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Review

Prenatal antidepressant exposure and the risk of autism spectrum disorders in children. Are we looking at the fall of Gods?

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ABSTRACT

Recent information suggests that antenatal exposure to psychotropics may impair child neurodevelopment. Thus, aim of this review is to examine systematically available literature investigating potential associations between prenatal use of selective serotonin reuptake inhibitors (SSRIs) and the risk of autism spectrum disorders (ASDs).

Methods: Medical literature published in English since 1988 identified using MEDLINE/PubMed, EMBASE, SCOPUS, and The Cochrane Library. Search terms: antidepressants, autism (spectrum disorders), childhood, children, neurodevelopment, pregnancy, SSRIs. Searches were updated until March 5, 2015.

Results: Six out of eight reviewed articles confirm an association between antenatal SSRI exposure and an increased risk of ASDs in children. However, the epidemiologic evidence on the link between prenatal SSRI exposure and ASD risk must still be cautiously interpreted, because of potential biases of analyzed research.

Limitations: Main limitations of reviewed studies include: lack of directly validated clinical evaluation, impossibility to identify women who really took the prescribed medications during pregnancy, no assessment of severity and course of symptoms in relation to the pregnancy, lack of information about unhealthy prenatal lifestyle behaviors.

Conclusions: Despite such limitations, available data show that some signal exists suggesting that antenatal exposure to SSRIs may increase the risk of ASDs. Thus, there is an urgent need for further, large, well-designed research finalized to definitively assess the existence and the magnitude of this severe risk, thus confirming or denying that we are truly looking at "the fall of Gods", since for many years SSRIs have been considered the first-choice agents for treating antenatal depression (Gentile, 2014; Gentile, 2011a; Gentile, 2005).

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1. Introduction

Autism is a set of heterogeneous neurodevelopmental conditions characterized by early-onset difficulties in social communication and unusually restricted, repetitive behavior and interests. The worldwide population prevalence is about 1%. Autism affects more male than female individuals, and comorbidity is common (> 70% have concurrent conditions). Patients diagnosed with autism spectrum disorders (ASDs) have both atypical cognitive profiles (such as impaired social cognition and social perception, executive dysfunctions), and atypical perceptual and information processing (Gray et al., 2014; Lai et al., 2014).

Magnetic resonance imaging (MRI) studies have attempted to identify morphological changes in brain architecture associated with ASDs. Preliminary neuroimaging findings evidence an increase in total brain volume (and, especially, in frontal lobe volume), increased thickness in temporal/parietal lobes, structural alterations involving corpus callosum, amygdala, and cerebellum, and changes in grey matter in the posterior cingulate cortex, medial prefrontal cortex, and temporal lobes (Brun et al., 2009; Carper et al., 2013; Palmen et al., 2005; Stigler et al., 2011; Uddin et al., 2011).

Recent studies have also provided evidence for an altered epigenetic landscape in ASDs and have hypothesized the central role of epigenetic mechanisms in their pathogenesis. Many of the genes linked to the ASDs actually encode proteins that are involved in transcriptional regulation and chromatin remodeling (Abrahams and Geschwind, 2008; Rangasamy et al., 2013).

Moreover, mitochondrial dysfunctions and changes in porphyrin metabolism have also been reported to occur with higher frequency among ASD patients than in general populations (Rossignol and Frye, 2012; Woods et al., 2010).

