Prenatal Exposure to SSRI Antidepressants and the Risk of Autism Spectrum Disorder (ASD) in Children

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Abstract

Background: Selective Serotonin Reuptake Inhibitors (SSRI) are the most commonly prescribed antidepressant and are continuously used during pregnancy. Some studies reported an increased risk of neurodevelopmental delays such as autism spectrum disorder (ASD) in children who have been exposed to SSRIs during pregnancy. Multiple findings of elevated platelet serotonin levels in roughly one third of children with ASD have lead many to believe that impaired serotonin levels may be associated to the disorder. Since serotonin is crucial for development in the fetal brain, there exists many concerns regarding prenatal exposure to medications such as SSRIs.
Objective: This study aims to examine the association between maternal use of SSRIs during pregnancy and the development of ASD in the offspring.
Methods: A structured literature review was conducted through PubMed and Medline databases. Relevant articles were retrieved using the keywords "antidepressants OR SSRIs OR selective serotonin reuptake inhibitors", "autism spectrum disorder OR ASD", and "pregnancy". Selected articles were peer-reviewed and published in English within the last 17 years.
Results: The original search using these keywords identified 577 relevant reports which were screened against the exclusion criteria and reviewed to obtain 9 relevant articles.
Conclusion: The evidence supports the possibility of an increase of the risk of ASD in children with mothers exposed to SSRIs, however, the observed results may be subject to confounding by indication and the severity of the mental illness. Further studies are needed to determine causality.

Introduction

According to the centre for disease control and prevention (CDC) 1 in 68 children have been identified with a form of ASD[1]. Autism spectrum disorder includes a group of developmental disorders with a wide range of symptoms, skills, and levels of disabilities[1]. The severity of the condition varies from individual with mild impairments, while others are severely disabled. Individuals with ASD often display ongoing social problems such as difficulties with communicating and interacting with others, symptoms that hurt their ability to function socially at work or at school, as well as repetitive behaviours[1]. Although the specific cause of ASD is unknown many studies have found that the development of the disorder seems to rely on the interaction of genetic, environmental, and biological factors[2]. It has also been found that children diagnosed with autism have impaired levels of serotonin. Elevated whole blood serotonin, or hyperserotonemia, was the first biomarker identified in ASD and is present in more than 25% of affected children[3]. Serotonin, also known as the "happiness hormone" is the target of the most prescribed antidepressant drugs during pregnancy, Selective Serotonin Reuptake Inhibitors (SSRIs) [4]. The use of SSRI's during pregnancy may modify serotonergic metabolism in the developing embryo and fetus.
Pregnancy is a period of high vulnerability to depression; it's the most prevalent psychiatric disorder during pregnancy[4]. Up to now, antidepressants are considered safe to use in the treatment of depression in pregnant women. However, since serotonin plays an important role in embryonic development, especially of the nervous system, it is of importance to explore the association between prenatal intake of SSRI's and the development of neurodevelopmental delays such as ASD in the offspring.

Figure 1. Different types of ASD

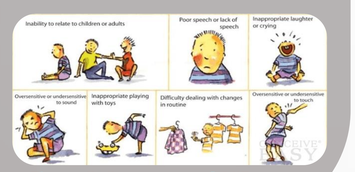

Figure 2. Symptoms of ASD

Research Question

Is the maternal prenatal intake of SSRIs associated with an increased risk of ASD in children?

Methods

PubMED and Medline search with keywords: "antidepressants OR SSRIs OR selective serotonin reuptake inhibitors", "autism spectrum disorder OR ASD", and "pregnancy".

N = 577 articles found originally → N = 33 abstract reviewed → N = 25 study methods reviewed → N = 9 articles used for this study

Inclusion criteria:
- English
- Peer reviewed
- After 2013

Exclusion criteria:
- No mention of keywords in title
- Before 2014
- Non-English
- Duplicates
- No abstract
- Full text not available
- No mention of SSRIs
- No relevance to research question
- Expert opinions/no method provided
- No statistical analysis
- Animal studies

Figure 1. Flow-chart demonstrating the methodology process used to select studies for our structured literature review.

Results

Table 1. Summary of findings of structured literature review examining the association between exposure of SSRI during pregnancy and ASD development in offspring.

