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GESTATIONAL WEIGHT GAIN AND RISK OF AUTISM SPECTRUM DISORDERS IN OFFSPRING : A SYSTEMATIC REVIEW

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Abstract

Autism spectrum disorder, more commonly abbreviated as ASD, is a neurodevelopmental condition that can be brought on by a number of different things. Although it is commonly accepted that genetic and environmental factors, as well as the interactions between the two, contribute to autistic phenotypes, the actual causal mechanisms that underpin this phenomena are not yet known to be fully understood by researchers. In this study, the significance of several criteria, including the age of the parents, teratogenic chemicals, prenatal dangers, medication, smoking and alcohol use, food, immunization, hazardous exposures, and the function of severe psychosocial factors, is methodically mapped out. There is a correlation between obesity and systemic inflammation, which can be seen in the increased production of cytokines that happens as a result of an increase in the amount of adipose tissue that has been stored in the body. The United States of America served as the location for the investigation's conduct. Furthermore, GWG that was adjusted for gestational age was associated with ASD, and this association was especially high in male offspring. This finding was consistent across all genders.

Keyword: *Autism Spectrum Disorders; Body Mass Index; Gestational Weight; Offspring*

INTRODUCTION

A range of neurodevelopmental diseases known together as autism spectrum disorder (ASD) is characterized by difficulties in communication and social interaction, as well as confined, repetitive patterns of behavior, interests, or activities.[1] Data from epidemiological surveys conducted over the course of the past 20 years indicate that the incidence of ASD has increased on a global scale, and its prevalence rate is currently believed to be somewhere around 1%. The outlook is not good for the vast majority of children who have ASD.[2,3]

When reaching adulthood, they are unable to maintain their independence in terms of living, studying, and working, and they become a drain not only on their family but also on society. Autism is a multifaceted condition that can be traced back to a confluence of inherited and acquired risk factors, as well as environmental influences. The potential risk factors for ASD include maternal gestational diabetes, maternal hemorrhage during pregnancy, prenatal exposure to valproate and antidepressant, and parental socioeconomic level.[4,5]

Pregnancy obesity and gestational diabetes increase the incidence of ASD, supporting the idea that postprandial hyperglycemia, not diabetes, causes ASD. Obese people are inactive, although aerobic exercise lowers glucose levels. Obesity before pregnancy and pregnancy weight gain over 18 kg increase the risk of ASD in children. Postprandial hyperglycemia and hyperinsulinemia develop from inactivity and a high-carb diet. Hyperinsulinemia, a lipogenic hormone, causes weight gain and obesity. Adipose tissue-derived cytokines disrupt insulin signaling, causing postprandial hyperglycemia in obese people.[6]

The most recent meta-analysis found that obesity in the mother before pregnancy is linked to an elevated risk of autism spectrum disorder (ASD) in the child. Several previous studies suggest that obesity in the mother before pregnancy may have an effect on the development of the nervous system of the offspring through the intestinal flora, oxidative stress and inflammation-induced mal-programming, and the leptin resistance mechanism in offspring, ultimately leading to an increased risk of autism spectrum disorder in the offspring.[5,7]

In addition, alterations in intestinal flora, elevated inflammatory levels, and an active leptin resistance mechanism are all connected with gestational weight gain (GWG). Using this framework, epidemiological research has been conducted to evaluate the possible links between GWG and ASD.[8,9] Yet, their findings do not all point to the same conclusion. For instance, the research conducted by Bilder et al. (2013)[10] and Xiang et al. (2015)[11] found a positive correlation between GWG and the risk of ASD. In contrast, the research conducted by Jo et al. (2015)[5] and Hendrix et al. (2012)[12] did not show any results that were statistically significant.

The goal of this study was to demonstrate a connection between maternal weight gain during pregnancy and an increased risk of autism spectrum disorders in the child.

METHODS

Protocol

Using the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 recommendations, the author ensured that this research adhered to the requirements. This is done to ensure the accuracy of the investigation's results.

