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Review

# Prenatal Exposure to Bisphenol A: Implications for Autism Spectrum Disorders

Menekşe Sultan Bulut[1], Oytun Erbaş[1]


## ABSTRACT

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is very common today. Endocrine disruptors, along with genetic and environmental factors, also influence this condition. These endocrine disruptors affect the functioning of hormones. Bisphenol A (BPA) is one of these endocrine disruptors. Accumulation or exposure to BPA can lead to fetal growth restrictions, neurological disorders, and various other conditions. Infants and young children are more sensitive to these pollutants compared to adults. Babies are exposed to these pollutants in the womb through the placenta. As a result, the endocrine system, as well as neurological, growth, and developmental processes, are significantly affected, leading to conditions such as ASD during growth. Autism spectrum disorder has a profound impact on both the individual and their family. However, ASD is not only caused by such pollutants but also by a variety of genetic and biological factors. In individuals with ASD, it may manifest as repetitive behaviors, communication difficulties, and social deficits. In this review, the following topics have been discussed: the effects of BPA on fetal development, its potential role in ASD, and other contributing genetic and biological factors.


**Keywords:** Autism spectrum disorder, bisphenol A, endocrine disruptors.

Autism spectrum disorder (ASD) is one of the most common neurodevelopmental disorders, affecting one in every 54 children worldwide.[1-6] In 1943, Dr. Leo Kanner[3] introduced the term 'autism' into medical terminology. Clinically, ASD is a complex and heterogeneous neurological condition that affects various developmental domains, including social interaction, communication skills, visual functioning, and stereotyped behaviors, interests, and attitudes.[7,8] These disorders typically emerge in early childhood before the age of three but may not fully manifest until later in life.[9] Abnormal T-cell function has been reported in patients.[9-16] A compromised or dysfunctional immune system can make individuals more neurologically vulnerable.[11,12,16]

## ENVIRONMENTAL FACTORS CONTRIBUTING TO AUTISM SPECTRUM DISORDER

Even when accounting for diagnostic challenges, the fivefold increase in autism cases in recent years, despite the absence of any known changes in the human gene pool, points to a strong environmental influence.[17-25]

Numerous pollutants, including pesticides, heavy metals, industrial solvents, air pollutants, particulate matter, bisphenol A (BPA), phthalates, and flame retardants, have been implicated in epidemiological studies.[23-25]

The balance of metal ions in our body is essential for the proper functioning of the brain, and when this balance is disrupted, neurological symptoms are inevitable. Zinc, one of these ions, plays a crucial role in cell division and differentiation, and its deficiency will lead to significant changes in neurological functions.[13] It is well established that zinc supplements are used in nutritional therapy for patients with autism.[14]

The primary issue in ASD lies in the brain; however, certain other organs may also have some influence

[1]ERBAS Institute of Experimental Medicine, Illinois, USA & Gebze, Türkiye

***Correspondence:*** Menekşe Sultan Bulut. Institute of Experimental Medicine, 41470 Gebze-Kocaeli, Türkiye

**E-mail:** meneksesultanbulut021@gmail.com

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on autism. The most significant of these organs is the gut. Recently, attention has been focused on the brain-gut axis for several reasons: the bidirectional relationship between gut and behavioral findings, the potential link between diet, the gastrointestinal system, and autism, and the collection of gut microbiota associated with autism. While knowledge on this subject is currently limited, scientific research is ongoing.[15]

Studies on the causes of autism have reported that exposure to thalidomide, especially valproic acid, anticonvulsants, certain viral infections, and various birth complications are associated with the development of autism.[17] It is also emphasized that psychological stress factors experienced by the mother during the prenatal period are associated with the development of ASD.[18]

Imaging studies have shown that some children with autism exhibit features such as macrocephaly, abnormal increases in cortical white matter, and abnormal growth in limbic structures like the frontal lobe, temporal lobe, and amygdala.[21] These structures play a crucial role in social relationships, communication, and motor skills, which are areas that show impairment in autism.[20]

The management of ASD depends on early diagnosis and intervention.[26-31] The social domain of ASD can be successfully addressed through behavioral interventions such as early behavioral therapy and positive interactions with social peers.[32]

The early diagnosis of ASD provides children with the opportunity to begin treatment sooner, which benefits both the child and society. It also allows for the examination of ASD's neurological features in the early stages of development and facilitates a better understanding of the underlying mechanisms of ASD. Early diagnosis and intervention are crucial for the effective management of ASD.[33]

Many genes have been implicated in autism, and some of these are directly related to detoxification processes. Many of these genes are also expressed in the frontal cortex during the prenatal period, when the effects of such toxins on neurodevelopment are most significant. For toxins to reach the fetal brain, they must cross the placenta and the blood-brain barrier, and they must also overcome the skin, airway, and intestinal barriers to access the blood of the mother or the child. Therefore, the significant role of autism susceptibility genes may be related to their ability to regulate the access of various toxins to children, adults, and the developing fetal brain during pregnancy.[22,23]

