

# Antidepressants in Pregnancy and Autism Spectrum Disorder: A Systematic Review

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## Abstract

**Purpose:** To determine the risk of autism spectrum disorder (ASD) in children following antidepressant use in pregnancy.

**Methods:** A systematic review using the CAPES platform for the January 2005 to May 2015 period. The descriptors used were (antidepressant) and (pregnancy) and (autism). Articles were selected based on pre-established inclusion/exclusion criteria, with quality evaluated using the STROBE checklist.

**Results:** Six articles were evaluated, with five favoring some form of association between antidepressant use in pregnancy and ASD in the child. In one paper, this association was found only with boys, while another identified the risk in children exposed to maternal depressive symptoms with no use of selective serotonin reuptake inhibitors.

**Conclusion:** Results show that in addition to the multiple factors linked to antidepressant use in pregnancy and child development, factors other than drug exposure may play a role in the development of ASD. Further studies are required to clarify this issue.

**Keywords:** Depression; Pregnancy; Stress; Psychiatric; Autism

## Introduction

The use of antidepressants in pregnancy has become increasingly common in clinical practice as a result of the prevalence of the conditions for which this treatment is indicated. These include major depressive disorder, generalized anxiety disorder, panic disorder, premenstrual dysphoric disorder, post-traumatic stress disorder, social anxiety disorder and migraine prophylaxis. In a study conducted in the United States, treatment with antidepressants in pregnancy was found to have increased 5.6% between 1996 and the 2004-2005 period [1].

Depression affects around 20% of pregnant women in developing countries and around 15% in industrialized nations [2,3]. Alterations resulting from this disease are debilitating [4] and involve risks to maternal and fetal health [3]. On the other hand, the use of psychiatric drugs in pregnancy has been questioned from a safety point of view, since antidepressants are known to be able to cross the placental barrier; [5] hence, it is assumed that their use could result in alterations in the development of the fetal brain. Studies have associated this treatment with the occurrence of congenital abnormalities, abstinence syndrome, pulmonary hypertension, [6] behavioral changes after birth and possible long-term alterations throughout the child's life [7]. Based on this information, there is a clear need for scientific evidence on the effects of these drugs during this cycle of a woman's life.

Data have led to speculation regarding a connection between the use of antidepressants in pregnancy and the development of autism spectrum disorder (ASD) in the child [8]. Selective serotonin reuptake inhibitors (SSRIs) represent a class of psychiatric drugs that merit attention in this respect, since they are the most commonly prescribed drugs, precisely because of their specificity and consequent fewer side effects [4].

Bearing in mind the previously mentioned increase in the use of antidepressants in pregnancy, the current rise in the incidence of ASD corroborates strongly with this hypothesis. Nevertheless, numerous

confounding factors still prevent any categorical affirmation from being made with respect to an increase in the prevalence of this disorder, and hamper the precise establishment of the factors associated with it. In this regard, various hypotheses have been put forward to justify the increasing number of cases of ASD, including modifications made to the diagnostic criteria, which used to be more restricted, and the fact that these criteria have become more widely known and applied, possibly resulting in the occurrence of false-positive diagnoses. The increasing availability of information regarding ASD may also contribute towards explaining the changes in the epidemiology of this disorder, since new data have resulted in the inclusion of different spectrums and in the understanding that ASD is associated with various morbidities, which may also result in an erroneous diagnosis [9]. The genetic component also represents an important confounding factor, since the need for antidepressants in pregnancy is associated with a primary cause that, in general, concerns maternal affective disorders, thus leading to difficulties in defining the effect generated by the action of the drugs used and that of the underlying cause of the use of these drugs.

The lack of conclusive studies, both on the possible consequences of antidepressant use in pregnancy [7,10,11] and on the increased prevalence of ASD [9], highlights the importance of investigating aspects related to these subjects, as well as a possible association between them.

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Various different studies have been published in the literature, some favoring an association between the use of these drugs and the development of autism in the exposed infant, and others not. These results emphasize the importance of investigating the consistency of the data, and highlight the gap that exists in currently available knowledge. The need for a systematic review on this issue is clear, since an analysis of the results obtained and the level of evidence attained in each relevant study would ultimately contribute towards improving current understanding.

