Austin Journal of Obesity & Metabolic Syndrome

Open Access

Austin Publishing Group

Mini Review

The Closeness between Maternal Diabetes and Autism Spectrum Disorder: A Mini Review

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Received: July 01, 2020; **Accepted:** August 03, 2020; **Published:** August 10, 2020

Abstract

Autism Spectrum Disorder (ASD) is a developmental disability characterized by persistent impairments in social interaction and the presence of restricted, repetitive patterns of behaviors, interests, or activities. ASD is regarded as multifactorial, with genetic and non-genetic risk factors acting together to produce the phenotype. The causes and contributing factors for ASD are still poorly understood. The studies indicate that autism is a neurobiological developmental disorder with a strong genetic basis. In addition, there is evidence that prenatal environmental conditions are associated with ASD, affecting the development of the fetal brain. The relationship between maternal diabetes and ASD in offspring shows inconsistent results; thus, a literature review is needed to assess the available evidence. The prevalence of maternal diabetes is increasing and approximately 87.5% of maternal diabetes is due to gestational diabetes, defined as glucose intolerance with onset or first recognition during pregnancy. Maternal diabetes can cause miscarriage, macrosomia and other adverse fetal outcomes, as well as impaired neurological development in the offspring. Although there are studies that do not prove a correlation between maternal diabetes and ASD, however, most of them conclude that maternal diabetes is associated with ASD in offspring.

Keywords: Diabetes; Inflammation; Offspring; Autism Spectrum Disorder

Background

Autism Spectrum Disorder (ASD) is a neurodevelopmental disability that is associated with repetitive behaviors and language deficits, being highly heterogeneous and associated with neuroinflammation [1]. The diagnosis of ASDs has increased substantially over time, about 1 in 54 children has been identified with Autism Spectrum Disorder (ASD) according to estimates from CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network [2]. It is known that both genetic and environmental factors are determinant for its physiopathology [3], being the prenatal period one of the most studied periods of environmental exposure [4].

Obesity and diabetes, clinical immune dysregulation conditions, are linked to several neuropsychiatric disorders in literature [5], and, as maternal metabolic pathologies, can be related to abnormal brain development and long-term conditions in the newborn. Epidemiological studies show that maternal obesity and metabolic complications such as diabetes increase the risk of children developing behavioral disorders, such as attention deficit hyperactivity disorder, Autism Spectrum Disorders (ASD), and schizophrenia [6]. We summarized literature data among this subject in order to try shedding a light on this discussion.

Diabetes and Autism Spectrum Disorder

Cordero et al observed, in a case-control study observing 2,564 mothers, that there was no association between diabetes in pregnancy and ASD, although it was found some statistically significant relation between diabetes in pregnancy and other developmental delays [7]. Saunders, Woodland and Gander in a study with small groups (181 children) didn't found statistically significant relation either, although metabolical conditions, such as medication use and smoking, were associated as prenatal risk exposure [8].

However, a retrospective cohort study identifying 3 types of diabetes, preexisting type 1, preexisting type 2 and gestational, diagnosed by 26 weeks' gestation, found an elevated risk of ASD development when compared with no diabetic mothers. Type 1 diabetes is considered to be the strongest factor to ASD. The results also suggest that the severity of maternal diabetes may also be associated with the development of ASD in the offspring [9]. However, the detailed mechanism for ASDs mediated by maternal diabetes remains uncertain.

Li et al concluded after a birth cohort study that both pregestational diabetes and obesity were associated with an increased risk of developing ASD, and the risks were even higher when the mother presented both conditions. They also revealed in this study that only a combination of obesity and diabetes can be associated with a significant risk of ASD, whereas each condition, independently, was not. The study theorizes that ASD is related to high blood glucose levels and untreated hyperglycemia during the central nervous system development [10].