Genetic research on autism has initiated early studies in the form of linkage and association studies aimed at identifying chromosomal regions and loci that may contribute to autism.[21] Despite the identification of many genes and candidate genes associated with autism, no major gene has been pinpointed. Significant results have been obtained in seven chromosomal regions related to autism. Additionally, other candidate genes thought to contribute to autism are being investigated. The presence of many genes responsible for social interaction, language, communication, and emotions suggests that there may be issues in multiple genes. With advancements in technology, it will become possible to evaluate these genes and candidate genes together, allowing for more insights into the etiology of autism.[22]

## BISPHENOL A

Bisphenol A is a high-volume chemical used in a wide range of products, including plastic bottles and canned foods. Given the common human exposure and the endocrine effects observed initially in animal studies and now in humans, this chemical is being extensively studied.[25]

Bisphenol A is a widely used chemical that has been shown to negatively impact health outcomes in experimental animal studies, particularly following fetal or early life exposure. Researchers hypothesize that the effects of BPA will increase in children based on its metabolism and endocrine effects. One study found a relationship between prenatal BPA exposure and increased hyperactivity and aggression in 2-year-old girls. Even in the absence of epidemiological studies, concerns about the negative effects of BPA are warranted, considering the unique vulnerability of the developing fetus and child.[26]

### Bisphenol A and Female Fertility

Bisphenol A has been reported to be associated with female infertility. In fact, it has been found that BPA is more frequently detected in infertile women, suggesting a possible impact of BPA on natural conception and spontaneous fertility. Additionally, exposure to BPA during early life stages may have an intergenerational effect, predisposing subsequent generations to develop diseases associated with BPA. Experimental studies have suggested that prenatal, perinatal, and postnatal exposure to BPA can disrupt various stages of ovarian development, lead to reorganization of ovarian morphology, impair ovarian

function-particularly affecting folliculogenesis-and also disrupt the morphology and function of the uterus in female adult animals and their offspring.[26,27]

Maternal prenatal exposures, including BPA, are associated with an increased risk of disease in offspring later in life.[28] It has been identified that BPA exposure promotes the development of abnormalities similar to polycystic ovary syndrome by disrupting the secretion of sex hormones, which affects ovarian morphology and function, particularly folliculogenesis.[27]

**Human Exposure to Bisphenol A**

Pregnancy and lactation are critical periods for human well-being and are sensitive windows for exposure to pollutants. Bisphenol A has been well-established as a toxic substance and has been replaced in the plastic industry by other bisphenol analogs that share similar structures and properties, most commonly bisphenol S (BPS) and bisphenol F (BPF). Maternal exposure to BPS or BPF can lead to their accumulation in the fetal compartment, resulting in chronic exposure and potentially limiting normal fetal growth and development.[28,29] Current findings indicate that exposure to two bisphenol analogs during pregnancy and lactation can lead to multiple disorders in offspring, including fetal growth restrictions, neurological dysfunctions, and metabolic disorders that may persist throughout childhood.[29,30,34]

The hypothesis that prenatal exposure to endocrine disruptors can lead to cancer arises from questioning two well-established concepts. Bisphenol A has been shown to trigger the development of ductal hyperplasias and carcinoma *in situ*. These highly proliferative lesions contained an increased number of estrogen receptor alpha-positive cells. Therefore, in the absence of any additional treatment aimed at increasing tumor incidence, fetal BPA exposure was sufficient to induce the development of estrogen-sensitive pre-neoplastic and neoplastic lesions in the mammary gland.[35]

There is now more evidence than previously described linking prenatal exposure to BPA, organophosphate pesticides, and polybrominated flame retardants with cognitive deficits and attention deficit disorder in children. The evidence is particularly strong for associations between perfluoroalkyl substances and obesity in children and adults, impaired glucose tolerance, gestational diabetes, low birth weight, poor semen quality, polycystic ovary syndrome, endometriosis, and breast cancer. Additionally, there is evidence connecting bisphenols with adult diabetes, poor semen quality, and polycystic ovary syndrome; phthalates with premature birth, reduced anogenital distance in males, childhood obesity, and impaired glucose tolerance; organophosphate pesticides with poor semen quality; and occupational exposure to pesticides with prostate cancer.[36]

Prenatal exposure to endocrine disruptors has the potential to affect early brain development. Neurodevelopmental toxicity in utero can manifest as psychosocial deficiencies later in childhood. Prenatal phthalate exposure has been associated with childhood social disorders in a multi-ethnic urban population. Even mild impairments in social functioning in otherwise healthy individuals can have significant negative effects throughout a child's life.[37]

In conclusion, the relationship between BPA and ASD is noteworthy. Various studies and articles have been written on this topic; however, more research is needed. The direct effects of BPA on autism can be further developed and interpreted through additional studies.

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