational SSRIs use are presented in table 2 and illustrated in (Fig. 4). Pastuszak et al. [16] noted an increase in spontaneous abortions in fluoxetine-exposed pregnancies, compared with the non-exposed group, but it did not reach statistical significance. In 1996, Chambers et al. [21] studied 228 women recruited from callers to the California TIS after exposure to fluoxetine. They were compared with a group of 254 women exposed to nonteratogenic
drugs. The investigators divided the population into two groups. The first group was the early exposure group, in which exposure occurred before 25 weeks of gestation; women in the second group (late exposure group) continued to take fluoxetine into the third trimester. This study has been criticized because the non-exposed group was not randomly selected; as a consequence fluoxetine-exposed women were older than the non-exposed women [39]. Whereas 8.5% of non-exposed pregnancies terminated in spontaneous abortion, 13.6% of fluoxetine-exposed women had a spontaneous abortion. In 2008, Diav-Citrin et al. [38] found on crude analyses higher prevalence of spontaneous abortion in the fluoxetine-group, but after adjustment this result was not statistically significant (OR = 1.27; 95% CI = 0.76 – 2.13).

**Paroxetine**

Paroxetine is the third most frequently prescribed antidepressant in the United States [40] and is the most often prescribed in Canada [6]. It’s increased from 37.5% of pregnancies exposed to antidepressant in 1995-1996 to 60.4% in 2003-2004 [41]. Paroxetine is now used by up to 2% of all pregnant American women [11]. In 2008, Diav-Citrin et al [38] found higher prevalence of spontaneous abortion in the paroxetine group but after adjustment these results were not statistically significant (OR = 0.85; 95% CI = 0.52 – 1.40). Nakhai-Pour [25] found that gestational use of paroxetine significantly increased the risk of spontaneous abortion (OR = 1.75; 95% CI = 1.31 – 2.34).
**Others SSRI**s

Sertraline is less used when compared to paroxetine or fluoxetine, except in Canada and the United States where this agent is among the most frequently used SSRIIs [6, 10, 11, 40, 42, 43]. Citalopram and fluvoxamine are the least commonly used SSRIIs. Less than 1% of pregnant women use citalopram, representing about 10% of SSRI-exposed pregnancies[10, 11, 40-42]. The use of fluvoxamine has decreased since the mid-90’s [41]. Today, fluvoxamine is the least frequently used SSRI [10]. Sivojelezova et al. [37] failed to demonstrate statistically significant differences in the prevalence of spontaneous abortion between women exposed to citalopram and those exposed to other SSRIIs (crude OR = 1.10; 95% CI = 0.50 – 2.45).

**Others antidepressants**

Venlafaxine is a serotonin-norepinephrine reuptake inhibitors (SNRI). SNRIIs have the same mechanism as SSRIIs except that these agents inhibit both 5-HT and norepinephrine reuptake [27]. To our knowledge, venlafaxine is the only SNRI used during pregnancy [6, 25]. Despite a lack of safety information, venlafaxine is increasingly used during pregnancy, with a 87.5% increase in its use from 2005 to 2007 [44]. Crude odds ratios are presented in table 2 and illustrated in (fig. 5) for “other antidepressants” use. Einarson[17] found that the use of venlafaxine during pregnancy was not associated with a statistically significant increase in the prevalence of spontaneous abortions. However, Nakhai-Pour [25] found that gestational use of venlafaxine significantly increased the risk of spontaneous abortion.
Bupropion, mirtazapine, trazodone and nefazodone are newer antidepressants not widely used during pregnancy [6]. Bupropion and mirtazapine are among the newer dual-action antidepressants used by pregnant women [45]. Bupropion is a dopamine and norepinephrine reuptake inhibitor [27]. It’s an aminoketone antidepressant related to phenylethylamines which also could be used as a smoking cessation treatment [23]. About 2% of antidepressant-exposed women took bupropion during pregnancy [6]. Chun-Fai-Chan et al. [23] found that gestational use of bupropion significantly increased the risk of spontaneous abortion.

Mirtazapine is a tetracyclic piperazino-azepine [6]. It’s a noradrenergic and specific serotoninergic antidepressant which may also be used the treatment of hyperemesis gravidarum [46]. This agent was used by 0.3% of antidepressant-exposed pregnant women[6, 46]. Djulus [24] found that mirtazapine exposed pregnant women had higher
prevalence of spontaneous abortions compared to a group of women exposed to nonteratogens, but the difference was not statistically significant (crude OR = 2.14; 95% CI = 0.97 – 4.75).

