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Does prenatal exposure to antidepressants cause autism? - literature review

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ABSTRACT

Autism spectrum disorder is an increasingly diagnosed disorder among children, yet its pathogenesis is still unknown. Possible causes are sought in genetic mutations, cellular processes occurring in the nervous system during development and external factors affecting the fetus during the prenatal period. In recent years, there have been an increasing number of reports linking the occurrence of the spectrum to antidepressant medications, especially from the SSRI group, taken by pregnant women for depressive disorders, which occur in up to a dozen percent of women in this group. The involvement of serotonin in the development of the nervous system during the fetal period is taken as the reason for this phenomenon. To date, no clear consensus has been reached on this issue, and many distractors in the research are highlighted, such as the effect of maternal depression on fetal development, among others. There is no doubt that further research is needed to better assess the risk of ASD associated with SSRI use and dosage during pregnancy

Keywords: autism spectrum disorder (ASD), major depressive disorder (MDD), SSRI prenatal exposure

INTRODUCTION

Autism spectrum disorder (ASD) is a term used to describe a range of neurodevelopmental features observed in children from about 2 years of age, which may include difficulties in entering and sustaining social interactions, repetitive, stereotyped behaviors or unusual responses to sensory stimuli [1, 2]. We can observe the first early symptoms, such as a lack of response to one's own name or limited communication and gesticulation, in the first two years of a child's life [3]. However, it is important to remember that ASD is an umbrella term, encompassing many symptoms ranging in severity from mild to very severe.

The diagnosis is based on criteria published in 2013 by The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 [4]. To meet diagnostic criteria for ASD according to DSM-5, a child must have persistent deficits in each of three areas of social communication and interaction as well as at least two of four types of restricted, repetitive behaviors (Table 1.).

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive; see text):

1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

Specify current severity:

Severity is based on social communication impairments and restricted, repetitive patterns of behavior. For either criterion, severity is described in 3 levels: Level 3 – requires very substantial support, Level 2 – Requires substantial support, and Level 1 – requires support

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text):

1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypes, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).
3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).
4. Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (e.g. apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

Specify current severity:

Severity is based on social communication impairments and restricted, repetitive patterns of behavior. For either criterion, severity is described in 3 levels: Level 3 – requires very substantial support, Level 2 – Requires substantial support, and Level 1 – requires support.

C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level. **Note**: Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of autism spectrum disorder. Individuals who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for autism spectrum disorder, should be evaluated for social (pragmatic) communication disorder. *Specify* if: **With or without accompanying intellectual impairment** **With or without accompanying language impairment** **Associated with a known medical or genetic condition or environmental factor** **Associated with another neurodevelopmental, mental, or behavioral disorder** **With catatonia**

Table 1. DSM-5 Diagnostic Criteria for ASD [4]

With the development of public awareness and the reduction of the stigma of mental disorders, the number of children who are diagnosed with ASD is steadily increasing, and yet we still can't answer the question of what causes autism. Studies on twins suggest a genetic basis, but show a significant influence of non-inherited factors on the occurrence of ASD [5, 6]. A higher incidence of ASD has been observed in children with a psychiatrically burdened family history [7, 8], and male gender, toxins, low socioeconomic status or obstetric complications, among other factors, have also been cited as contributors to autism spectrum

disorders [9]. Researchers pose many theories about the pathogenesis of ASD, such as oxidative stress, damage to the nervous system during fetal development, and abnormalities in brain neurochemistry [10, 11].

The source of the disorder has been traced to impaired brain development and factors acting on the fetus during the prenatal period [7, 12]. One of these may be medications taken by the mother and crossing the placenta.

DEPRESSIVE DISORDERS IN PREGNANCY AND THEIR TREATMENT

It is estimated that up to 15-18% of pregnant women develop major depressive disorder (MDD), and risk factors include race, young age and the patient's history of burdened psychiatric disorders [13, 14, 15]. When a pregnant woman is diagnosed with MDD, the suggested first-line treatment is non-pharmacological methods such as psychotherapy. Unfortunately, abandoning pharmacological treatment is not possible in all cases, such as the severe course of the disorder or the occurrence of suicidal thoughts [16].

In such cases, the drugs of choice are those from the selective serotonin reuptake inhibitors (SSRIs) group, such as sertraline, escitalopram or fluoxetine [17, 18]. Despite their good efficacy in treating MDD in the general population [19], their use is associated with side effects. In recent years, there have been an increasing number of reports on the effects of SSRI use by pregnant women on the fetus. Drugs in this group cross the placenta, and their active metabolites penetrate into a woman's milk, so they can be ingested by the infant with the breastmilk [20].

The most commonly listed complications include preterm delivery, low birth weight, reduced APGAR score, respiratory failure, hypoglycemia, epileptic seizures, and even miscarriage and fetal death [15, 21, 22]. Studies also suggest an effect of the length of exposure and the period of pregnancy in which it occurred on the occurrence of the aforementioned defects, but at the same time emphasize the need to differentiate fetal exposure to antidepressants from maternal exposure [23, 24].

It should also be noted that, based on current knowledge in 2005, paroxetine, which also belongs to the SSRI group, has been classified in the D category of safety for use in

pregnancy, due to reports of negative effects of its use on the fetus, such as birth defects, particularly cardiac defects [14].

