Hyperglycemia as a gestational factor associated with Autism Spectrum Disorder: a review of the literature

Hiperglicemia como fator gestacional associado ao Transtorno do Espectro Autista: uma revisão da literatura

Hipergluceemia como factor gestacional asociado al Trastorno del Espectro Autista: una revisión de la literature

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ABSTRACT

Introduction: Autism Spectrum Disorder is a neurodevelopmental disorder characterized by deficits in social interaction, communication, and repetitive behaviors. The etiology, which has been the subject of studies, is influenced by a range of factors, including genetic, environmental, and gestational aspects. Methods: This article aims to review the literature, exploring the gestational causes associated with ASD, concentrating on intrauterine hyperglycemia. Results: The analysis reveals a scarcity of empirical studies, highlighting the need for additional research, especially in the Brazilian context. Conclusion: The results show that hyperglycemia during pregnancy can increase the risk of ASD, highlighting the importance of further research in this area.

Keywords: Autism Spectrum Disorder, gestational diabetes mellitus, hyperglycemia, gestational factors.

RESUMO

Introdução: Transtorno do Espectro Autista, um transtorno do neurodesenvolvimento caracterizado por déficits na interação social, comunicação e comportamentos repetitivos. A etiologia, que vem sendo objeto de estudos, é influenciada por uma gama de fatores, abrangendo aspectos genéticos, ambientais e gestacionais. Métodos: Este artigo tem como objetivo, revisar a literatura, explorando as causas gestacionais associadas ao TEA, com foco na hiperglicemia intrauterina. Resultados: A análise revela uma escassez de estudos empíricos, destacando a necessidade de pesquisas adicionais, especialmente no contexto brasileiro. Conclusão: Os
resultados apontam que a hiperglicemia durante a gestação pode aumentar o risco de TEA, evidenciando a importância de investigações mais aprofundadas nessa área.

**Palavras-chave:** Transtorno do Espectro Autista, diabetes mellitus gestacional, hiperglicemia, fatores gestacionais.

**RESUMEN**
Introducción: El trastorno del espectro autista es un trastorno del neurodesarrollo caracterizado por déficits en la interacción social, la comunicación y el comportamiento repetitivo. La etiología, que ha sido objeto de estudios, está influenciada por una serie de factores, incluyendo aspectos genéticos, ambientales y gestacionales. Métodos: El objetivo de este artículo es revisar la literatura, explorando las causas gestacionales asociadas al TEA, con especial atención a la hiperglucemia intrauterina. Resultados: El análisis revela una escasez de estudios empíricos, destacando la necesidad de investigaciones adicionales, especialmente en el contexto brasileño. Conclusión: Los resultados muestran que la hiperglucemia durante el embarazo puede aumentar el riesgo de TEA, destacando la importancia de nuevas investigaciones en esta área.

**Palabras clave:** Trastorno del Espectro Autista, diabetes mellitus gestacional, hiperglucemia, factores gestacionales.

**1 INTRODUCTION**

1.1 AUTISM SPECTRUM DISORDER

From the Greek autós, autism means “of oneself” and is a disorder that forms part of the list of neurodevelopmental disorders. The term autism was coined in 1908 by Eugen Bleuler, a Swiss psychiatrist, who used the term to describe the escape from reality into an inner world (Cunha, 2012). Although the concept of autism was introduced at the beginning of the 20th century, understanding and formal recognition of the syndrome have come a long way. In 1978, autism was finally classified as a disorder of cognitive development, but it was not included in the World Health Organization's International Classification of Diseases until 1993.

According to Gomes (2015), the characteristics of autism spectrum disorder are evident throughout the first three years of life, extending into adulthood. Surén et al. (2019) calculated the percentage of children with ASD using patient registration data and data obtained from the National Registry. In this study, the authors concluded that, for the most part, ASD diagnoses are more prevalent in boys, with 1.1% of boys and 0.3% of girls. It should be noted that this study corroborates the data obtained by Rocha et al. (2019), where of the 685 children diagnosed with ASD, 83.8% were male.
It is defined from a behavioral point of view, with multiple etiologies and varying degrees of severity. However, Zanolla et al., (2015) present two groups of factors mostly associated with the development of ASD. The first group includes genetic syndromes and some environmental syndromes; the second group includes effects related to the development of the fetus, which can be influenced by gestational complications.

