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Prenatal selective serotonin reuptake inhibitor use and the risk of autism spectrum disorder in children: A systematic review and meta-analysis

Yusuf C. Kaplan (M.D.) (Associate Professor of Pharmacology)[a,b,*], Elif Keskin-Arslan (M.D.)[a,b], Selin Acar[a,b], Kaan Sozmen (M.D.)[c]

[a] Terafar – Izmir Katip Celebi University Teratology Information, Training and Research Center, Izmir, Turkey
[b] Izmir Katip Celebi University School of Medicine, Department of Pharmacology Izmir, Turkey
[c] Izmir Katip Celebi University School of Medicine, Department of Public Health, Izmir, Turkey

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ABSTRACT

Objective: To determine whether an up-to-date systematic review and meta-analysis of observational studies would support the previously suggested associations regarding prenatal selective serotonin reuptake inhibitor (SSRI) use and the risk for autism spectrum disorders (ASD) in children.
Methods: PubMed/MEDLINE, Cochrane Central Register of Controlled Trials and Reprotox databases were searched; observational studies with an exposed and unexposed group were included.
Results: The meta-analysis of case-control studies demonstrated a significantly increased risk of ASD in the children whose mothers were prenatally exposed to SSRIs during different exposure time windows (except third trimester). The qualitative review of the cohort studies suggested inconsistent findings.
Conclusions: The significant association between preconception-only SSRI exposure and ASD in the children and negative/inconsistent findings among cohort studies weaken the significant associations detected in this meta-analysis. We suggest that confounding by indication still cannot be ruled out regarding prenatal SSRI exposure and ASD in children.

1. Introduction

Depression during pregnancy and post-partum period is a significant public health problem which may lead to detrimental effects on maternal, fetal, child and even adolescent health [1–3]. Untreated maternal depression was shown to be associated with various adverse pregnancy outcomes such as preeclampsia [4], preterm delivery [5], low birth weight [4,5], increased rates of admissions to neonatal intensive care unit and post-partum depression [6]. A recent study from U.S. reported the rates of minor and major depression in pregnant women as 16.6% and 6.1%, respectively [7] and similar rates [7.4%–12.0%] were reported in a previous systematic review [8]. The most frequently used antidepressants in pregnant women are selective serotonin re-uptake inhibitors [SSRIs], of which use has been reported in 3.3–4.5% of pregnant women in Europe [9,10] and 3.8–0% in North America, respectively [11–13]. Prevalence estimates of depression and SSRI use during pregnancy, however, are reported to vary widely between studies depending on geographical, cultural factors and sampling and assessment methods [7,9,11].

The possible adverse effects of SSRIs on pregnancy and infant outcomes has been a field of debate in the last decade. Some studies suggest significant associations between the use of SSRIs during pregnancy and spontaneous abortions [14], postpartum hemorrhage [15], preterm birth [16], persistent pulmonary hypertension of newborn [17], major congenital and cardiac malformations [18] while others found no associations implicating a possible confounding by indication [19–25]. Stronger associations, however, were suggested regarding transient Poor Neonatal Adaptation Syndrome [PNAS], which has been shown to occur in up to one-third of infants whose mothers had used SSRIs during pregnancy [25–27].

Controversies also exist regarding the possible adverse effects of SSRIs on different domains of infant and child neurodevelopment, except cognition [28–32]. The reported significant associations between prenatal SSRI use with lower scores on psychomotor development [33–35], socio-emotional and adaptive behavior [35],

* Corresponding author at: Izmir Katip Celebi Universitesi Ataturk Egitim ve Arastirma Hastanesi, Klinik Farmakoloji ve Toksikoloji Birimi, 35360, Karabaglar, Izmir, Turkiye.
E-mail address: seawise@gmail.com (Y.C. Kaplan).

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anxiety symptoms [36] and attention-deficit hyperactivity disorder [ADHD] [37] in infants and children are not confirmed in some other studies [28–31,38–41].

Previous and emerging preclinical data indicate that the dysregulation of the serotonergic system with genetic or pharmacological (SSRIs) interventions may lead to the neurochemical or behavioral findings of autism spectrum disorder (ASD) in the offspring [42,43]. Earlier reports regarding significant elevations of blood serotonin levels, or hyperserotonemia, in autistic patients [44–46] was confirmed in a recent meta-analysis [47]. As a result, the possible association between prenatal SSRI exposure and ASD became an increasing focus of clinical research recently as indicated by the publication of six case-control [37,48–52], four cohort studies [53–56] and two meta-analyses [57,58] from January 2010 to December 2015. Three of the case-control [48,49,51] and three of the cohort studies [54–56] suggested a significant association, respectively. Two recent meta-analyses [57,58] detected a significant association between prenatal SSRI use and ASD in children while the significance in the latter was reported to be lost after restricting the analysis to the mothers with psychiatric disorders [58].