The objective of the present study was to review the currently available literature on the subject and to investigate whether there is sufficient evidence supporting an association between the use of antidepressants in pregnancy and the development of ASD in the exposed child.

## Methods

The CAPES platform was initially used to conduct the literature review for the study, followed by searches of the Web of Science; MEDLINE/PubMed; Directory of Open Access Journals (DOAJ); ScienceDirect (Elsevier BV); SpringerLink; Science & Business Media BV; Gale Academic OneFile; Karger; Oxford Journals; SAGE (Journals online); Annual Reviews; Social Services Abstracts (ProQuest); Pollution Abstracts; Engineering Research Database; Hindawi Journals; PLoS; ERIC (U.S. Dept. of Education); Nature Publishing Group (CrossRef) and Future Science Medicine. Since this subject is relatively recent, the study focused on publications from the past ten years; hence the search was limited to the period between January 1, 2005 and January 1, 2015. In view of the scarcity of studies published in the Portuguese language, the search was limited to articles in English. The descriptors used were: (antidepressant), (pregnancy), (autism) and their combinations using the Boolean operator "AND".

The inclusion criteria established for the study were: studies conducted with humans, involving pregnant women and the use of antidepressants. The exclusion criteria consisted of: studies that did not deal with the correlation between the use of antidepressants in pregnancy and ASD, review articles and studies not written in English.

The quality of the papers selected for the review was analyzed using the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) checklist. Two separate independent investigators conducted the evaluations at each stage of the study, with any divergences being resolved by consensus.

## Results

A total of 70 studies were identified in the literature review. The titles and abstracts of these papers were analyzed and 64 studies were then eliminated because they did not fulfill the required criteria, as follows: 1) exclusion based on the subject matter; 2) exclusion based on the type of study; 3) exclusion because of file repetition; 4) exclusion based on accessibility. These categories encompassed, respectively, studies that did not focus on the correlation between the use of antidepressants in pregnancy and ASD; studies that were not case-control or cohort studies and/or studies not conducted with human beings; studies published in more than one journal and for this reason appearing repeatedly; and studies that were inaccessible. Consequently, 6 studies were approved for analysis of their entire contents, with all of these going on to be included in the final selection (Figure 1).

The sample sizes included in the studies ranged from 966 to 668,468 and the mean score according to the STROBE checklist was 16.5. No

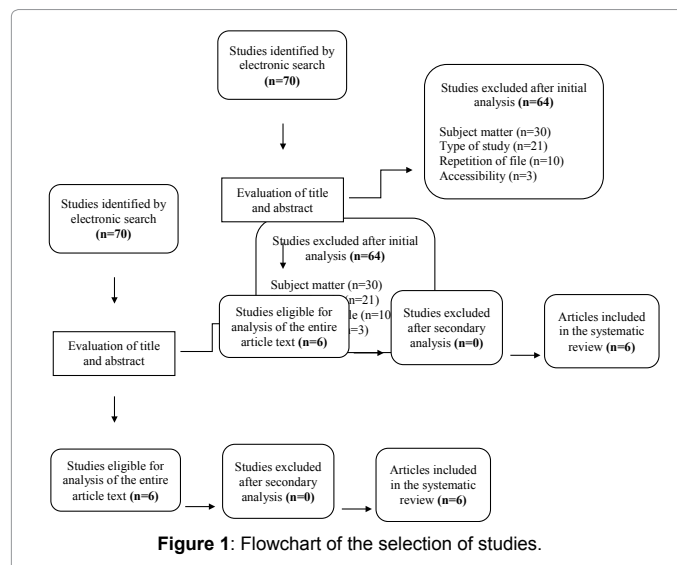


Figure 1: Flowchart of the selection of studies.

particular type of study predominated among the articles analyzed, with three cohort studies and three case-control studies being included (Table 1) [12-17].

The studies that fit the criteria for analysis were up-to-date, with all having been published between 2011 and 2014 despite the fact that the literature search encompassed a 10-year period. The lack of any Brazilian studies linking the use of antidepressants in pregnancy to ASD was also noteworthy.