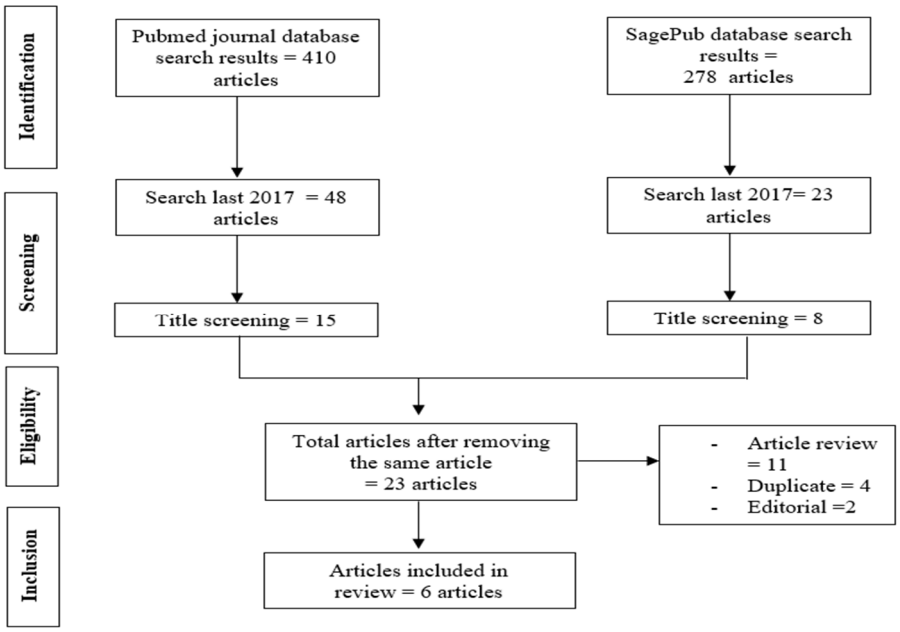

Figure 1. Article search flowchart

Criteria for Eligibility

This review explores the association between maternal weight gain during pregnancy and the likelihood of autism spectrum disorders in kids. This is achieved by evaluating or analyzing prior studies on the subject. This essay's objective is to highlight the significance of the issues covered. Researchers who participated in the study met the following requirements: 1) In order for the manuscript to be accepted for publication, it must be written in English and focus on the association between fetal weight gain and the risk of autism spectrum disorders. 2) This assessment includes works published after 2017, but previous to the time period under consideration. Inadmissible research includes editorials, submissions without a DOI, already published review articles, and entries that are almost identical to previously published journal articles.

Search Strategy

We used "gestational weight gain" and "autism spectrum disorders" as keywords.The search for studies to be included in the systematic review was carried out from February, 25th 2023 using the PubMed and SagePub databases by inputting the words: *("gestational weight gain"[MeSH Terms] OR ("gestational"[All Fields] AND "weight"[All Fields] AND "gain"[All Fields]) OR "gestational weight gain"[All Fields]) AND ("autism spectrum disorder"[MeSH Terms] OR ("autism"[All Fields] AND "spectrum"[All Fields] AND "disorder"[All Fields]) OR "autism spectrum disorder"[All Fields] OR ("autism"[All Fields] AND "spectrum"[All Fields] AND "disorders"[All Fields]) OR "autism spectrum disorders"[All Fields])* used in searching the literature.

Data retrieval

After reviewing each study's abstract and title, the authors evaluated if it met the inclusion criteria. The authors then chose historical books as sources for this subject. This result was obtained after examining many studies that all demonstrated the same pattern. All contributions must be written in English and must be previously unpublished. In the systematic review, only studies that met all inclusion criteria were reviewed. This restricts the search results to relevant results only. We do not examine research findings that do not meet our requirements. After then, the research will be analyzed in depth. Throughout the course of the study's examination, the following information was uncovered: names, authors, publication dates, location, study activities, and parameters.

The search results were transferred to an Endnote file, and duplicate articles were eliminated. Two separate reviewers evaluated the titles and abstracts of the remaining publications to identify those within the scope of this review. The full texts of the papers that passed the initial screening were then evaluated for eligibility and data extraction. Excluded were review articles, animal studies, conference papers, and research that evaluated the link between GWG and other health concerns, such as diabetes or hypertension. During conversation, disagreements between the two reviewers were overcome.

Quality Assessment and Data Synthesis

Before deciding which publications to research further, each author conducted their own analysis of the studies listed in the publication's title and abstract. Then, we will assess all papers that meet the inclusion requirements of the review and are, therefore, worthy of inclusion. Then, based on our findings, we will choose which papers to include in the review. This criterion is used to select the manuscripts for evaluation. To simplify as much as possible the selection of papers for review. What previous studies were conducted, and what aspects of those studies qualified them for inclusion in the review?

RESULT

Matias, et al (2021)[9] showed class 2/3 maternal obesity was related to ASD (adjusted odds ratio [AOR] = 1.87, 95% confidence interval [CI] = 1.40-2.51) and DD (AOR = 1.61, 95% CI = 1.22-2.13). GWG z score was not associated with DD (AOR = 1.14, 95% CI: 0.95-1.36), whereas the highest tertile of GWG z score was associated with increased risks of ASD, especially in male children (AOR = 1.47, 95% CI = 1.15-1.80). The results reveal that severe maternal obesity before to pregnancy increases the likelihood of ASD and DD in children and that high gestational-age-adjusted GWG is a risk factor for ASD in male children.

