Neuroscience and Biobehavioral Reviews 49 (2015) 82–89

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Exposure to selective serotonin reuptake inhibitors during pregnancy and risk of autism spectrum disorder in children: A systematic review and meta-analysis of observational studies

Kenneth K.C. Man[a], Henry H.Y. Tong[b,a], Lisa Y.L. Wong[a], Esther W. Chan[a], Emily Simonoff[c], Ian C.K. Wong[a,d,*]

[a] Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, 2/F Laboratory Block, 21 Sassoon Road, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region
[b] School of Health Sciences, Rua de Luís Gonzaga Gomes, Macao Polytechnic Institute, Macao
[c] Kings College London, Institute of Psychiatry and NIHR Biomedical Research Centre for Mental Health, De Crespigny Park, London SE5 8AF, United Kingdom
[d] University College London, School of Pharmacy, 29-39 Brunswick Square, London WC1N 1AX, United Kingdom

ARTICLE INFO

Article history:
Received 12 August 2014
Received in revised form
18 November 2014
Accepted 21 November 2014
Available online 9 December 2014

Keywords:
SSRI
Serotonin reuptake inhibitor
Autism spectrum disorder
Pregnancy

ABSTRACT

This study is a critical analysis of the association between selective serotonin reuptake inhibitors (SSRIs) exposure during pregnancy and autism spectrum disorder (ASD) risk in children. Electronic databases were searched for observational studies published from January 1946 to June 2014 related to the association between SSRI exposure during pregnancy and ASD in children. Studies relevant to the association between SSRI exposure during pregnancy and ASD in children were extracted and compiled for meta-analysis evaluation. Ninety-five citations were identified and seven observational studies were included. Four case–control studies were eligible for the meta-analysis and two cohort studies were narratively reviewed. The pooled crude and adjusted odds ratios of the case–control studies were 2.13 (95% CI 1.66–2.73) and 1.81 (95% CI 1.47–2.24) respectively. Low heterogeneity was observed between studies. The two population-based cohort studies, utilizing the same Denmark data set, have conflicting results. The findings of this meta-analysis and narrative review support an increased risk of ASD in children of mothers exposed to SSRIs during pregnancy; however, the causality remains to be confirmed.

Contents

* Corresponding author at: Department of Pharmacology and Pharmacy, 2/F Laboratory Block, 21 Sassoon Road, Li Ka Shing Faculty of Medicine, University of Hong Kong, Pokfulam, Hong Kong Special Administrative Region. Tel.: +852 3917 9441; fax: +852 2817 0859.
E-mail address: wongick@hku.hk (I.C.K. Wong).

http://dx.doi.org/10.1016/j.neubiorev.2014.11.020
0149-7634/

1. Introduction

Untreated maternal depression has been associated with poor health outcomes for both mothers and children (Sontag-Padilla et al., 2013). Antidepressants are therefore indicated for pregnant women if the benefits outweigh the risk (National, 2007; Joint Formulary Committee, 2014). Selective serotonin reuptake inhibitors (SSRIs) are the most frequently prescribed anti-depressant classes. Substantial placental transfer occurs with SSRIs (Rampono et al., 2009) and may cause unwanted effects to the unborn child. Currently, meta-analysis results demonstrate that SSRI exposure during pregnancy is associated with preterm birth and low birth rate (Huang et al., 2014), congenital malformation (Myles et al., 2013), and persistent pulmonary hypertension (Grigoriadis et al., 2014). The use of SSRIs in pregnant women is a complex decision that requires weighing the effectiveness of treating depressive symptoms while considering potential adverse events in mother and child.

Recent studies have indicated a possible association between the use of SSRIs in pregnancy and the risk of autism spectrum disorder (ASD) in children (Croen et al., 2011; Eriksson et al., 2012; Gidaya et al., 2014; Harrington et al., 2014; Hviid et al., 2013; Rai et al., 2013; Sorensen et al., 2013). SSRIs are able to cross not only the blood–brain barrier for intended pharmacological actions but also the placental barrier for possible unintended consequences (Kendall-Tackett and Hale, 2010). This is evidenced by the high SSRI cord/maternal distribution ratio, i.e., 0.70–0.86 (Rampono et al., 2009). Animal studies demonstrate that transient usage of fluoxetine during early development produces abnormal emotional behaviors in adult mice, suggesting the role of serotonin transporter modulation during development of brain systems involved in emotional and stress related responses (Ansorge et al., 2004). Pharmacokinetic and pharmacodynamic data, albeit weak and indirect in nature, suggest a plausible biological mechanism between in utero exposure of SSRIs and ASD in children. However, in the scientific literature, evidence of this association contradicted several epidemiological studies supporting a positive association (Croen et al., 2011; Eriksson et al., 2012; Gidaya et al., 2014; Sorensen et al., 2013) whilst others indicated no association (Harrington et al., 2014; Hviid et al., 2013; Rai et al., 2013). Given conflicting results from studies, it is difficult to reach a consensus as to whether there is a link between the use of SSRIs in pregnancy and ASD in children.