Trazodone and nefazodone are serotonin modulators [6]. Trazodone and nefazodone are used by 6.1% and 2.2% of antidepressant-exposed pregnant women, respectively [6]. McElhatton et al. [22] found prevalence of spontaneous abortion within the 12-15% expected range whether trazodone use was combined with other drugs such as benzodiazepine. Einarson et al. [19] found that the prevalence of spontaneous abortions was higher in the group exposed to trazodone and nefazodone but the study did not have enough statistical power to show an effect. Yaris et al. [47] published in 2004 a case-series on the combined use of venlafaxine, mirtazapine and nefazodone during pregnancy. Among the 21 exposed women, only one spontaneous abortion was observed in a mirtazapine-exposed woman, but we cannot clearly attribute this pregnancy loss to mirtazapine because this woman used also alprozolam, diazepam and trifluoperazine.
Discussion

In the studies reviewed, the reported prevalence of spontaneous abortion in antidepressant-exposed women ranged from 9.5% [38] to 24.7% [25], whereas in unexposed women, it ranged from 4.5% [23] to 9.8% [37]. Hence, an increased risk of spontaneous abortion in mothers treated with antidepressants during early pregnancy cannot be ruled out. We suggest that gestational exposure to antidepressants, especially paroxetine and venlafaxine, could lead to an increased risk of spontaneous abortion.

Potential biological mechanisms include the fact that maternal SSRI use lead to an increase in the 5-HT concentration in the fetal cerebral cortex in rats [48], and therefore this could play a role in craniofacial development [49] or cause a transient delay in motor development [48]. If these malformations are being overwhelming to a viable fetus, this could result in a spontaneous abortion. Moreover, 5-HT mechanism could antagonize progesterone and prolactin secretion [50, 51] (progesterone is critical for implantation and the maintenance of human pregnancy [14]).

Prescribing of antidepressants to women during pregnancy requires balancing the benefits to the mother against the risks for the developing fetus. The impact of antidepressant use during pregnancy on the risk of spontaneous abortion is an important issue; all the more that a spontaneous abortion complicating a pregnancy in a women suffering from depressive symptoms may have a devastating effect on her already compromised mental health.
Clinicians must work collaboratively with future mothers to reach the safest evidence-based decision. The higher prevalence of spontaneous abortion in fetuses whose mothers were exposed to antidepressants, may in fact, be attributable to effects of the depression itself and this is an issue that requires further clarification. The recent increase in the number of pregnant antidepressants users, especially venlafaxine [10] will allow researchers to conduct more powerful studies about the impact of these agents.
Table 1. Characteristics of included studies on the association between antidepressant use during pregnancy and risk of spontaneous abortions.