Shen, et al (2018)[13] conducted a study with parents of 705 Han Chinese children with autism and 2,236 unrelated typically developing children. After correcting for children's gender, parental age, and family annual income, high GWG was related with autism risk in the overall population (OR = 1.327, 95% CI = 1.021–1.771), whereas the association between maternal pre-pregnancy BMI and autism was not significant. Stratification studies revealed that high GWG increased the incidence of autism in overweight/obese moms (OR = 2.468, 95% CI = 1.102–5.50), but not in underweight or normal weight mothers.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Matias, 2021[9]	United State (US)	Retrospective cohort study	ASD (n = 1,159) and DD (n = 1,617), versus control children (n = 1,633)	The findings imply that a high gestational-age-adjusted GWG is a risk factor for autism spectrum disorder in male offspring and that severe obesity in the mother prior to pregnancy raises the risk of autism spectrum disorder and developmental delay in children.
Shen, 2018[13]	China	Case control	Parents of 705 Han Chinese children with autism and 2,236 unrelated typically developing children	It is possible that the maternal BMI before pregnancy is not independently related with the risk of autism. However, GWG levels that are too high may be linked to an increased risk of autism in children born to women who are overweight or obese.
Lee, 2022[14]	Sweden	Retrospective cohort study	467,485 patients	No matter the mother's BMI at the beginning of pregnancy, our data indicate that an increased risk of IDD in the children may be associated with inadequate maternal GWG. Nevertheless, this is only the case for moms whose BMI was below 25 kg/m2 when they were pregnant with their first child if the GWG was really excessive (more than 25 kg).
Kyoung, 2021[15]	USA	Retrospective cohort study	1,164 mother-child	Prepregnancy The use of body mass index (BMI) and adiponectin during pregnancy may be helpful as a monitoring technique for autism risk. It's possible that raising adiponectin levels in pregnant women can help avoid autism spectrum disorders.
Qiu, 2018[16]	China	Case control	36 children who were diagnosed with ASD (ASD group) and 72 non-ASD	Because the presence of excess weight or obesity in the father prior to the mother becoming pregnant is a risk factor in and of itself for autism spectrum disorder in the child, it is essential for the father to maintain a body mass index that falls within the normal range prior to the mother becoming pregnant.
Windham, 2019	USA	Case control	ASD: n = 540, Developmental delays: n = 720, Control: n = 776/Singleton births	It was found that children who had various developmental impairments had a greater chance of having moms who were overweight or obese before pregnancy, but not mothers who acquired more weight during pregnancy. It's possible that being overweight and gaining weight are indicators of variables that can be changed.

Other study showed insufficient GWG was linked with a 21% increased risk of IDD in offspring (95% CI = 1.11–1.31) compared to optimal GWG. Using the LifeCycle categorization, however, offspring of mothers with inadequate GWG (HR = 1.14, 95% CI = 1.05–1.24) or excessive GWG (HR = 1.09, 95% CI = 1.01–1.17) had greater odds of IDD than those of mothers with optimal GWG. Very low GWG (20th centile) and low GWG (20th–40th centile) were associated with an increased incidence of IDD in children. A stratified analysis by maternal early-pregnancy body mass index (BMI) revealed that overweight/obese mothers (BMI 25 kg/m2) with severely excessive GWG (>25 kg) were associated with a higher risk of IDD in their offspring.[14]

Kyoung, et al (2021)[15] showed the higher second-trimester adiponectin levels were associated with a lower risk of ASD in offspring (AOR 0.49; 95% CI, 0.30-0.78; and OR 0.54; 95% CI, 0.32-0.91 after adjusting for maternal race/ethnicity, education, child sex, and BMI, gestational weight gain, gestational diabetes, and smoking status). ASDs were not associated with maternal leptin, cord blood leptin, or adiponectin levels. The use of body mass index (BMI) and adiponectin during pregnancy may be useful as an autism risk monitoring approach. Increasing adiponectin levels in pregnant women may help prevent autism spectrum disorders.

When the mother became pregnant, the detection rate of overweight or obesity in the father was considerably greater in the ASD group (56% vs. 32%; P=0.018) in comparison to the control group. The odds ratio for autism spectrum disorder (ASD) in offspring was calculated to be 2.66 and 2.58, respectively, when univariate and multivariate logistic regression analyses were performed. This indicated that a father's overweight or obesity before the mother became pregnant was a risk factor for ASD in offspring.[16]

Windham, et al (2019)[8] showed that relationships with higher GWG were stronger (Quintile5 vs. Quintile3 AOR = 1.58, 95%CI 1.08-2.31), and this was especially true for overweight/obese women (AOR = 1.90, 95%CI 0.98-3.40). DD was linked with maternal overweight and obesity (obesity AOR = 1.48, 95%CI 1.01-2.01) but not with total GWG or clinical

recommendations. High maternal BMI and GWG are risk factors for other pregnancy and infant outcomes, and our data imply they may also reflect modifiable neurodevelopmental risk factors.