ASD is a complex developmental disorder that has implications for communication and social interaction skills (Mascarenhas, 2024). The behavioral manifestations that define autism include qualitative deficits in social interaction and communication, repetitive and stereotyped behavior patterns, and a restricted repertoire of interests and activities (Rutter & Schopler, 1992). From a biological point of view, ASD alters the brain's ability to process sensory stimuli, such as smells, tastes, textures, sounds, lights, colors, and others, which can lead to hypersensitivity to these sensations (Gadia, 2006). Although ASD can manifest itself in varying degrees, specific signs can be considered “standard” and lead to the diagnosis, including repetitive and patterned behaviors with minimal interest in certain subjects and activities and a lack of social interaction and communication. These signs can appear in early childhood, which corresponds to the period between birth and 6 years of age, and limit the individual's daily performance, leading to atypical development (Gomes et al., 2015).

1.2 GESTACIONAL FACTORS

Complications during pregnancy can have a negative impact on the development of the fetus. In this context, diabetes mellitus (DM) is one of the non-communicable diseases, included in an unprecedented way in the global agenda of the World Health Organization (2015–2030) (Ministry of Health, 2019), and has a significant prevalence in the population of Central and South America, affecting around 10.4% of pregnant women in this region (Wang, H., 2022).

Gestational diabetes mellitus (GDM) is defined as hyperglycemia first observed during pregnancy (World Health Organization Guidelines, 2014). The relationship between in utero hyperglycemia and outcomes in fetal programming was first described in the Pima Native American population, among whom a high prevalence of obesity, type 2 DM, and GDM is found (Tam, 2017).

In association with pregnancy, DM increases maternal and fetal risk depending on the type of DM, levels of hyperglycemia, and chronic complications of pre-existing DM (Pires, 2024). In addition, this metabolic syndrome is linked to perinatal morbidity (Metzger, 2014), a potential long-term risk of diabetes and cardiovascular disease in the mother (Song, 2017), and
childhood obesity in the offspring (Tam, 2017).

Studies have reported a relationship between GDM and ASD. A meta-analysis pointed to GDM as a risk factor (Wang, 2016) for this disorder, and there is evidence of the impact on the child's fine and gross motor development, which can culminate in impaired learning and attention deficit hyperactivity disorder (Ornoy, 2001). The effects of maternal hyperglycemia on the brain of the developing fetus can result in intrauterine fetal oxidative stress as well as epigenetic changes in the expression of various genes (Yong, 2022). In addition, GDM may be related to the development of fetal macrosomy, as well as hypoglycemia and hypocalcemia in infants (Moscardini, 2024).

Given that the etiology of ASD is not fully defined in the literature and that pregnancy plays a fundamental role during the formation of the fetus, the aim of this article is to carry out a narrative literature review, seeking to explain the gestational causes that are associated with the development of this disorder, emphasizing intrauterine hyperglycemia as a causative agent of ASD.

2 METHODOLOGY

This is a literature review aimed at analyzing the relationship between pregnancy (ASD) and perinatal complications. To this end, the databases Elsevier, ScienceDirect, Scielo, and PubMed were searched using the descriptors “pregnancy”, “autism spectrum disorder”, “children”, “complications”, “perinatal”, “prenatal” and “hyperglycemia”.

The search included articles with clinical studies and complete experimental studies published online between 2004 and 2023. Incomplete articles or those that did not specifically address the topic were excluded.

3 RESULTS AND DISCUSSIONS

The aim of this study was to present and discuss the findings in the literature regarding gestational factors that may influence the cause of autism spectrum disorder, with a greater focus on the prevalence of ASD in mothers who had hyperglycemia during pregnancy. The study was based on clinical and experimental research. After analyzing 37 articles, 16 were selected to corroborate the production of this review.
3.1 STUDIES THAT POINT TO A RELATIONSHIP BETWEEN GESTATIONAL FACTORS AND ASD

The studies below point to a relationship between gestational factors and autism spectrum disorder. As mentioned, emphasis was placed on hyperglycemia as a gestational risk factor for the development of ASD. Table II shows the title, authors, and year of publication.