<table>
<thead>
<tr>
<th>Author</th>
<th>Source population, country</th>
<th>Design</th>
<th>Exposure definition</th>
<th>Data source</th>
<th>Confounding variables</th>
<th>Results (n, %)</th>
<th>Over results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pastuszak 1993</td>
<td>N = 330 Teratogen Information Services Toronto (Canada) Philadelphia, Camden and Salt Lake City (US)</td>
<td>Cohort</td>
<td>Fluoxetine during 1st trimester (all women) throughout the pregnancy (some women)</td>
<td>Telephone interviews</td>
<td>Age (matched variable) Date of enrolment (matched variable)</td>
<td>Fluoxetine 19 / 128 (14.8%) NTC 10 / 128 (7.8%) AND Fluoxetine 10 / 74 (13.5%) TCA 9 / 74 (12.2%) NTC 5 / 74 (6.8%)</td>
<td>Fluoxetine vs NTC p = 0.03 RR: 1.9 (0.92 - 3.92) Spontaneous abortions vs live births, excluding elective abortions p = 0.31</td>
</tr>
<tr>
<td>Chambers 1996</td>
<td>N = 482 Teratogen Information Service California (US)</td>
<td>Cohort</td>
<td>Fluoxetine on Early pregnancy (&lt; 25 wks of gestation) Late pregnancy (&gt;25 wks of gestation)</td>
<td>Questionnaire + Telephone interviews + Form returned by the infant's physician</td>
<td>Date of enrolment (matched variable)</td>
<td>Fluoxetine 23 / 169 (13.6%) NTC 22 / 254 (8.5%)</td>
<td>p = 0.59</td>
</tr>
<tr>
<td>McElhatton 1996</td>
<td>N = 689 Teratogen Information Services France, Israel Italy, Germany Netherlands Spain, UK Switzerland</td>
<td>Descriptive large case series</td>
<td>TCAs Non TCAs during Any trimester</td>
<td>Questionnaire</td>
<td></td>
<td>TCAs 38 / 330 (11.5 %) Fluoxetine 13 / 96 (13.5 %) Fluvoxamine 6 / 66 (9.1 %) Paroxetine 0 / 3 (0 %) Trazodone 0 / 12 (0 %) Total Non TCAs 19 / 177 (10.7 %) TOTAL 79 / 689 (11.5 %)</td>
<td></td>
</tr>
<tr>
<td>Kulin 1998</td>
<td>N = 534 Teratogen Information Services Toronto and London (Canada) Philadelphia, Farmington, Salt Lake City, Tampa, Burlington, Chicago, Indianapolis (US)</td>
<td>Cohort</td>
<td>SSRIs (Sertraline, Paroxetine and Fluvoxamine) during 1st trimester (all women) throughout the pregnancy (some women)</td>
<td>Interviews</td>
<td></td>
<td>SSRIs 30 / 267 (11.2 %) NTC 21 / 267 (7.9 %)</td>
<td>p = 0.24</td>
</tr>
<tr>
<td>Einarson 2001</td>
<td>N = 450 Teratogen Information Services Toronto and London (Canada) Farmington and San Diego (US) Rome and Milan (Italy) Porto Allegre (Brazil)</td>
<td>Cohort</td>
<td>Venlafaxine during 1st trimester (all women) throughout the pregnancy (some women)</td>
<td>Questionnaire + Sending a letter to the child's primary care physician to corroborate the mother's information</td>
<td></td>
<td>Venlafaxine 18 / 150 (12.0 %) SSRIs 16 / 150 (10.7 %) NTC 11 / 150 (7.3 %)</td>
<td>Venlafaxine vs SSRIs p = 0.90 Venlafaxine vs NTC p = 0.24 Three Groups compared p = 0.38</td>
</tr>
<tr>
<td>Einarson 2003</td>
<td>N = 441 Teratogen Information Services Toronto and London (Canada) Milan (Italy) Farmington, Detroit (US)</td>
<td>Cohort</td>
<td>Trazodone Nefazodone during 1st trimester (all women) throughout the pregnancy (some women)</td>
<td>Structured questionnaire + Sending a letter to the child's primary care physician to corroborate the mother's information</td>
<td>Diagnostic of depression (matched variable) Time of enrolment (matched variable)</td>
<td>Trazodone-Nefazodone 20 / 147 (13.6 %) Other antidepressants 17 / 147 (11.6 %) NTC 12 / 147 (8.2 %)</td>
<td>p = 0.39</td>
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<tr>
<td>Yaris 2004</td>
<td>N = 21 Toxicology Information and Follow-up Turkey</td>
<td>Descriptive large case series</td>
<td>Newer antidepressants (Venlafaxine, mirtazapine and nefazodone) during Any trimester</td>
<td>Data from &quot;Toxicology Information and Follow-up Service&quot;</td>
<td></td>
<td>Mirtazapine + other drugs 1 / 21 (4.8 %)</td>
<td></td>
</tr>
<tr>
<td>Sivojelezova 2005</td>
<td>N = 396 Teratogen Information Services Toronto (Canada)</td>
<td>Cohort</td>
<td>Citalopram during Any trimester</td>
<td>Standardized intake form completed over the telephone + Telephone follow-up interview + Sending a letter to the child's primary care physician to corroborate the mother's information</td>
<td>Age (matched variable) Gestational age at the time of enrolment (matched variable) Diagnostic of depression (matched variable)</td>
<td>Citalopram 14 / 132 (11 %) Other SSRIs 13 / 132 (10 %) NTC 13 / 132 (10 %)</td>
<td></td>
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</tbody>
</table>