This systematic analysis highlighted the predominance of studies in which a positive association was found between the use of antidepressants by pregnant women and the development of ASD in the exposed child. Of the six articles evaluated, five defended the existence of some form of association; nevertheless, based on the data obtained (Table 2), [12-17] it is clear that, despite the causal association found in most of the studies, the risk identified was low in all cases, with the unadjusted odds ratio (OR) reaching a maximum of 2.3.

## Discussion

The results of this study show an increased risk of ASD with the use of antidepressants in pregnancy. These data are compatible with data from meta-analyses conducted by Man et al. [18] and by Rais and Rais [19] whose results point to an increased risk of ASD in children exposed, respectively, to SSRIs and to antidepressants in general during pregnancy.

Nevertheless, although more articles were found that defended some degree of correlation between ASD and the use of antidepressants, it should also be emphasized that in one paper this risk was identified only in boys, [15] and in another, the risk was also found when the child had been exposed to maternal symptoms of depression but SSRIs were not used [14]. Furthermore, Sørensen et al. [12] concluded that following adjustment for important confounding factors, the association found between the use of drugs and the occurrence of ASD in their study was not significant. These data show that among the many factors involving the use of antidepressants in pregnancy and the child's consequent development, others, in addition to exposure to the drug, may exert an effect on the occurrence of ASD.

Indeed, Sørensen et al. [12] analyzed children exposed to antidepressants in pregnancy and reported an increased risk of

Author	Type of Study	Sample (n)	STROBE	Association between AD and ASD
Sørensen et al. [12]	Retrospective cohort	6,68,468	15	Yes
Gidaya et al. [13]	Case-control	6,28,408	16	Yes
El Marroun et al. [14]	Prospective cohort	5,976	18	Yes
Harrington et al. [15]	Case-control	966	15	Yes
Hviid et al. [16]	Retrospective cohort	6,26,875	19	No
Croen et al. [17]	Case-control	1,805	16	Yes

**Table 1:** Characteristics of the studies included, according to sample size, STROBE classification and suggestion of some form of association between antidepressant (AD) use in pregnancy and the development of autism spectrum disorder (ASD).

Author	Drug evaluated	Sample Size (n)	ASD Cases	Control	Evaluation of statistical significance (*HR/ OR/ RR)	
					Unadjusted	Adjusted
Sørensen et al. [12]	Antidepressants	8,833	104		1.8 (1.5–2.2)	1.5 (1.2–1.9)
	**SSRIs	7,506	91		1.9 (1.5–2.4)	1.6 (1.3–2.0)
	**SNRIs	673	7		1.9 (0.9–4.0)	1.7 (0.8–3.5)
	**TCAs	642	9		1.8 (0.95–3.5)	1.5 (0.8–2.9)
	Unexposed	6,46,782	5,333			
Gidaya et al. [13]	SSRIs		76	365	2.2 (1.6–2.7)	2.0 (1.6–2.6)
						1.9 (1.5–2.5)
						1.8 (1.4–2.3)
						(3 models)
El Marroun et al. [14]	SSRIs	69	50			2.58 (1.46–4.54)
	Unexposed	5,531	3,992			1.91 (1.13–3.47)
						(2 models)
Harrington et al. [15]	SSRIs		29 (n=492)	11 (n=320)	1.52(0.65–3.53)	1.55 (0.59–4.08)
Hviid et al. [16]	SSRIs	42,400	52		1.62(1.23–2.13)	1.20 (0.90–1.61)
Croen et al. [17]	Antidepressants		20	50	2.1 (1.2-3.6)	2.0 (1.2-3.6)
	SSRIs		15	34	2.3 (1.2-4.3)	2.2 (1.2-4.3)
	SNRIs and/or TCAs		5	16	1.6 (0.6-4.5)	1.6 (0.5-4.5)
	Unexposed		278	1457		

**Table 2:** Systematization of the results identified on the association between antidepressant use in pregnancy and autism spectrum disorders (ASD).