DISCUSSION

Autism spectrum disorder (often referred to as ASD) is a neurodevelopmental illness that can have a variety of causes. Although it is generally accepted that genetic and environmental factors, as well as the interactions between the two, contribute to autistic phenotypes, the exact causal mechanisms that underlie this phenomenon are not yet fully known. The significance of parameters such as parental age, teratogenic substances, prenatal hazards, medicine, smoking and alcohol use, diet, vaccination, hazardous exposures, and the role of extreme psychosocial factors are all meticulously mapped out in this study.[8,12]

In addition, study investigate the part that possible preventive variables play, such as the consumption of folate and fatty acids. There is mounting evidence that factors such as advanced maternal and paternal age, consumption of valproate, exposure to toxic chemicals, maternal diabetes, enhanced steroidogenic activity, immune activation, and possibly altered zinc–copper cycles and treatment with selective serotonin reuptake inhibitors are associated with an increased risk of autism spectrum disorder in offspring.[8,12]

This large multisite case–control study found that severe maternal obesity (obesity Class 2/3) was associated with approximately double the risks of ASD (with or without ID), as well as higher odds of DD. The investigation was carried out in the United States. In addition, GWG that was adjusted for gestational age was associated with ASD, and this association was particularly strong in male offspring. Nevertheless, there was no association found between GWG and DD. There were no relationships found between GWG rate and either ASD or DD when the data was analyzed according to the degree to which it adhered to clinical recommendations.[9]

Shen, et al (2018)[13] showed that the maternal BMI before pregnancy is not independently related with the risk of autism. However, GWG levels that are too high may be linked to an increased risk of autism in children born to women who are overweight or obese. Only children born to moms who are overweight or obese, but not those whose mothers are underweight or of normal weight, could be at a greater risk of developing autism if their mothers had an excessively high GWG. Hence, there is a possibility that the interactions between BMI and GWG are related to the risk of autism.[17]

The research conducted by Shen et al. was a case-controlled study, which means that it did not investigate the association between BMI and GWG with risk of autism among obese mothers separately, nor did it adjust for the confounding variables related to the risk of autism, such as gestational diabetes or gestational hypertension. Instead, it focused solely on the risk of autism in children born to mothers who were obese. Diabetes mellitus during pregnancy and obesity in the mother before pregnancy have both been shown to increase the risk of autism in offspring in a number of earlier studies.[13]

There is a correlation between obesity and systemic inflammation, which may be seen in the increased cytokine production that occurs as a result of an increase in the amount of adipose tissue.[18,19] Because they are able to pass the blood–placenta barrier, inflammatory mediators can have an effect on the neurodevelopment of the fetus.[20] As a result, the primary mechanisms through which maternal obesity might affect child neurodevelopment are related to maternal inflammation. These mechanisms include neuroinflammation; increased oxidative stress; dysregulated insulin, glucose, and leptin signaling; dysregulated serotonergic and dopaminergic signaling; and perturbations in synaptic plasticity.[21]

In particular, a dysfunction in the control of serotonin production in the placenta, which is produced by inflammation in the mother, modifies neurogenesis and axonal growth in the fetal forebrain, which has the potential to alter the course that fetal brain development takes.[22] Also, there is a possibility that epigenetic modulation of inflammatory pathways is linked to changes that occur in the brain as a consequence of the prenatal environment.[18] In comparison to women of normal weight, obese women's fetuses' umbilical cord gene expression profiles showed patterns that are associated with neurodegeneration, lower survival of sensory neurons, and decreased neurogenesis. These findings were seen in the fetuses' umbilical cords.[23]

The discovery that pre-pregnancy obesity paired with gestational diabetes more than doubles the risk of autism spectrum disorder (ASD) lends credence to the concept that postprandial hyperglycemia, and not diabetes, is the culprit in the pathogenesis of autism spectrum disorder (ASD). Aerobic exercises are known to be quite beneficial in regulating glucose levels; however, people who are fat typically do not engage in physical activity. Before to pregnancy obesity and a weight gain of less than 18 kilograms during pregnancy are two factors that raise the likelihood of having a kid who has autism spectrum disorder (ASD).[6,17]

Postprandial hyperglycemia may be both a cause and a consequence of these factors. Postmeal hyperglycemia and hyperinsulinemia are the results of insufficient time spent being physically active paired with a diet that is high in carbohydrates. Hyperinsulinemia is associated with weight growth and, in the long run, obesity because insulin is a hormone that promotes fat storage. Adipose tissue-derived cytokines are responsible for the impairment of insulin signaling that leads to postprandial hyperglycemia in obese patients.[6,17]

CONCLUSION

A consistent association was found in ASD patients whose mothers gained excessive weight during pregnancy. However, the relationship between prepregnancy BMI and the incidence of ASD is inconsistent.

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