<table>
<thead>
<tr>
<th>Nº</th>
<th>TITLE</th>
<th>AUTHORS</th>
<th>YEAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Influência da Diabetes gestacional nos casos de Transtorno do Espectro Autista: uma revisão de literatura</td>
<td>Beatriz de A. Borghi, et al.</td>
<td>2022</td>
</tr>
<tr>
<td>3</td>
<td>Fatores Gestacionais Que Podem Influenciar No Transtorno Do Espectro Autista</td>
<td>Flávia P dos Santos, et al.</td>
<td>2019</td>
</tr>
<tr>
<td>4</td>
<td>Autism spectrum disorders: let’s talk about glucose?</td>
<td>Silvia Hoirisch-Clapauch and Antonio E. Nardi</td>
<td>2019</td>
</tr>
<tr>
<td>5</td>
<td>Fatores de risco para macrossomia fetal em gestações complicadas por diabete ou por hiperplicemia diária</td>
<td>Luciane T. R. L. Kerche, et al.</td>
<td>2005</td>
</tr>
<tr>
<td>6</td>
<td>Systematic review investigating the relationship between autism spectrum disorder and metabolic dysfunction</td>
<td>Angela Y. Chieh, et al.</td>
<td>2021</td>
</tr>
<tr>
<td>7</td>
<td>Maternal Diabetes and Fetal Programming Toward Neurological Diseases: Beyond Neural Tube Defects</td>
<td>Berenice Márquez-Valadez et al.</td>
<td>2018</td>
</tr>
<tr>
<td>10</td>
<td>Modeling the Interplay Between Neurons and Astrocytes in Autism Using Human Induced Pluripotent Stem Cells.</td>
<td>Beltrão-Braga, P. C., Et Al.</td>
<td>2018</td>
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<tr>
<td>11</td>
<td>The pathophysiology of the fetus of the diabetic mother.</td>
<td>Eidelman, A. &amp;.</td>
<td>2002</td>
</tr>
<tr>
<td>13</td>
<td>Fatores de risco gestacional em mães de crianças diagnosticadas com autismo</td>
<td>Hione T. dos Santos, et al.</td>
<td>2022</td>
</tr>
<tr>
<td>15</td>
<td>Alterações Gestacionais E O Transtorno Do Espectro Autista: Uma Revisão De Literatura.</td>
<td>Rayane M. Botelho</td>
<td>2020</td>
</tr>
</tbody>
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Source: Author.

3.2 CONSIDERATIONS ABOUT THE STUDIES

The etiology of ASD is complex and multifactorial, involving both genetic and environmental factors. Studies have shown that modifications found in the brains of children diagnosed with autism indicate that these alterations are developed during the gestational
period and that the combination of genes and environmental factors, such as maternal infections during pregnancy, exposure to toxins, and prematurity, can increase the risk of developing ASD (Walker et al., 2016).

Recently, researchers have shown experimentally that an inflammation in brain cells called astrocytes, cells responsible for transmitting and storing information in the brain, may be correlated with the onset of autism spectrum disorders (ASD), since, according to research, these cells are more immature in people with ASD (Beltrão-Braga et al., 2018). In one of the analyses that made up this study, biologist Fabiele Russo collected neuron and astrocyte cells from the milk teeth of three Brazilian children diagnosed with the disorder. Through detailed analysis, the biologist observed distinct characteristics in the cells of individuals diagnosed with ASD compared to the cells of neurotypical children. The cells extracted from the teeth of children with ASD were immature and less complex, as well as having significantly fewer branches, directly affecting connections with other neurons—the opposite result compared to the cells extracted from the teeth of neurotypical children (Figure 1).

Figure 1: Effects of inflammation on astrocytes.

The development of the brain during pregnancy and the first few years of life is crucial for shaping an individual's general level of neuropsychological performance. Several studies, such as Tomalski & Johnson (2023), corroborate this idea, highlighting the importance of this
phase for mental and physical health throughout life. Cusick & Georgieff (2012) reinforce this importance by pointing out that changes in the intrauterine environment during pregnancy, such as maternal metabolic pathologies, can have repercussions on the development of the fetus and lead to long-term conditions for the newborn. Neuronal migration is a primordial process for the formation and development of the brain, beginning in the first weeks of pregnancy and concluding around 26 to 29 weeks (Kostovic & Jovanov-Milosevic, 2006). The formation of neuronal connections, a crucial stage in the development of cognitive and behavioral functions, begins only in the fifth week of gestation, reaching a peak around 24 to 28 weeks (Clancy et al., 2001).