In recent years, case reports and studies have been published linking the use of drugs from the antidepressant groups during pregnancy with the subsequent diagnosis of ASD in the child, but the processes that may cause this link remain a mystery. The cause is sought in damage to serotonin receptors in the developing fetal brain via a negative feedback mechanism under the influence of SSRIs in the mother's blood [25]. Serotonin (5-HT) modulates developmental processes in both peripheral tissues and the brain, including cell proliferation, migration and differentiation [26]. This theory may be supported by studies showing impaired levels of serotonin and its metabolites, including 5-hydroxyindoleacetic acid (5-HIAA), in the blood and cerebrospinal fluid of children on the autism spectrum [27, 28]. Bhat et al [10] published a paper examining the prenatal effects of fluoxetine on brain neurochemical changes in rats, confirming the link in several mechanisms suspected to be involved in the etiopathogenesis of autism such as oxidative stress, nervous system inflammation, altered neurochemistry, apoptosis and impaired energy metabolism.

One of the first studies linking ASD to SSRI exposure was published by Croen et al. [29] in 2011. The study included 298 children on the autism spectrum (and their mothers), as well as 1507 randomly selected control group children (and their mothers). In these groups, prenatal exposure to SSRIs was 6.7% and 3.3%, respectively. The researchers found a 2-fold increase in the risk of ASD in the children of mothers using selective serotonin reuptake inhibitors during the year before delivery (adjusted odds ratio, 2.2 [95% confidence interval, 1.2-4.3]), with the first trimester of pregnancy identified as the most sensitive period (adjusted odds ratio, 3.8 [95% confidence interval, 1.8-7.8]).

Subsequent years have seen further publications on this topic, as well as meta-analyses of these studies. While some of them support the theory of an association between the incidence of autism and prenatal exposure to SSRIs [30, 31], others have the opposite conclusion [32, 33]. Similarly, the issue of the trimester of pregnancy in which the exposure occurred is debatable, with some studies like Croen et al. finding the first trimester to be the most sensitive, others the second and third [34]. A paper published by Kapra et al. [35] analyzed 17 studies for an association between autism and prenatal exposure to SSRIs and found positive evidence of this association in these studies. They also emphasized that the number

of reported cases of pregnant women's depression is underreported, resulting in an underestimation of confounding factors between studies and analysis of available data.

Similar meta-analyses were conducted by Andalib et al. [36] and Kaplan et al. [37], among others, finding a higher incidence of ASD in the children of mothers taking SSRIs during pregnancy compared to the general population, but again emphasizing the influence of confounding factors to unequivocally confirm the association.

More recently, in a meta-analysis published by Leshem et al [38], which considered 18 studies, the researchers suggest that the association between SSRI exposure during pregnancy and ASD may be due to confounding factors, and that the association between SSRIs and ASD is also statistically significant for mothers who took SSRIs before pregnancy but whose offspring were not exposed to them.

There is no doubt that further research is needed to better assess the risk of ASD associated with SSRI use and dosage during pregnancy.

CONCLUSIONS

The etiology of ASD has been linked to genetic, epigenetic and environmental factors. The contribution of genetic factors is estimated to be about 80% [39]. A psychiatrically burdened family history has also been cited among factors predisposing to ASD, thus suggesting that the increased incidence of ASD in the offspring of women with MDD may be due to the mother's own onset of the disease. Both maternal stress and depression have been linked to perinatal and neurodevelopmental problems [38].

The results of the work are non-conclusive. Studies to date have potential limitations, such as the lack of adequate adjustment for maternal mental illness and genetic predisposition to ASD. The relationship is debatable, due to multiple distractors. For example, the use of SSRIs predisposes to preterm birth, which in turn is a risk factor for ASD, leaving room for speculation about the actual relationship.

It should also be noted that a loaded family history of psychiatric illnesses is mentioned among the factors that predispose to ASD. Here we can speculate whether maternal depression is not a sufficient risk factor in itself.

Also worth mentioning is a paper published by Yang et al [40], in which the researchers found an increased incidence of ASD in the offspring of fathers using SSRIs during the pre-conception period, while suggesting that this association may be due to the father's mental illness or confounding factors, which again draws our attention to family history being a predisposing factor for ASD, rather than SSRI intake per se.

There is no doubt that mental health is a growing social health issue. The prevalence of both MDD and ASD is increasing every year, which may be due to a number of external factors, but also to the public's increasing awareness of the issue.

With the increase in MDD diagnoses, especially those during pregnancy, further observation of risk factors and the safety and effectiveness of therapies will be necessary. For this reason, further studies of SSRI drugs and their effects on prenatal development are needed. For ethical reasons, testing of drug preparations for pregnant women is limited, making it much more difficult to assess the actual effects of SSRIs on fetal development.

Thus, it seems that the decision to use SSRIs should be made after analyzing the profit and loss account. This is a highly complex issue, because unlike other exposures, such as alcohol or drugs, which we aim to eliminate completely during pregnancy, in many cases failure to use or discontinue therapy for depression can have serious consequences. Untreated depression can lead not only to harmful consequences for the mother, but also for the baby.

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