v. 4, n. 59, 2024

International Journal of Health Science

INFLUENCE OF MATERNAL HEALTH ON THE RISK OF AUTISM SPECTRUM DISORDER IN OFFSPRING: CURRENT PERSPECTIVES

Marília Marcon Baião
Faculdade Brasileira de Cachoeiro (MULTIVIX), Cachoeiro de Itapemirim - ES
https://orcid.org/0009-0001-8949-5622

Thaís Angelim de Oliveira
Universidad Nacional de Rosario (UNR)
Rosário - AR
https://orcid.org/0009-0009-0098-2351

Juliana de Morais Azevedo
Faculdade Brasileira de Cachoeiro (MULTIVIX), Cachoeiro de Itapemirim - ES
https://orcid.org/0009-0002-1848-6814

Mariana Moreno Rocha
Centro Universitário Tocantinense Presidente Antônio Carlos (UNITPAC)
Araguaína - TO
https://orcid.org/0000-0001-7489-8608

Lennyne de Oliveira Sampaio
Universidade Anhembi Morumbi, Campus São José dos Campos (UAM SJC)
São José dos Campos - SP
https://orcid.org/0009-0003-9661-1577

Mariana Bonadiman Gonçalves
Faculdade Brasileira de Cachoeiro (MULTIVIX), Cachoeiro de Itapemirim - ES
https://orcid.org/0009-0004-2702-5432

All content in this magazine is licensed under a Creative Commons Attribution License. Attribution-Non-Commercial-Non-Derivatives 4.0 International (CC BY-NC-ND 4.0).

Eduarda Nogueira Possato
Faculdade Santa Marcelina (FASM)
São Paulo - SP
https://orcid.org/0009-0006-2848-1151

Heitor Moreira Araujo
Faculdade Brasileira de Cachoeiro (MULTIVIX), Cachoeiro de Itapemirim - ES
https://orcid.org/0009-0008-7477-9957

Louise Barbosa
Universidade Estácio de Sá campus Presidente Vargas (UNESA)
Rio de Janeiro
https://orcid.org/0009-0009-5486-0413

Paulo Cesar Ribeiro Junior
Faculdade de Medicina de Jundiaí (FMJ)
Jundiaí
https://orcid.org/0009-0007-7265-3122

Larissa Leccas Carvalho
Universidade Estácio de Sá campus Presidente Vargas (UNESA), Rio de Janeiro
https://orcid.org/0009-0003-8533-2273

Myrna Maria Costa de Melo Silveira
CENBRAP, São Paulo - SP
https://orcid.org/0009-0000-7749-7180

Abstract: Goal: To investigate the relationship between maternal health during pregnancy, including nutritional, environmental and psychosocial factors, and the risk of Autism Spectrum Disorder (ASD) in offspring, with the aim of identifying potential preventive strategies. Methods: Bibliographic review, developed by the PVO strategy, using thesearch terms in combination with the Boolean operators "AND" and "OR": (Maternal Pregnancy Health) OR (Pregnancy) AND (Autism Disorder) OR (Autism Spectrum Disorder), on the basis ofPubMed data - MEDLINE (Medical Literature Analysis and Retrieval System Online). 1692 articles were identified with a 5-year filter. Considering the exclusion and inclusion criteria, 19 articles were selected. Review: It was identified that there is an influence of maternal diet during pregnancy in addition to vitamin D deficiency, psychosocial stress, environmental factors and prolonged use of medications, such as paracetamol, impacting behavior and neural development. Several studies investigate how prenatal and perinatal factors can affect the risk of Autism Spectrum Disorder (ASD). Evidence especially highlights the role of folic acid supplementation and vitamin D deficiency during pregnancy. The analysis of this research reveals the complexity of the interactions between maternal nutrition and fetal neurological development, highlighting the urgency of additional studies to clarify these associations and develop more effective preventive and early intervention strategies to combat ASD. Final considerations: It is observed that the diagnosis of Autism Spectrum Disorder is influenced by maternal health and well-being during pregnancy in several aspects. Studies that seek to determine the intensity and importance of such influence must be conducted so that it is possible to develop perinatal prevention strategies for such pathology.

Keywords: Maternal health during pregnancy; Pregnancy; Autism Spectrum Disorder.