Identifying biomarkers for ASDs (Voineagu and Yoo, 2013) has been the focus of intense research since the first description of the disease in the early 1940s (Kanner, 1943). Biomarkers of oxidative stress, as a result of impaired antioxidant mechanism and aberrant neuroimmune responses, have been associated with ASDs (Frustaci et al., 2012; Wei et al., 2013). However, one of the main biomarkers of ASDs includes changes in several neurotransmitter levels. Serotonin has long been of interest in autism. Repeated findings of elevated platelet serotonin levels in approximately one third of children with autism has led to the hypothesis that dysfunctional serotonin signaling may be a causal mechanism for the disorder. Increased blood levels of serotonin were observed in a proportion of autistic patients as high as 35%. Serotonin levels are regulated by genetic variants of serotonin receptor genes, such as *SLC6A4* and *ITGB3* (Abney et al., 2001; Weiss et al., 2005). Thus, it has been theorized that an increase in serotonergic activity during brain development may facilitate the onset of ASDs (Whitaker-Azmitia, 2005). Several data support the hypothesis that somatodendritic 5-HT_{1A} autoreceptors situated in the raphe nuclei play an important role in the mechanism of action of substances that manipulate serotonin levels (Gardier et al., 1996). Because serotonin is critical to fetal brain development, concerns have arisen regarding prenatal exposure selective serotonin reuptake inhibitors [(SSRIs) – Harrington et al., 2013]. A 4-fold increase in the use of antidepressants during pregnancy has been observed during the period 1996–2005, with nearly 8% of pregnant women prescribed antidepressants during the years 2004–2005 (Andrade et al., 2008). Conversely, the rate of use of psychotropic drugs has remained relatively stable between 2006 and 2011. The most commonly used psychotropics during pregnancy are SSRIs (Hanley and Mintzes, 2014; Meunier et al., 2013).

Given this background, the aim of this review is to examine available literature investigating potential associations between prenatal antidepressant SSRI exposure and the risk of ASDs in children.

2. Methods

Fig. 1 shows the systematic literature search and results.

3. Results

Studies suggest no link between antenatal antidepressant exposure and ASDs (shown in Table 1). A population-based study collected prospectively data considering both SSRI exposure and mental history of mothers (Croen et al., 2011). The study sample was drawn from the Californian Childhood Autism Perinatal Study, a case–control study aiming to investigate potential risks factors for ASDs. In the ASD cases, 15/298 children were exposed to SSRIs (3.4% to fluoxetine (FLX), 4.4% to paroxetine (PAR), 5.0% to sertraline (SER), and 3.4% to fluvoxamine (FVX)). The study found a 2-fold increase in the risk of ASDs associated with SSRI treatment during the year before delivery and a 3-fold increased risk associated with first trimester exposure, independent of maternal psychiatric diagnosis.

The case–control study by Rai et al. (2013) included all young people aged 0–17 years and residing in Stockholm, Sweden, between 2001 and 2007 ($n=589{,}114$). The cohort contained prospectively recorded data on the probands and their first degree relatives collected by record linkage with national and regional healthcare, social, and administrative registries. The characteristics of cases and controls with all available data were similar to the 4429 cases and 43,277 controls with complete data used in the main analysis. Approximately 1% ($n=44$) of mothers of the 4429 case children with ASDs were diagnosed with depression recorded before the birth of the index child, compared with 0.6% ($n=272$) of 43,277 control mothers. Maternal history of depression was associated with a higher risk of ASDs in offspring, but there was no evidence of a relation with paternal depression. This association was limited to children of mothers who reported using antidepressants at the first antenatal interview. The increase in the risk of autism seemed to be confined to those forms of ASDs without intellectual disability. Sørensen et al. (2013) identified all children born alive in Denmark 1996–2006 ($n=668{,}468$) and their parents in the Danish Civil Registration System. The Authors obtained information on the mother's prescriptions filled during pregnancy from the Danish National Prescription Registry, on diagnosis of ASDs in the children, and on diagnosis of psychiatric disorders in the parents from the Danish Psychiatric Central Register. Exposure window was defined from 30 days before conception to the day of birth. Main study results were that, after controlling for several confounding factors, the association between prenatal maternal SSRI use and later ASDs in the child, albeit statistically significant, was weaker than that reported in other recent epidemiologic studies (Croen et al., 2011; Ray et al., 2013). The association was found for high as well as for low dose levels, and risk estimates were comparable regardless of timing of exposure.

To further investigate this association, a recent study used Denmark's health and population registers to obtain information regarding prescription drugs, ASD diagnosis, and health and socioeconomic status (Gidaya et al., 2014). An increased risk of ASDs associated with in utero exposure to SSRIs was observed in this large population-based, case–control study. The effect was present for all exposure windows considered (but the strongest effect was found for third trimester exposure) and persisted after adjustment for SSRI indications.

A recent population-based case–control study (Harrington et al., 2014) included families enrolled in the Childhood Autism Risks from Genetics and the Environment (CHARGE) Study. This population-based, case–control investigation recruited children