In experiments using in vivo rats was possible to observe that maternal diabetes, after the hyperglycemia effect, can suppress the amygdala (a brain area implicated in social cognition), causing an ASD-similar behavior. This study observed that hyperglycemia mediates persistent oxidative stress, causing the superoxide dismutase 2 (SOD2) suppression in the amygdala, while SOD2 overexpression in the same cerebral area ameliorates autism-like behavior. The authors

Citation: Lima MES, Aragão FA and Aragão GF. The Closeness between Maternal Diabetes and Autism Spectrum Disorder: A Mini Review. Austin J Obes & Metab Synd. 2020; 4(3): 1022.

suggest that diabetes causes persistent epigenetic changes during neural development and resulting in an increased risk of ASD [11].

Studies show that transient hyperglycemia induces epigenetic changes and altered gene expression during subsequent normoglycemia and that maternal diabetes is associated with epigenetic changes and impaired neurological development and resulting in an increased risk of ASD [12-14].

A recent nationwide cohort study in Finland observed that maternal diabetes, especially when associated with maternal obesity, is related not only with increased risk of ASD, but several psychopathologic disorders, such as sleeping, anxiety and mood disorders [11->15]. This study concurs with Li et al [10], and establishes that the severity of obesity is directly proportional to ASD developing risk.

Gestational diabetes, Type 1 Diabetes (T1DM) and Type 2 Diabetes (T2DM) can affect endocrine functions and placental metabolic, exposing the fetus to maternal hyperglycemia, lipotoxicity, oxidative stress, inflammation, and insulin resistance, which are thought to have long-lasting outcomes on organ development and function. The outcomes associated with hyperglycemia may, in part, be mediated by epigenetics [15].

Another study using transcranial magnetic stimulation related the use of insulin or metformin during pregnancy with a reduction in cortical excitability and neuroplasticity, noticing that insulin resistance is one of the main perinatal factors that reflects suboptimal or delayed neurodevelopment of neural structures, leading to ASD. The results of this paper show that even gestational diabetes properly treated can have important effects on neurophysiological processes that persist until adolescence, such as changes in neuroplasticity and cortisol secretion. The extent of these effects may be linked to the severity of maternal diabetes, particularly insulin resistance [16].

In a systematic review and meta-analysis entitled, maternal diabetes and the risk of autism spectrum disorders in the offspring, the authors concluded that maternal diabetes was significantly associated with a greater risk of ASD in the offspring. This work brings a discussion that in utero exposure to hyperglycemia, by all types of maternal diabetes, may increase the risk of offspring ASD involving several biological mechanisms [17].

The authors explain that maternal hyperglycemia can result in hypoxia in the fetus, and a depleted oxygen supply to the fetus may impair neurodevelopment and thus contribute to a greater risk of ASD. Maternal hyperglycemia has been associated with increased free-radical production and impaired antioxidant defense system that lead to oxidative stress in the cord blood and placental tissue. It is also known that excessive adiposity that commonly accompanies T2DM and gestational diabetes are inducers of chronic inflammation. Moreover, T1DM is an autoimmune disorder resulted from a cellular-mediated autoimmune destruction of pancreatic beta-cells. Finally, epigenetic modification by hyperglycemia may also be implicated in the pathogenesis of ASD, but the current evidence is still sparse [17].

Finally, this work allows us to conclude that early detection and treatment of gestational diabetes can attenuate or prevent alterations in the neurodevelopment of offspring, as the evidence shows that gestational diabetes can be a risk factor for autism, so we reiterate the need for adequate support to monitor the health of women of childbearing age during their gestational period.

Conclusion

Maternal diabetes and its consequences, as well as obesity, may be related to pathological processes in neural system development, leading to ASD in offspring. Given the complexity of ASD physiopathology, combining immune and genetic factors that can be associated with inflammation, it is possible that the diabetes inflammation process is strictly related to it. Thus, further studies are necessary to confirm the correlation.

Acknowledgement

We thank the Study Group on Neuroinflammation and Neurotoxicology of Autistic Spectrum Disorder from Estadual University of Ceará – GENIT/UECE.

Authors' Contribution

The authors contributed to the concept and design, data acquisition, data analysis and interpretation; write the article or review it critically for important intellectual content; and final approval of the version to be published, conclusions and writing. All authors read and approved the final manuscript.

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