INTRODUCTION

Autism Spectrum Disorder (ASD) encompasses a variety of neurodevelopmental disorders that impact social interaction and communication skills, resulting in stereotypical behaviors and restricted interests, significantly affecting the quality of life of those with it (Ou et al., 2024). Although ASD does not have a specific etiology, it is associated with genetic and environmental factors. Previous research has revealed that autism is highly heritable, and many factors can increase the propensity for its onset, including maternal age over 35 years, high paternal age, gestational hypertension, maternal excess weight, pre-eclampsia, cesarean section, hypoxia, maternal autoimmune diseases, and the use of antidepressants and paracetamol during pregnancy. Studies focusing on the potential role of maternal stress, environmental pollutants, and other factors in conjunction with maternal atopic conditions in influencing ASD risk are still scarce, indicating that understanding the multifactorial nature of the causes of ASD is partial. Addressing this topic is crucial for the development of targeted preventive strategies, early interventions and personalized treatments (Seker et al., 2023).

It is extremely important to recognize that epigenetic modifications in response to environmental factors, such as Maternal Immune Activation (MIA), can influence changes in the immune system and gene expression related to the pathophysiology of ASD. Studies in animal models and human populations have demonstrated associations between maternal asthma, atopy and increased risk of ASD in offspring, emphasizing the role of prenatal factors in neuroinflammation. This guides treatment strategies for maternal atopic conditions with the goal of promoting healthy neurodevelopment in children (Lin et al., 2023).

To understand the influence of genetic and environmental factors on the origin of Autism Spectrum Disorder is fundamental due to its comorbidities and the significant impact on patients' quality of life, ensuring an early and adequate diagnosis. Therefore, this article seeks to investigate the relationship between maternal health during pregnancy, including nutritional, environmental and psychosocial factors, and the risk of ASD in offspring, with the aim of identifying potential preventive strategies.

METHODOLOGY

Bibliographic review developed according to the criteria of the PVO strategy, an acronym that represents: population or research problem, variables and outcome. Used to prepare the research through its guiding question: "How does maternal health and well-being during pregnancy influence the risk of autism spectrum disorder (ASD) in offspring?". In this sense, according to the parameters mentioned above, the problem of this research refers to the relationship between maternal health during pregnancy and the risk of ASD in the offspring, with the aim of identifying potential preventive strategies, aiming to minimize the risk of ASD.

The searches were conducted through searches in the PubMed; MEDLINE (Medical Literature Analysis and Retrieval System Online) database. Search terms were used in combination with the Boolean operators "AND" and "OR" through the following search strategy: (Maternal Pregnancy Health) OR (Pregnancy) AND (Autism Disorder) OR (Autism Spectrum Disorder). From this search, 1701 articles were identified and subsequently submitted to the selection criteria. The inclusion criteria cover articles in the English language, published between

2019 and 2024 and which addressed the themes proposed for this research, review-type studies, original studies, observational studies and meta-analysis studies, available in full. The exclusion criteria consider duplicate articles, available in abstract form, that did not directly address the proposal studied and that did not meet the other inclusion criteria. of 52 potential studies. After applying the inclusion and exclusion criteria, 19 articles were selected from the PubMed database to compose the collection of the present study.

DISCUSSION

Autism Spectrum Disorder (ASD) is a complex condition characterized by deficits in social interaction, communication and repetitive patterns of behavior. Although its etiology is multifactorial, prenatal and perinatal factors have been increasingly recognized as significant influences on the development of ASD. In this context, folic acid (FA) supplementation before and during the first months of pregnancy has been promoted as a preventive measure against neural tube defects, but its specific impact on the risk of ASD is not yet fully understood (Sampaio et al., 2021).

Since 2004, Brazil has adopted mandatory food fortification with folic acid to reduce the prevalence of maternal anemia and neural tube defects, demonstrating a significant advance in maternal and fetal health (Sampaio et al., 2021).

However, this practice may have generated a population group with high levels of unmetabolized folic acid, which raises concerns about possible adverse effects, including the association with ASD. For Sampaio et al. (2021), excessive consumption of folic acid during pregnancy can negatively influence pregnancy, increasing the possibility of the occurrence of ASD, suggesting the importance of adequate and monitored consumption.

