Review

Maternal Diabetes and Autism Spectrum Disorders in the Offspring: A Review of Epidemiological Evidence and Potential Biologic Mechanisms

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Gestational diabetes is a common pregnancy complication whose prevalence is increasing among women of reproductive age and results in both short-and long-term adverse outcomes for the offspring. Hyperglycemia or other consequences of adverse maternal metabolic profiles in pregnancy may contribute to autism risk through several potential mediating mechanisms, such as inflammation, oxidative stress, and epigenetics. The present review aims to summarize recent studies exploring the association between maternal pre-gestational diabetes, gestational diabetes, obesity and autism spectrum disorders (ASD) in the offspring. We will also explore potential biologic mechanisms to explain the association between in utero exposure to a hyperglycemic environment and risk for ASD, including inflammation, oxidative stress and epigenetics. Considering the concurrent rise in obesity and diabetes in pregnancy, as well as the modifiable nature of these disorders, their associations with ASD and the underlying molecular mechanisms should be explored further.
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Key Words: *gestational diabetes mellitus (GDM), autism spectrum disorders (ASD), type 2 diabetes (T2DM)*

INTRODUCTION

Gestational diabetes (GDM), defined as glucose intolerance with onset or fist recognition in pregnancy, is one of the most common pregnancy complications.[1] The prevalence of GDM has been and continues to increase, mirroring the obesity epidemic among women of reproductive age. In addition, pre-existing type 2 diabetes (T2DM) has been estimated to affect around 1.85 million women of reproductive age with approximately one third of those being undiagnosed cases[2] and with many cases recognized for the first time during pregnancy. Maternal diabetes in pregnancy is associated with an increased risk of miscarriage, macrosomia and other adverse fetal outcomes[3] as well as poor neurologic outcomes in the offspring.[4] The risks to the developing fetal brain are due in part to inadequate maternal glycemic control, regardless of whether the pregnancy was the first onset of diabetes 5 and therefore adverse outcomes may result from type 1 diabetes, T2DM or GDM. Additionally, an insulin resistant and hyperglycemic intrauterine environment resulting from obesity could present an adverse environment for the fetal brain. Mechanisms explaining the link between hyperglycemia and neurodevelopment in the offspring include inflammation, oxidative stress and epigenetics.

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In addition, even in cases of well controlled diabetes, fetuses of GDM pregnancies are exposed to hypoxia as well as higher glucose and lactate than fetuses of normal pregnancies,[6] presenting additional biologic pathways for adverse neurodevelopment of the offspring.

Neurodevelopmental disorders include impairment of growth or development of the brain or central nervous system due to malformation or injury to the developing brain.[7] Examples of neurodevelopmental disorders include autism spectrum disorders (ASD), cerebral palsy, intellectual disability, sensory impairments (visual and hearing), attention-deficit/hyperactivity disorder (ADHD), and learning disabilities as well as behavioral problems and social-emotional difficulties.[7] The prevalence of neuro-developmental disorders is quite high with ASD alone estimated to affect more than 1 in 150 children.[8]

The ASD are a collection of pervasive developmental disorders, including autism, Asperger's and pervasive developmental disorder-not otherwise specified (PDD-NOS), characterized by delayed or absent language development, lack of interest in other people, repetitive or stereotyped behavior and in some cases regression of early speech and sociability.[9] While ASD are highly heritable, with some estimates greater than 90%,[10] a lack of complete concordance among both mono (MZ)- and dizygotic (DZ) twins suggests a possible contribution from environmental risk factors. For

instance, it has been postulated that the range of concordances estimated from MZ pairs, as well as the clinical heterogeneity of MZ twins may be explained by the difference in the uterine environment,[11] such as maternal nutrition status and pregnancy complications.

Pregnancy complications have long been a topic of research towards identifying risk factors for ASD. In fact, the most highly replicated non-genetic risk factors for ASD are adverse conditions of pregnancy, which are generally evaluated using composite measures of obstetric suboptimality.[12-20] A recent meta-analysis identified GDM as the strongest risk factor for ASD.[21] Although biologically plausible, other recent studies didn't support the results.[22,23] Discrepancies in the findings may be due to differences in study populations (with respect to both geography and sample size), study design as well as exposure and outcome assessments. The objective of this review is to summarize the literature describing the association between maternal diabetes in pregnancy (i.e. pre-gestational diabetes and GDM), and ASD. In addition, we will describe potential biologic mechanisms that may link hyperglycemia in pregnancy to the pathogenesis of ASD.