developing ASD compared to unexposed children, with a hazard ratio (HR) of 1.5 (95%CI: 1.2–1.9). Nevertheless, after evaluation using different models and taking into consideration the confounding factors “maternal affective disorder” and “risk of ASD in siblings not exposed to antidepressants”, the values found were not significant: HR=1.2 (95%CI: 0.7–2.1) and HR=1.1 (95%CI: 0.5–2.3), respectively. Those authors reported a statistically significant association only when the use of SSRIs alone was compared to non-use (HR=1.3; 95%CI: 1.0–1.6). However, when this analysis was limited to the children of parents with an affective disorder the risk was not significant. Likewise, Hviid et al. [16] analyzed the use of SSRIs and reported a relative risk (RR) of 1.62 (95%CI: 1.23–2.13). Following adjustment for age and the duration of the follow-up period, these investigators obtained results that were similar to those reported by Sørensen et al. [12] with an RR of 1.64 (95%CI: 1.25–2.16); however, following adjustment for maternal age at birth, psychiatric diagnoses prior to delivery, use of other drugs during pregnancy and other relevant factors including socioeconomic aspects, no causal association was found, with an RR of 1.20 (95%CI: 0.90–1.61).

Evaluating the entire period of pregnancy, Croen et al. [17] reported an odds ratio (OR) following adjustments of 2.0 (95%CI: 1.2–3.6) for the use of any antidepressant during pregnancy. Gidaya et al. [13] reported an OR of 2.0 (1.6–2.6) following adjustment for the parents’ age and the sex of the child and OR of 1.9 (1.5–2.5) and 1.8 (1.4–2.3) following adjustment for these variables and also for maternal depression and an indication for the use of SSRIs, respectively.

El Marroun et al. [14] reported a higher risk of the overall occurrence

of general developmental delays in children exposed to SSRIs prenatally (OR=2.58; 95%CI: 1.48–4.54). However, prenatal exposure to maternal depressive symptoms was also associated with developmental disorders, even without the use of SSRIs (OR=2.02; 95%CI: 1.53–2.66). In a second model, El Marroun et al. [14] adjusted for the presence of postnatal depressive symptoms over a three-year period, obtaining an OR of 1.91 (95%CI: 1.13–3.47). The importance of the familial component as a possible contributing factor in the occurrence of ASD was clear, particularly considering that the use of antidepressants in pregnancy occurs in the presence of a maternal affective disorder, which could represent a genetic influence for neurodevelopment alterations in the child.

Croen et al. [17] analyzed risks by gestational trimester and identified an increased risk of ASD in children whose mothers had used SSRIs, particularly during the first trimester of pregnancy. In support of these data, Harrington et al. [15] reported an odds ratio of 3.22 (1.17–8.84) when SSRIs were used during the first trimester compared to 2.25 (0.54–9.42) and 2.91 (0.76–11.0) in the second and third trimesters, respectively. These, however, were the adjusted rates in boys and no statistically significant values were found when girls and boys were evaluated together, with an OR of 1.55 (95%CI: 0.59–4.08) during pregnancy, an OR of 1.38 (95%CI: 0.48–4.01) in the first trimester, an OR of 0.89 (95%CI: 0.24–3.24) in the second trimester and an OR of 1.18 (95%CI: 0.35–4.02) in the third trimester.

Psychiatrists, professionals working with mental health and pediatricians should be aware of the possibility of an increased risk of ASD in children who were exposed to antidepressants during pregnancy.

Prenatal exposure to maternal depressive symptoms, without the use of SSRIs, was also associated with developmental alterations in some studies; therefore, being attentive to depressive states during pregnancy is important, not only for mental health professionals but also for obstetricians. Clearly, health professionals should not neglect mood disorders in pregnant women, even when symptoms are mild.

In view of the importance of these data, further studies need to be conducted to clarify this important gap in currently available knowledge. The need for antidepressants during pregnancy should be weighed up carefully and discussed openly with the pregnant woman. Mild depressive episodes or mild states of anxiety could perhaps be treated with psychotherapy and strict psychiatric monitoring to decide the best moment at which to introduce antidepressants.

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#### Conflict of Interest

The authors declare that there are no conflicts of interest associated with this study.

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