MMany studies around the world have sought to answer a question that plagues many families: what causes ASD? The diversity of correlations explored reflects the anguish behind this question. Costa et al. (2024) and Niltschke et al. (2023) tried to associate, respectively, stress and the use of antibiotics during the prenatal period with the subsequent diagnosis of autism in the offspring, however, both remained unsuccessful. The first sought to associate the stress trigger with the production of maternal autoantibodies during the intrauterine period of the offspring with the subsequent presentation of the spectrum, but its sample was not sufficient toprove such a relationship. The second managed to prove the relationship between the use of prenatal antibiotics and later atypical neurodevelopment, however, when the brothers were observed of the patients studied, it was foundwho also belonged to the spectrum, but had no exposure to antimicrobials during intrauterine life, disproving the previously proven hypothesis.

Fortunately, other studies have been successful in their associations, although each one establishes a different relationship. Tadesse et al. (2024), sought to relate the use of Cannabis during pregnancy with the neurological development of the offspring. This cohort study with extensive analysis material brought to light the diagnosis of ADHD and ASD in children of mothers who used cannabis during prenatal care, whichhas also been proven through experimental studieswhen using animals to demonstrate THC crossing the placental barrier and also the fetal blood-brain barrier.

Furthermore, vitamin D deficiency during pregnancy has been associated with a greater risk of ASD, highlighting the complexity of the interactions between nutrients and fetal neurological development (Uçar; Grant; Pereita-Costa; Suarez-Varela., 2020).

Epidemiological studies have provided evidence on the role of maternal diet in regulating behavior and neural development, which may have long-lasting effects on offspring (Majerczyk et al., 2022). However, for Sourander et al. (2023), the direct relationship between vitamin D deficiency and the risk of ASD still requires further investigation, as not all studies are conclusive.

Egorova et al. (2020) highlighted the role of folate in ASD. Despite always reinforcing its low patient sample, the relationship between folate supplementation during pregnancy and the reaction of the fetal immune system capable of triggering, years later, the diagnosis of autism was evident. Furthermore, this study was also able to explain the 3:1 prevalence of ASD in males through the production of tryptophan triggered by folate in the intrauterine life of this group. The study showed that folate supplementation during pregnancy can influence the fetal immune system, potentially leading to the diagnosis of autism years later. An important discovery was the association between folate supplementation and the production of tryptophan, an essential amino acid for the synthesis of serotonin and melatonin. These neurotransmitters are crucial for neurological development. In male fetuses, folate-triggered tryptophan production may be more pronounced, resulting in differential impacts on brain development. Sex differences in the response to folate may be mediated by hormonal and genetic factors, which influence tryptophan metabolism. Increased tryptophan production can lead to greater serotonin synthesis, and imbalances in this signaling are associated with ASD. Furthermore, folate can modulate the fetal immune response, and aberrant immune responses have been linked to ASD. Another relevant pathway is the metabolism of tryptophan into kynurenine, which influences inflammatory and neurotoxic processes. Changes in this pathway may increase the predisposition to ASD, especially in male fetuses. These differences may contribute to the higher prevalence of ASD in boys compared to girls (approximately 3:1). These findings suggest that nutritional interventions during pregnancy must consider sex differences in metabolism and immune response to better prevent neuropsychiatric conditions such as TEA.

In short, prenatal and perinatal factors such as folic acid supplementation and vitamin D deficiency play a crucial role in ASD risk. Although preventative measures such as food fortification and appropriate supplementation have established benefits on maternal and fetal health, it is essential to consider potential adverse effects, especially when it comes to neurological development (Sampaio et al., 2021). More research is needed to clarify the relationship between these factors and ASD in order to develop more effective prevention and early intervention strategies.

Numerous studies have also explored how the environmental exposure of pregnant women to various factors may be associated with the development of ASD in their offspring. Traditionally, these studies have focused on isolated risk factors, but in reality, exposure occurs to multiple variables concomitantly. One of the variables that stands out is poor maternal mental health. The presence of a maternal family history of neurological and psychiatric disorders indicates an important genetic component in the relationship between mental health during pregnancy and ASD in their offspring.