MATERNAL DIABETES AND ASD

Epidemiologic studies on the association of maternal diabetes in pregnancy and risk of ASD in the offspring are sparse. A meta-analysis of prenatal risk factors for ASD estimated the combined risks from studies conducted through March 2007.[21] This meta-analysis included 4 studies on maternal pre-gestational diabetes or GDM and autism;[15,16,18,24] in total 2,764 study participants and 685 autism cases. Among the prenatal risk factors, GDM was one of the strongest risk factors for autism with a 2-fold risk for autism across studies (summary effect estimate =2.07, 95% confidence interval (CI): 1.24, 3.47, p value for heterogeneity=0.96).[21]

In addition, a population-based retrospective study from Australia identified an almost 3-fold increased risk for having a child with autism for mothers who had pre-gestational diabetes or GDM, comparing mothers of 119 autistic children with an intellectual disability to 236,964 controls born between 1983 and 1992 (OR=2.89 (95% CI: 1.28, 6.51)).[25] Evaluating pregnancy complications and obstetric suboptimality as risk factors among women in the Nurses' Health Study II, GDM was significantly associated with having a child with any of the ASD (OR=1.76 (95% CI 1.34, 2.32), p <0.0001).[13]

Other studies found no association between maternal diabetes and ASD. A report of cases found no difference in the association between a family history of diabetes and autism.[22] While a comparison of autistic cases to controls identified an association for a history of endocrine disorders, the contribution from diabetes in unclear.[26] Most recently, in a study including 95 cases of ASD and gender and birth year matched controls, no association between maternal diabetes and ASD was observed.[23]

Discrepancies in the findings may be due to differences in study populations (with respect to both geography and sample size), study design as well as exposure and outcome assessments. For example, in some studies GDM was assessed through varying sources, such as medical records and interview,[15,16,18] while others relied solely on self-report.[13,24] In addition, in some cases GDM was combined with other outcomes such as pre-gestational diabetes[15,23,25] and epilepsy.[16] Typically, the ASD diagnoses were rigorous and used standard assessments, such as the Autism Diagnostic Interview-Revised (ADI-R) and/or Autism Diagnostic Observation Schedule (ADOS), however for one study the ASD diagnosis of was reported by the mothers.13 Moreover, several studies included fewer than 50 cases of autism, limiting the power to estimate modest effects.[16,22,26] The association between maternal diabetes in pregnancy and ASD requires further examination. For valid estimates of the risk for ASD resulting from maternal diabetes, future studies should emphasize careful definitions of both GDM, for example based on guidelines put forth by the American Diabetes Association and ASD, using validated assessment tools, such as the ADOS and ADI-R, and have sufficient sample size.

MATERNAL OBESITY AND ASD

An underappreciated risk factor for ASD is maternal obesity (i.e. body mass index (BMI) ≥ 30 kg/m2). Greater maternal pre-pregnancy BMI is an important predictor of gestational hyperglycemia and therefore may be related to an increased risk of neurodevelopmental outcomes in the offspring. Maternal obesity affects a large number of pregnancies in the United States as one third of all women of childbearing age are obese.[27] Obesity, independent of diabetes, is associated with other adverse birth outcomes, including neural tube defects.[28] In fact, a recent systematic review of the literature found that offspring of obese pregnancies may be at risk for neurodevelopmental outcomes, including cognitive impairment and attention deficit disorder in childhood,[29] although autism was not a subject of this review.

Several,[30-32] but not all[33] epidemiologic studies have identified significant associations between high pre-pregnancy maternal BMI and increased risk of ASD. For instance, among the 60,853 eligible women in the Nurses' Health Study II, 743 reported a child diagnosed with ASD. The risk of reporting a child with ASD was nearly two-fold for women with a BMI ≥30 at age 18.[30] However, BMI later in adulthood, measured at the study baseline (age range 25-42 years) was not associated with an increased risk.30 Wilkerson et al identified perinatal complications using the Maternal Perinatal Scale and using factor analysis predicted autism using 183 cases and 209 controls.[31] Maternal morphology differed significantly between groups (p<0.0001), and the item with the greatest contribution to this factor was the mother's weight just prior to pregnancy.[31] An association with pre-pregnancy weight was confirmed in a retrospective longitudinal cohort of all live births (129,733) between 1990 and 2002 in Nova Scotia, in which 924 of the offspring went on to be diagnosed with autism.[32] Dodds et al identified an increased risk for autism for women with a pre-pregnancy weight of 90 kg (198 lbs) or greater with a RR=1.72 (95% CI: 1.39, 2.13).[32] They additionally identified and increased risk for maternal weight at delivery ≥ 120 kg

(264 lbs) with a RR=2.18 (95% CI: 1.52, 3.16) and pregnancy weight gain ≥ 18 kg (39.6 lbs) RR=1.26 (95% CI: 1.08, 1.47).[32] However, in a population based matched case-control study using linked databases from the Danish Civil Registration Systems, no association between maternal pre-pregnancy BMI and autism risk in the offspring was observed.[33] Interestingly, the studies that identified significant and positive association between pre-pregnancy BMI and autism were conducted in United States and Canada, two countries with a stark obesity problem, whereas the study with the null result was conducted in Denmark where a substantially lower burden of obesity presents.[33,34] Follow-up to further describe the association between maternal BMI and autism is warranted, including evaluating the effect of weight loss or limited weight gain prior to and during pregnancy.