ASD affects 1 in 88 children in the United States (US) and prevalence is approximately 1–1.2% in the United Kingdom (UK) (Baird et al., 2006; Baron-Cohen et al., 2009). Due to ASD's early onset, their lifelong persistence and associated pervasive impairment (Simonoff et al., 2008), there is significant impact on social outcomes, education and health of patients and their families (Bolton et al., 1998; Buescher et al., 2014). In the US and UK, the cost of supporting an ASD individual with intellectual disability throughout their lifetime is estimated to be US$2.2–2.4 million and US$1.4 million for an ASD individual without intellectual disability (Buescher et al., 2014). Additionally, there is a high prevalence of mental health conditions in individuals with ASD, including attention deficit hyperactivity disorder, global and specific learning disabilities, emotional disorders, anxiety and depressive disorders, and chronic tic disorder (Bradley and Bolton, 2006; Green et al., 2005; Simonoff et al., 2008). Understanding the risk factors for the development of ASD is an important public health issue.

In view of the above issues, we undertook a systematic review and meta-analysis of published observational studies to evaluate whether SSRI exposure during pregnancy increases the risk of ASD in children.

2. Method

A systematic literature search was conducted using the search terms (SSRI OR Serotonin uptake inhibitor OR antidepressant) AND pregnancy AND (autism OR autistic OR pervasive developmental disorder OR Asperger syndrome OR Asperger's syndrome OR ASD). PubMed, EMBASE, PsycINFO and the Cochrane Review databases were searched up to 25 June 2014. English titles and abstracts were screened and full texts of relevant articles were retrieved for further review to identify relevant studies. A hand-search of selected articles was conducted to further identify pertinent studies. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for the flow chart and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) to ensure clear and comprehensive reporting.

2.1. Inclusion and exclusion criteria

Observational studies, including cohort and case–control study designs, which investigated the association between SSRI use and ASD were included. Case reports and animal studies were excluded.

2.2. Quality assessment

As recommended by the Cochrane Collaboration (Higgins and Green, 2011), the methodological quality of the included studies were assessed using the Newcastle–Ottawa Scale (NOS) (Wells et al., 2000). Two authors (HT and LW) independently reviewed and scored each study. Separate NOS criteria were used for case control and cohort studies. A maximum of nine stars could be allocated for the following categories: selection, comparability and outcome/exposure. The total score was obtained by adding the number of stars in the sub-categories where a higher score indicated better quality.

2.3. Data extraction

Data from the included studies were extracted using a standardized data collection form. These included study duration and design, data source, covariates, exposure groups, and sample size. Authors HT and LW independently extracted data and completed the characteristics form that was subsequently cross-matched to ensure consistency and accuracy.

Outcome parameters such as relative risk (RR), crude odds ratio (OR), adjusted OR and the corresponding 95% confidence intervals (CI) were extracted and included in the meta-analysis if appropriate.

The primary outcome of interest was the risk or odds of developing ASD following exposure to SSRIs, either at preconception, or during pregnancy.

2.4. Statistical analysis

To estimate the association between the use of SSRIs during pregnancy and ASD in children, the results of the included studies were combined using DerSimonian and Laird's random-effects model (DerSimonian and Laird, 1986) to account for heterogeneity among studies. The Mantel–Haenszel fixed-effect model was used to validate the results and control for overweighting of the included small studies. All formulations of SSRIs were included. Analysis was performed on both the crude and adjusted estimates from the studies. The pooled estimates with 95% CI were calculated.

Sensitivity analysis was performed to assess the robustness of the results. This was conducted by substituting the findings of Rai et al. (2013) with those of Eriksson et al. (2012) as the subjects in these two studies came from the same data source.