[a] = [16]; [b] = [21]; [c] = [22]; [d] = [18]; [e] = [17]; [f] = [19]; [g] = [47]; [h] = [37].
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<th>Results: spontaneous abortions / total of pregnancies</th>
<th>Over results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chun-Fai-Chan 2005 [i]</td>
<td>N = 358 Teratogen Information Services Toronto (Canada) Farmington (US) Drug Safety Research Unit Southampton (UK)</td>
<td>Cohort</td>
<td>Bupropion (for depression and smoking cessation) 1st trimester (all) throughout the pregnancy (some) Questionnaire filed by mother by telephone + Questionnaire filed by patient’s physician by letter</td>
<td>Questionnaire filed</td>
<td>Age (matched variable) Alcohol consumption (matched variable) Smoking (matched variable) Gestational age at the time of call (matched variable) Nb of cigarettes / day before pregnancy (matched variable) Depression (matched variable)</td>
<td>Bupropion for any indication 20 / 136 (14.7 %) NTC 6 / 133 (4.5 %) AND Bupropion for depression 14 / 91 (15.4 %) Other antidepressants 11 / 89 (12.3 %) NTC 6 / 133 (4.5 %)</td>
<td>Bupropion vs NTC p = 0.009 Three Groups compared p = 0.18</td>
</tr>
<tr>
<td>Hemels 2005 [ii]</td>
<td>N = 3567 1+2+3+4+5+7</td>
<td>Meta-analysis</td>
<td>Antidepressants 1st trimester (all) throughout the pregnancy (some)</td>
<td>Telephone interview + Questionnaire + Sending a questionnaire to patient's physician</td>
<td>Maternal age (matched variable) Gestational age at the first contact (matched variable) Tobacco use (matched variable) Alcohol consumption (matched variable) Depression (matched variable) Chronic conditions (matched variable)</td>
<td>Antidepressants 192 / 1534 (12.5 %) SSRIs 110 / 880 (12.4 %) TCAs 44 / 357 (12.3 %) Trazodone - Nefazodone 20 / 147 (13.6 %) Venlafaxine 18 / 150 (12.0 %) NTC 181 / 2033 (8.9 %)</td>
<td>TCAs vs NTC RR: 1.23 (0.84 - 1.78) SSRIs vs NTC RR: 1.52 (1.17 - 1.98) DAA vs NTC RR: 1.65 (1.02 - 2.69) Any antidepressant vs NTC RR: 1.45 (1.19 - 1.77)</td>
</tr>
<tr>
<td>Rahimi 2006 [k]</td>
<td>N = 2378 1+2+4+5+6</td>
<td>Meta-analysis</td>
<td>SSRIs Any trimester</td>
<td>Telephone interview + Structured questionnaire</td>
<td>Maternal age (matched variable) Gestational age at call Maternal age Smoking Previous spontaneous abortion Country Concomitant psychiatric medications</td>
<td>SSRIs 117 / 950 (12.3 %) NTC 108 / 1428 (7.6 %)</td>
<td>SSRIs vs NTC OR: 1.70 (1.28 - 2.24)</td>
</tr>
<tr>
<td>Dijus 2006 [l]</td>
<td>N = 312 Teratogen Information Services Toronto (Canada) Farmington (US) Jerusalem (Israel) Rome (Italy) Sydney (Australia) Southampton (UK)</td>
<td>Cohort</td>
<td>Mirtazapine During pregnancy</td>
<td>Telephone interview + Questionnaire + Sending a questionnaire to patient's physician</td>
<td>Maternal age (matched variable) Gestational age at the first contact (matched variable) Tobacco use (matched variable) Alcohol consumption (matched variable) Depression (matched variable) Chronic conditions (matched variable)</td>
<td>Mirtazapine 20 / 104 (19 %) Other antidepressants 18 / 104 (17 %) NTC 11 / 104 (11 %)</td>
<td>Mirtazapine vs other antidepressant p = 0.86 Mirtazapine vs NTC p = 0.12</td>
</tr>
<tr>
<td>Diav-Citrin 2008 [m]</td>
<td>N = 2276 Teratogen Information Services Jerusalem (Israel) Padua (Italy) Berlin (Germany)</td>
<td>Cohort</td>
<td>Paroxetine Fluoxetine Any trimester</td>