The objective of this study was to assess whether an updated systematic review and meta-analysis, involving the recently published observational studies [37,56], would support or reject the previously suggested association between prenatal SSRI exposure and risk of ASD in children We also sought to analyze whether the significance, if any, would change with regard to the different prenatal exposure time windows and non-SSRI antidepressants.

2. Methods

2.1. Search strategy

Searches were conducted in PubMed/MEDLINE, Cochrane Central Register of Controlled Trials and Reprotox databases from inception to December 26th 2015 using the search terms (serotonin uptake inhibitors OR SSRI OR antidepressive agents OR antidepressants OR antidepressant drugs) AND (pregnancy) AND (autism OR autistic disorder OR pervasive child development disorders OR asperger syndrome OR rett syndrome) by the authors. No language or date restrictions were applied. We also searched manually through the reference list of the previous meta-analysis, systematic reviews and the studies included in this meta-analysis for any additional eligible studies. Corresponding authors of all the cohort and case-control studies were contacted about the additional information or other relevant questions. The flow chart was prepared in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [59] and was presented in Fig. 1. We adhered to Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guideline [60] while reporting our findings.

2.2. Inclusion and exclusion criteria

Observational cohort and case-control studies investigating the link between prenatal exposure to SSRIs and ASD were included in this meta-analysis. A study was considered eligible if it met the following criteria: (1) Exposure to SSRIs during pregnancy was reported either as main or subgroup analysis. (2) A control (unexposed) group was included. (3) Either an odds ratio (OR), risk ratio (RR) or hazard ratio (HR) was reported. (4) The data reported were not overlapping with another study. If an overlap between two studies was detected, the most recent one was included; ensuring that both had similar methodological qualities. (5) Study sample size larger than ten. The exclusion criteria were case reports and series, animal studies, editorials and reviews.

2.3. Quality assessment

The Newcastle-Ottawa scale [61] was used for quality assessment of the study methodologies.

2.4. Outcome measures

The main outcome of interest for this meta-analysis was ASD.

2.5. Data extraction

Two authors (EK-A and SA) independently reviewed the studies. The data were extracted by using a standardized data extraction form and presented in Tables 1 and 2. Any disagreements were resolved by discussion and consulting with another author (YCK).

2.6. Meta-analytic methods

Adjusted estimates were extracted from eligible case-control studies. Some of the studies used different models for the adjustment of confounders and calculated different ORs accordingly. We carefully evaluated each model in the particular study and extracted the ORs relating to the models which cover similar covariates. For Croen et al.,[48] Gidaya et al., [51] and Clements et al., [37] we used the adjusted ORs for Model 2 and for Rai et al. [50] and Harrington et al., [52] we extracted the single adjusted OR reported, respectively. The log odds ratios (log [OR]) and standard errors (SE) were combined using generic inverse variance method and random-effects model in RevMan 5.3 (Review Manager 5.3; Cochrane Collaboration, Oxford, UK) [62]. Heterogeneity was assessed utilizing the Q and I-square statistic. An I-square value between 25%-50% signified low heterogeneity, between 50%- 75% moderate and >75% signified high heterogeneity [63]. A funnel plot was not utilized to assess publication bias since it is suggested to have low power for detecting asymmetry with good accuracy if the number of included studies is below ten [64].

3. Results

Six case-control [37,48–52] and four cohort studies [52–56] were identified as eligible. However, we were unable to undertake a meta-analysis of cohort studies since the outcome reporting with regard to the exposure time windows were not uniform. For instance, Hviid et al. [53] and Marroun et al. [55] reported rate (RR) and odds ratios (OR) of ASD risk in children whose mothers were exposed to SSRIs for two exposure time windows; anytime during pregnancy and the first trimester. Sorensen et al. [54] reported ORs of ASD risk in children whose mothers exposed to antidepressants or SSRIs for anytime during pregnancy, the first, second and third trimester. Boukhris et al. [56] reported hazard ratios (HRs) for ASD risk in children prenatally exposed to antidepressants (not SSRIs) during the first trimester while they reported HRs for both antidepressants and SSRI exposures during the second and/or third trimester. Moreover, the data from the two Danish cohorts, Hviid et al. [53] and Sorensen et al. [54] were largely overlapping.

All corresponding authors of cohort studies [53–56] were contacted in order to retrieve the unpublished data. Three of them replied [50,54,55], however, none were able to provide any data which would enable us to conduct a meta-analysis. Therefore we decided to progress with a qualitative review of cohort studies.

3.1. Case-control studies

Three of the eligible case-control studies were from the U.S. [37,48,52] two from Sweden [49,50] and one from Denmark, respectively. [51] The number of cohorts from which the cases were