Furthermore, socioeconomic disadvantages during pregnancy, which induce psychosocial stress, can affect the baby's brain development and are related to the increase in the number of ASD cases in offspring. This occurs due to the possible association between the

pregnant woman's socioeconomic problems and the reduction in the concentration of the pro-inflammatory cytokine interleukin-8 (IL-8) during pregnancy, which is related to neurological irregularities in the progeny. During periods of psychosocial stress, there is an imbalance of the hypothalamic-pituitary-adrenal axis, which can also impact child development (Brito; Franco; Brentani; Beltrão-Braga, 2023).

Maternal exposure to environmental factors such as lithium used in drinking water and atmospheric pollutants has also been the subject of study. Lithium can cross the placenta and the fetal blood-brain barrier, in addition to modulating an important molecular pathway involved in autism and neurodevelopment, Wnt/B-catenin signaling, thus influencing fetal brain development. A case-control study revealed that maternal prenatal exposure to lithium in drinking water is related to an increased risk of autism spectrum disorder in offspring, highlighting the importance of further investigation into maternal exposure to lithium, for example: through diet (Liew et al., 2023). Regarding maternal exposure to air pollutants, evidence is limited regarding the effects of NO2, ozone and PM10 on the development of ASD in offspring, and there is some evidence that exposure to PM2.5 may increase the risk of ASD. However, more studies are needed that explore exposure to other pollutants and better detail the relationship between exposure time and the development of ASD (Chun et al., 2019).

For Guo, Li, Zhai, Ding (2019), there is a correlation between maternal multivitamin supplementation during prenatal care and the risk of Autism Spectrum Disorder in children. It was shown that mothers who supplemented had a significant reduction in risk compared to those who did not supplement, especially those who started supplementation before pregnancy (60% vs 43% risk reduction). Geographically, studies were more significant in North America compared to Europe (37% vs 9% risk reduction), suggesting that differences in nutritional contexts may influence these results.

On a more obstetric aspect, Jenabi, Farashi, Salehi, and Parsapoor (2023) observed a less evident relationship between post-term babies and ASD. The study showed considerable heterogeneity in results, and the relationship of ASD to post-term birth was not clearly elucidated, but several theories were proposed, including: prolonged labor, cephalopelvic disproportion, and shoulder dystocia that may lead to perinatal hypoxia and, subsequently, to neurobehavioral problems; placental insufficiency due to an "old" placenta that provides fewer nutrients and oxygen needed for fetal development, possibly leading to atypical neurobehavioral development; and dysfunctions of the "placental clock" that regulates the duration of pregnancy, which can be influenced by stressors such as noise, air pollution, heat and traffic density.

Finally, Costa et al. (2024) investigated the relationship between the consumption of alcohol, tobacco and illicit drugs during pregnancy and the development of autism in offspring, finding no evidence of an association with ASD. However, it is important to consider that information about the consumption of these substances is susceptible to memory bias and may be underestimated.

Recent research indicates that prolonged use of paracetamol during pregnancy can increase the risk of developing Autism Spectrum Disorder (ASD) by up to 20%. This increased risk is associated with paracetamol's ability to cross the placenta and the fetal blood-brain barrier, interfering with neurogenesis, causing oxidative stress and triggering maternal immune activation. These mechanisms can result in abnormalities in fetal brain development, highlighting the

need for a careful approach when prescribing acetaminophen to pregnant women and the importance of further research to fully understand this association.

FINAL CONSIDERATIONS

It is clear that maternal health and well-being during pregnancy influence the risk of ASD. ASD and its association with genetic, environmental and maternal factors during pregnancy, including the influence of variables such as folic acid supplementation, vitamin D deficiency, exposure to substances such as cannabis, lithium and atmospheric pollutants, were observed as likely factors, in addition to the impact of maternal stress, mental health and consumption of certain substances during pregnancy, such as paracetamol. The previously mentioned prenatal and perinatal factors play an important role in the risk of ASD, proving the need for preventive approaches and early interventions.

A portrait of the benefit of adequate prenatal care is the guidance on folic acid replacement, which must be started even before management. In addition to helping to close the neural tube, it also works as a protector of neurodevelopment. However, more research is needed to clarify such associations, and thus enable the development of targeted strategies that are more effective in prevention and early intervention.

REFERENCES

BRITO, Anita; FRANCO, Felipe; BRENTANI, Helena; BELTRÃO-BRAGA, Patricia Cristina Baleeiro. Assessment of vulnerability dimensions considering Family History and environmental interplay in Autism Spectrum Disorder. BMC Psychiatry, vol. 23, no. 1, p. 254, 2023.