<td>Structured questionnaire + Telephone interview or mailed questionnaire</td>
<td>Gestational age at call Maternal age Smoking Previous spontaneous abortion Country Concomitant psychiatric medications</td>
<td>Paroxetine 42 / 463 (9.1 %) Fluoxetine 41 / 346 (11.8 %) NTC 97 / 1467 (6.6 %)</td>
<td>Fluoxetine vs NTC p = 0.05 Paroxetine vs NTC OR: 0.85 (0.52 - 1.40) Fluoxetine vs NTC OR: 1.27 (0.76 - 2.13)</td>
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<tr>
<td>Nakhai-Pour 2009 [n]</td>
<td>N = 56364 All pregnant women from Quebec covered by RAMQ drug plan</td>
<td>Nested case-control</td>
<td>Antidepressants Up to index date</td>
<td>Quebec Pregnancy Registry</td>
<td>Gestational age at index date Maternal age Urban dweller Welfare Diabetes mellitus Cardiovascular diseases Depression Duration of exposure Obstetrics history Health services utilization during pregnancy Co-morbidities during pregnancy</td>
<td>TCAs 45 / 248 (18.1 %) Fluoxetine 27 / 153 (17.6 %) Paroxetine 103 / 605 (17.0 %) Sertraline 33 / 215 (15.3 %) Citalopram 24 / 122 (19.7 %) Fluvoxamine 6 / 43 (18.6 %) Any SSRIs 192 / 1115 (17.2 %) Venlafaxine 43 / 196 (21.9 %) Other antidepressants 42 / 170 (24.7 %) Any antidepressant 284 / 1685 (16.9 %) No antidepressant 4840 / 54679 (8.9 %)</td>
<td>TCAs OR: 1.27 (0.85 - 1.91) Fluoxetine OR: 1.44 (0.86 - 2.43) Paroxetine OR: 1.75 (1.31 - 2.34) Sertraline OR: 1.33 (0.85 - 2.08) Citalopram OR: 1.55 (0.89 - 2.68) Fluvoxamine OR: 2.19 (0.79 - 6.08) Any SSRIs OR: 1.61 (1.28 - 2.04) Venlafaxine OR: 2.11 (1.34 - 3.30) Other antidepressant OR: 1.53 (0.86 - 2.72) Combination use OR: 3.51 (2.20 - 5.61) Any antidepressant OR: 1.68 (1.38 - 2.06)</td>
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<tr>
<td>Einarson 2009 [o]</td>
<td>N = 1874 Teratogen Information Services Toronto (Canada)</td>
<td>Cohort</td>
<td>Antidepressants Prior to pregnancy, through the first trimester</td>
<td>Telephone contact + Follow-up telephone interview</td>
<td>Maternal age. Gestational age at the first contact, smoking and alcohol use (matched variables)</td>
<td>Any antidepressant 122 / 937 (12.0 %) NTC 75 / 937 (8.0 %)</td>
<td>Antidepressant vs NTC RR: 1.63 (1.24 – 2.14) OR: 1.64 (1.21 – 2.23)</td>
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[i] = [23]; [j] = [20]; [k] = [35]; [l] = [24]; [m] = [38]; [n] = [25]; [o] = [26].
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<tr>
<th>Author</th>
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<th>Results after excluding therapeutic abortions: spontaneous abortions / deliveries</th>
<th>Crude OR and 95% CI calculated from available data</th>
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<tr>
<td>Pastuszak 1993</td>
<td>N = 330 Cohort Teratogen Information Services Toronto (Canada) Philadelphia, Camden and Salt Lake City (US)</td>
<td>Fluoxetine 19 / 117 (16.2 %) NTC 10 / 120 (8.3 %) AND Fluoxetine 10 / 68 (14.7 %) TCAs 9 / 69 (13.0 %) NTC 5 / 72 (6.9 %)</td>
<td>Fluoxetine vs TCAs 1.29 (0.55 - 3.04) Fluoxetine vs NTC 2.13 (0.95 - 4.81) TCAs vs NTC 1.65 (0.64 - 4.28) Older antidepressant vs NTC 1.95 (0.91 - 4.18)</td>
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<tr>
<td>Chambers 1996</td>
<td>N = 482 Cohort Teratogen Information Service California (US)</td>
<td>Fluoxetine 23 / 145 (15.9%) NTC 22 SA / 232 (9.5 %)</td>
<td>Fluoxetine vs NTC 1.80 (0.96 - 3.36)</td>
</tr>
<tr>
<td>McElhatton 1996</td>