3.3 DIABETES AS A GESTATIONAL FACTOR IN THE DEVELOPMENT OF ASD

According to Elsabbagh (2012), the prevalence of autism spectrum disorder (ASD) has been increasing in recent decades, and epidemiological studies suggest that environmental and maternal factors may contribute to this increase. Among the potential risk factors, maternal obesity and diabetes during pregnancy have been the subject of increasing research (Krakowiak et al., 2012).

According to a study by Xu et al. (2013), diabetes mellitus was found to increase the chances of having a child diagnosed with autism spectrum disorder (ASD) by 50%. The risk seems to be more pronounced in type 1 diabetes compared to type 2, and even more significant in type 2 diabetes compared to gestational diabetes. It is important to note that when gestational diabetes is diagnosed after 26 weeks of pregnancy, the chances of having a child with ASD are equivalent to the chances of the general population. This suggests that intrauterine hyperglycemia, or high glucose concentration in utero, can play a detrimental role in brain development, especially during critical periods of neuronal migration and synaptic connection formation (Hoirisch-Clapauch & Nardi, 2019).

According to Balsells (2015), studies have shown that pre-pregnancy obesity combined with gestational diabetes more than doubles the risk of ASD. Pre-pregnancy overweight and accelerated weight gain during pregnancy is a highly relevant public health issue, mainly due to its association with gestational diabetes mellitus (GDM), which is characterized by glucose intolerance during pregnancy. GDM is a prevalent condition, affecting around 15% of pregnant women worldwide. It can cause various complications for maternal and fetal health (Ortega-Senovilla et al., 2010).
3.4 HYPERGLYCEMIA AS A GESTATIONAL FACTOR IN THE DEVELOPMENT OF ASD

However, Hoirisch-Clapauch (2019) hypothesized that postprandial hyperglycemia, and not diabetes itself, could be a critical factor in the pathogenesis of ASD. Maternal hyperglycemia can result in fetal hypoxia, a condition in which not enough oxygen reaches the cells and tissues of the body (Eidelman, 2002), and an impoverished oxygen supply is detrimental to the neurological development of the fetus and thus contributes to an increased risk of ASD (Burstyn, 2011).

By definition, hyperglycemia is when blood sugar levels are too high. Postprandial hyperglycemia is characterized by an increase in blood glucose levels after eating. In general, after meals, there is a temporary increase in blood glucose levels due to the absorption of nutrients from the gastrointestinal tract. However, in people with postprandial hyperglycemia, this increase can be excessive or prolonged (Geloneze et al., 2006).

Scientist and pediatrician Michelle Baack (2014) experimented with non-diabetic pregnant rats to investigate the connection between intrauterine hyperglycemia and congenital malformations. The study found that only embryos exposed to high concentrations of glucose showed a high rate of malformations. This is because intrauterine hyperglycemia, independently of maternal diabetes, is teratogenic, i.e., it can cause congenital malformations in the fetus. This ability to generate malformations is due to the capacity of excess glucose to interfere with embryonic and fetal development, which can cause alterations in the structure and function of the offspring. In the experiment, the result was found after the infusion of saline solution into the left uterine artery of non-diabetic pregnant rats during the gestational period of 7 to 9 days, while another group received an infusion of a high concentration of glucose into the left uterine artery. Nevertheless, a second study of 2,734 mother-child pairs, with an average follow-up of 6 years, found that mothers of children with ASD were significantly older and more affected by GDM than mothers of children with typical development (TD) (Li et al., 2016).
4 CONCLUSIONS

This article aimed to carry out a literature review, with an emphasis on studies that have looked at possible gestational interconnections as a factor in the development of autism spectrum disorder, with a greater focus on intrauterine hyperglycemia as a causal agent.

By studying the correlation between fetal hyperglycemia and autism spectrum disorder, it was possible to find and interconnect some information that presents a connection as proposed.

Intrauterine hyperglycemia is teratogenic and can cause congenital malformation in the fetus, while it can also cause fetal hypoxia, blocking the flow of oxygen to the body's cells and tissues. Both factors affect neurological development in the gestational period. During the studies, one of the studies showed inflammation in the brain cells of people with autism spectrum disorder, where these cells were less complex and had fewer branches in the neurons, affecting the connection between them.

Limitations were identified in the literature related to the quantity and variety of research and the locations where the studies were carried out. However, as this is a literature review article, it was clear that there is a lack of empirical studies, especially in Brazil. The number of studies found is low, revealing the importance of producing new materials with more robust methodological designs that can shed more light on these discussions.
REFERÊNCIA