Author and year	Population		Methods	Major relevant findings	Association
	Demographic	n			
Sujan et al. 2017	Sweden	1 580 629 offspring born to 943 776 mothers	**Study design:** Retrospective cohort study **Exposure**: SSRIs **Covariates:** Parity; country of birth; age at childbearing; level of education; history of criminal conviction; MH[1] history	5.28% exposed vs 2.14% unexposed diagnosed with ASD by age 15	N
Brown et al. 2017	Ontario	35 906 singleton births at a mean gestational age of 38.7 weeks	**Study design**: Retrospective cohort study **Exposure**: SSRIs **Covariates**: Maternal age; parity; neighborhood income quintile; rural residence; medical and psychiatric diagnoses; health service use before and during pregnancy; use of other prescribed medications; prenatal care; child sex; gestational age at birth	- Incidence of ASD was 4.51 per 100 person-years among children exposed vs 2.03 per 1000 person-years among unexposed	N
Malm et al. 2016	National register data in Finland	15 729 exposed to SSRIs; 9 651 unexposed to SSRIs, with psychiatric disorder; 31 394 unexposed	**Study design**: Cohort study **Exposure**: SSRI **Covariates**: Maternal age; place of residence; marital status; SES[2]; parity; mother's native country;	- Rates of ASD diagnoses in SSRI exposed group were comparable to rates in offspring of mothers with a psychiatric disorder unexposed to SSRIs	N
Viktorin et al. 2017	Sweden	179 007 parents with child born in 2006-2007	**Study design**: Cohort study **Exposure** : SSRIs, non-SSRI antidepressant psychotropic drugs **Covariates**: parental age; MH[1] history; fathers medication; mother's dispensations of psychotropic drugs	- Only certain SSRIs displayed an increased risk of ASD in offspring (RR[3]: 1.71)	N
Rai et al. 2017	Stockholm County, Sweden	254 610 individuals aged 4-17	**Study design**: Observational prospective cohort study **Exposure**: SSRIs, and other antidepressants **Covariates**: psychiatric indications for ADs[4]; parental age at birth of child; family income; mother's birth place; maternal smoking status; BMI; number of diagnoses of maternal depression; MH[1] history	- Exposure to ADs[4] during was associated with higher odds of ASD diagnosis than exposure to a maternal psychiatric disorder without ADs[4] (aOR[5]: 1.45, 95% CI[6])	N
Boukhris et al. 2016	Quebec	145 456 Singleton infants	**Study design:** Register-based study **Exposure:** SSRIs, tricyclic ADs[4], monoamine oxidase inhibitors, serotonin norepinephrine reuptake inhibitors, and other ADs[4] **Covariates**: Maternal sociodemographic characteristics; history of maternal psychiatric and chronic physical conditions; infant characteristics	- Use of SSRIs only during the was significantly associated with an increased risk of ASD (aHR[7]: 2.17; 95% CI[6]) even after considering maternal depression	Y
Kaplan et al. 2017	Denmark; Netherlands; Canada	4 cohort studies	**Study design**: Meta-analysis **Exposure**: SSRIs **Meta-analytic methods**: Q and I^2 ;	- Significant association between SSRI exposure and risk of ASD (aHR[7]: 1.61; 95% CI[6]), insignificant heterogeneity - Both SSRI exposure and maternal psychiatric disorder were associated with ASD	Y
Gidaya et al. 2014	Denmark	5 215 cases; 52 150 controls	**Study design:** Population based case-control study **Exposure**: SSRIs at preconception & during pregnancy **Covariates** Parental age; psychiatric history; gestational age; birth weight; parental history of AI disease; number of live births; obstretic complications; SES[2]; psychiatric conditions treated with SSRIs	- aOR[5] of ASD for any SSRI use during pregnancy was 2.0 (95% CI[6]) - Simulation based-approach to account for confounding by indication resulted in the observation that an independent effect of SSRI usage on ASD is possible	Y
Harrington et. 2014	Children 2-5 years old born in California	492 ASD cases; 145 DD[8] cases; 320 controls	**Study design**: Case-control study **Exposure:** SSRIs **Covariates**: Child gender; child's birth year; regional center; mother's birth place; maternal mental illnesses	- In boys, prenatal SSRI exposure was nearly 3 times as likely in children with ASD (aOR[5]: 2.91; 95% CI[6])	Y

Abbreviations: [1]**MH**: Mental Health; [2]**SES**: Socioeconomic status; [3]**RR**: Rate Ratio; [4]**Ads**: Antidepressants; [5]**aOR**: Adjusted Odds Ratio; [6]**CI**: Confidence Interval; [7]**aHR**: Adjusted Hazard Ratio; [8]**DD:** Developmental Delay

Discussion

Key Findings

- 5 studies indicate no association that supports the possibility of an increase of the risk of ASD in children with mothers exposed to SSRIs, while 4 studies showed an association
- The use of antidepressants such as SSRI during 2nd and 3rd trimester was statistically associated with an increased risk of ASD in some of the studies
- After confounder adjustment, SSRIs exposure and association to ASD was not significant in studies indicating no association
- The studies revealing no associations suggest that any risk associated with the use of SSRIs during pregnancy may be related to the indications for their use rather than an effect of these drugs

Limitations of our methods

- Limited to Pubmed and Medline
- Limited to English → Exclusion Bias
- Limited to studies accessible through the University of Ottawa's subscribed journals

Limitations within studies

- Limited to human studies mentioning SSRIs and no other types of antidepressants
- Lack of access of the severity of depression during pregnancy and physical health, genetic predispositions for ASD, as well as insufficient control for maternal mental health → Recall Bias
- Discontinuation of antidepressants before and after pregnancy, including self-report and medical records, were not generated in most studies, nor the analogy of different antidepressant treatment regimens.
- Limited to Northern European countries

Overall, we are not surprised by the inconsistency within the results since:
1) The severity of depression and individual differences between mothers (context) during pregnancy varies
2) The etiology of this disorder is not well understood, it is therefore understandable that the results aren't conclusive

Future Research

- Conduct more studies in different countries to get more representative data
- Mother's physical Health should be taken into consideration to determine possible risk in offspring
- Future research should have larger samples and follow children all the way up to their late teens
- Studies should consider physical environmental factors
- More research is needed to determine the biological gradient of the exposure and the outcome

Conclusion

Since results remain inconclusive, no legitimate association between maternal prenatal intake of SSRIs in the development of ASD in the offspring can be established. Therefore, further research must be conducted to determine causality.

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