<td>N = 689 Case series Teratogen Information Services France, Israel Italy, Germany Netherlands Spain, UK Switzerland</td>
<td>TCAs 38 / 282 (13.5 %) Fluoxetine 13 / 81 (16.0 %) Fluvoxamine 6 / 57 (10.5 %) Paroxetine 0 / 3 (0 %) Trazodone 0 / 10 (0 %) Total Non TCAs 19 / 151 (12.6 %) TOTAL 79 / 689 (11.5 %)</td>
<td>SSRIs vs TCAs 1.00 (0.55 - 1.81) Fluoxetine vs TCAs 1.22 (0.62 - 2.43)</td>
</tr>
<tr>
<td>Kulin 1998 [d]</td>
<td>N = 534 Cohort Teratogen Information Services Toronto and London (Canada) Philadelphia, Farmington, Salt Lake City, Tampa, Burlington, Chicago, Indianapolis (US)</td>
<td>SSRIs 30 / 252 (11.9 %) NTC 21 / 258 (8.1 %)</td>
<td>SSRIs vs NTC 1.53 (0.85 - 2.74)</td>
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<tr>
<td>Einarson 2001 [e]</td>
<td>N = 450 Cohort Teratogen Information Services Toronto and London (Canada) Farmington and San Diego (US) Rome and Milan (Italy) Porto Alegre (Brazil)</td>
<td>Venlafaxine 18 / 143 (12.6 %) SSRIs 16 / 140 (11.4 %) NTC 11 / 148 (7.4 %)</td>
<td>Venlafaxine vs SSRIs 1.12 (0.54 - 2.29) Venlafaxine vs NTC 2.21 (0.29 - 24.69) SSRIs vs NTC 1.60 (0.72 - 3.60) Newer antidepressants vs NTC 1.79 (0.82 - 3.95)</td>
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<tr>
<td>Einarson 2003 [f]</td>
<td>N = 441 Cohort Teratogen Information Services Toronto and London (Canada) Milan (Italy) Farmington, Detroit (US)</td>
<td>Trazodone-Nefazodone 20 / 141 (13.6 %) Other antidepressants 17 / 139 (11.6 %) NTC 12 / 144 (8.2 %)</td>
<td>Trazodone-Nefazodone vs other antidepressants 1.19 (0.59 - 2.37) Trazodone-Nefazodone vs NTC 1.82 (0.85 - 3.88) Other antidepressants vs NTC 1.53 (0.70 - 3.34) Any antidepressant vs NTC 1.67 (0.84 - 3.32)</td>
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<tr>
<td>Yaris 2004 [g]</td>
<td>N = 21 Case series Toxicology Information and Follow-up Turkey</td>
<td>Mirtazapine + other drugs 1 SA / 19 (5.3 %)</td>
<td>Any antidepressant vs NTC 3.57 (1.42 - 8.98)</td>
</tr>
<tr>
<td>Sivojelezova 2005 [h]</td>
<td>N = 396 Cohort Teratogen Information Services Toronto (Canada)</td>
<td>Citalopram 14 / 130 (10.8 %) Other SSRIs 13 / 129 (10.1 %) NTC 13 / 132 (9.8 %)</td>
<td>Citalopram vs other SSRIs 1.08 (0.49 - 2.39) Citalopram vs NTC 1.10 (0.50 - 2.45) Other SSRIs vs NTC 1.03 (0.46 - 2.31) All SSRIs vs NTC 1.07 (0.53 - 2.14)</td>
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<tr>
<td>Chun-Fai-Chan 2005 [i]</td>
<td>N = 358 Cohort Teratogen Information Services Toronto (Canada) Farmington (US) Drug Safety Research Unit Southampton (UK)</td>
<td>Bupropion for any indication 20 / 126 (15.9 %) NTC 6 / 132 (4.5 %) AND Bupropion for depression 14 / 86 (16.3 %) Other antidepressants 11 / 86 (12.8 %) NTC 6 / 132 (4.5 %)</td>
<td>Bupropion for any indication vs NTC 3.96 (1.54 - 10.23) Bupropion for depression vs other antidepressants 1.33 (0.56 - 3.11) Bupropion for depression vs NTC 4.08 (1.50 - 11.09) Other antidepressants vs NTC 3.08 (1.09 - 8.67) Any antidepressant vs NTC 3.57 (1.42 - 8.98)</td>
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[a] = [16]; [b] = [21]; [c] = [22]; [d] = [18]; [e] = [17]; [f] = [19]; [g] = [47]; [h] = [37]; [i] = [23].
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<tr>
<td>Hemels 2005</td>
<td>N = 3567</td>
<td>Any antidepressant 190 / 1440 (13.2 %)</td>
<td>TCAs vs NTC 1.60 (1.08 - 2.36)</td>
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<td>Méta-analyse</td>