CHUN, HeeKyoung, et al. Maternal exposure to air pollution and risk of autism in children. Environmental Pollution, vol. 256, p. 113307, 2019.

COSTA, Amanda de Andrade, *et al.* Maternal and paternal licit and illicit drug use, smoking and drinking and autism spectrum disorder. **Ciência & Saúde Coletiva**, v. 29, p. e01942023, 2024.

COSTA, Amy N, et al. The Relationship between Maternal Antibodies to Fetal Brain and Prenatal Stress Exposure in Autism Spectrum Disorder. Metabolites, v. 13, no. 5, p. 663, 2023.

CROEN, Lisa A, et al. Inflammatory Conditions During Pregnancy and Risk of Autism and Other Neurodevelopmental Disorders. Biological Psychiatry Global Open Science, v.4, n. 1, p. 39-50, 2023.

DOI, Miyuki; USUI, Noriyoshi; SHIMADA, Shoichi. Prenatal Environment and Neurodevelopmental Disorders. Frontiers in Endocrinology, vol. 13, 2022.

EGOROVA, Olga, et al. Maternal blood folate status during early pregnancy and occurrence of autism spectrum disorder in offspring: a study of 62 serum biomarkers. Molecular autism, vol. 11, p. 1-15, 2020.

GUO, Bao-Qiang; LI, Hong-Bin; ZHAI, De-Sheng; DING, Shi-Bin. Maternal multivitamin supplementation is associated with a reduced risk of autism spectrum disorder in children: a systematic review and meta-analysis. Nutrition research, vol. 65, p. 4-16, 2019.

JENABI, Ensiyeh; FARASHI, Sajjad; SALEHI, Amir Mohammad; PARSAPOOR, Hamideh. The association between post-term births and autism spectrum disorders: an updated systematic review and meta-analysis. European Journal of Medical Research, v.28, n.316, p.327-345, 2023.

LIEW, Zeyan, et al. Association between estimated geocoded residential maternal exposure to lithium in drinking water and risk for autism spectrum disorder in offspring in Denmark. JAMA pediatrics, v. 177, n.6, p. 617-624, 2023.

LIN, Yu-Chun; LIN, Ching-Heng; LIN, Ming-Chih. The Association of Prenatal Antibiotic Use with Attention Deficit and Autism Spectrum Disorders: A Nationwide Cohort Study. Children, vol. 10, p. 1128, 2023.

MAJERCZYK, Daniel, et al. Systemic maternal inflammation promotes ASD via IL-6 and IFN-γ. Bioscience Reports, vol. 42, no. 11, p. BSR20220713, 2022.

NITSCHKE, Amanda S, et al. Association between prenatal antibiotic exposure and autism spectrum disorder among term births: a population: based cohort study. Pediatric And Perinatal Epidemiology, v.37, n.6, p.516-526, 2023.

OU, Jianjun, et al. Development and validation of a risk score model for predicting autism based on pre- and perinatal factors. Frontiers in Psychiatry, vol. 15, p. 1291356, 2024.

SAMPAIO, Adalberto Cruz, *et al.* Association of the maternal folic acid supplementation with the autism spectrum disorder: A systematic review. **Revista Brasileira de Ginecologia e Obstetrícia/RBGO Gynecology and Obstetrics**, v. 43, n. 10, p. 775-781, 2021.

SEKER, Asilay et al. Maternal atopic conditions and autism spectrum disorder: a systematic review. European Child & Adolescent Psychiatry. 03 September 2023.

SOURANDER, Andre, et al. Maternal serum vitamin B12 during pregnancy and offspring autism spectrum disorder. Nutrients, vol. 15, no. 8, p. 2009, 2023.

TADESSE, Abay Woday, et al. Prenatal cannabis use and the risk of attention deficit hyperactivity disorder and autism spectrum disorder in offspring: A systematic review and meta-analysis. Journal of Psychiatric Research, vol. 171, p. 142-151, 2024.

UÇAR, Nazli; GRANT, William B; PERAITA-COSTA, Isabel; SUAREZ-VARELA, Maria Morales. How 25 (OH) D levels during pregnancy affect prevalence of autism in children: systematic review. Nutrients, vol. 12, no. 8, p. 2311, 2020.