<td>SSRIs 107 / 795 (13.5 %)</td>
<td>SSRIs vs TCAs 1.06 (0.73 - 1.53)</td>
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<td>TCAs 45 / 351 (12.8 %)</td>
<td>SSRIs vs NTC 1.69 (1.24 - 2.31)</td>
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<td>Trazodone - Nefazodone 20 / 151 (13.3 %)</td>
<td>Venlafaxine vs SSRIs 0.93 (0.54 - 1.58)</td>
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<tr>
<td></td>
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<td>Venlafaxine 18 / 143 (12.6 %)</td>
<td>Venlafaxine vs other antidepressants 0.94 (0.56 - 1.58)</td>
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<td></td>
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<td>NTC 76 / 902 (8.4 %)</td>
<td>Venlafaxine vs NTC 1.57 (0.91 - 2.70)</td>
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<tr>
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<td>Trazodone-Nefazodone vs other antidepressants 1.00 (061 - 1.65)</td>
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<td>Rahimi 2006</td>
<td>N = 2378</td>
<td>SSRIs 117 / 890 (13.2 %)</td>
<td>SSRIs vs NTC 1.79 (1.36 - 2.36)</td>
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<tr>
<td>Mét-a-analyse</td>
<td>Méta-analyse</td>
<td>NTC 108 / 1387 (7.8 %)</td>
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<td>Djulus 2006</td>
<td>N = 312</td>
<td>Mirtazapine 20 / 98 (20.4 %) Other antidepressants 18 / 101(17.8 %) NTC 11 / 103 (10.7 %)</td>
<td>Mirtazapine vs other antidepressants 1.18 (0.58 - 2.40)</td>
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<td>Mirtazapine vs NTC 2.14 (0.97 - 4.75)</td>
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<td>Other antidepressants vs NTC 1.81 (0.81 - 4.06)</td>
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<td>Farmington (US) Jerusalem (Israel) Rome (Italy) Sydney (Australia) Southampton (UK)</td>
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<td>Diav-Citrin</td>
<td>N = 2276</td>
<td>Fluoxetine 41 / 318 (12.9 %) Paroxetine 42 / 441 (9.5 %) NTC 97 / 1423 (6.8 %)</td>
<td>Fluoxetine vs NTC 2.02 (1.37 - 2.98)</td>
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<td>2008</td>
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<td>Paroxetine vs NTC 1.44 (0.99 - 2.10)</td>
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<td>TCAs 1.27 (0.85 - 1.91) Fluoxetine 1.44 (0.86 - 2.43) Paroxetine 1.75 (1.31 - 2.34) Sertraline 1.33 (0.85 - 2.08) Citalopram 1.55 (0.89 - 2.68) Fluvoxamine 2.19 (0.79 - 6.08) Any SSRIs 1.61 (1.28 - 2.04) Venlafaxine 2.11 (1.34 - 3.30) Other antidepressants 1.53 (0.86 - 2.72) Combination use 3.51 (2.20 - 5.61) Any antidepressant 1.68 (1.38 - 2.06)</td>
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<td>2009</td>
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<td>Einarson 2009</td>
<td>N = 1874</td>
<td>Any antidepressant 122 / 911 (13.4 %) NTC 75 / 929 (8.1 %)</td>
<td>Any antidepressant vs NTC 1.76 (1.30 – 2.38)</td>
</tr>
</tbody>
</table>
| [j] = [20]; [k] = [35]; [l] = [24]; [m] = [38]; [n] = [25]; [o] = [26].


Abbreviations

5-HT = 5-hydroxytryptamine
CI = confidence interval
FDA = Food and Drug Administration
MAOIs = monoamine oxidase inhibitors
NTC = nonteratogenic controls
OR = odds ratio
RR = risk ratio
SNRIs = serotonin-norepinephrine reuptake inhibitors
SSRIs = selective serotonin reuptake inhibitors
TCAs = tricyclics antidepressants
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