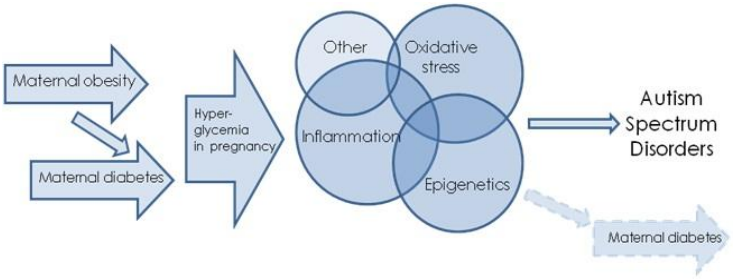

Figure 1. Potential biologic mechanisms linking material hyperglycemia to autism spectrum disorders. The mechanisms may not be mutually exclusive, but may jointly contribute to impaired development. Dotted shapes represent potential common causes.

POTENTIAL BIOLOGIC MECHANISMS

Although precise molecular mechanisms are unclear, there are several plausible pathways that may contribute to the association between maternal diabetes and ASD in the offspring, namely, inflammation, oxidative stress, and epigenetics. Specific pathways are discussed below and described in **Figure 1**.

Inflammation/Immune Irregularities

Immune irregularities in autism were first described in 1977[35] and since then numerous studies have identified evidence of both neuro- and systemic inflammation in autism.[36] Examples include evidence of auto-antibodies in post-mortem brain samples and cerebro-spinal fluid (CSF), as well as pro-inflammatory cytokine profiles in CSF and blood.[36] In addition, epidemiologic studies have identified an association between a maternal auto-immune disorders, such as rheumatoid arthritis,[37] psoriasis,[38] type 1 diabetes and ulcerative colitis 39 and having a child with autism.

Obesity, T2DM and GDM represent states of altered immune function.[40-42] Obesity leads to a persistent state of low-grade inflammation through recruitment of macrophage derived pro-inflammatory cytokines as well as the secretion of inflammatory cytokines by hypertrophic adipokines.43 Multiple lines of evidence suggest that low-grade inflammation and activation of the innate immune system are involved in the pathogenesis of T2DM and GDM.[41] For example, markers of inflammation, such as CRP and IL-6 were found associated with and predictive of T2DM.[41] Development and a history of GDM are also associated with an inflammatory response. Women with a history of GDM compared to controls demonstrated subclinical inflammation with greater mean levels of C-reactive protein, IL-6, plasminogen activator inhibitor-1 and lower levels of adiponectin.[44] A prospective study evaluating leukocyte count in 2,753 women of whom 98 went on to develop GDM found that the mean leukocyte count was linearly associated with the results of the glucose tolerance test.[42] Finally, TNF-α, a pro-inflammatory cytokine, has been linked to insulin resistance during pregnancy.[45]

It is plausible that the inflammatory state related to obesity and diabetes may contribute to the pathophysiology of autism. Altered immune dysfunction has been postulated to impact the neurological processes impaired in autism, including neural development, synaptic plasticity, and structural abnormalities of the brain.[36] An additional line of evidence for a common immunologic pathway includes genetic associations with the human leukocyte antigen (HLA) system. The A allele at rs9268852 of HLA-DRB1 was observed being associated with decreased risk for T2DM in Pima Indians in Arizona.[46] Similarly, HLA-DRB1 subtypes were found in higher frequency of HLA-DR4 in mothers and their sons with autism, supporting a theory that the maternal-fetal immune interaction can affect fetal brain development.[47] HLA-DRB1 allele frequencies were also significantly different between autistic and controls in a Han Chinese population.[48]

Oxidative Stress

Oxidative stress is an imbalance between the production of free radicals, including reactive oxygen and nitrogen species, and endogenous and exogenous antioxidant mechanisms to detoxify these reactive intermediates. While free radicals are a natural bi-product of aerobic respiration and a necessary component of the immune system, excess production can cause damage to DNA, proteins and fat. Several studies have shown a positive association between oxidative stress and autism leading to the hypothesis that increased oxidative damage is, in part, responsible for the pathophysiological processes that underlie the autistic phenotype.[49] The developing brain is highly susceptible to oxidative stress given the high concentrations of fatty acids, high oxygen consumption, low concentration of antioxidants, and high availability of redox-active iron.[50] Several studies have identified higher levels of oxidative damage in children with autism versus control children without autism.[51-53]

Both excessive body adiposity and hyperglycemia are sources of oxidative stress.[54] Obesity has been associated with systemic oxidative stress, independent of blood glucose.[55] In addition, it has been suggested that a unifying cause of glucose mediated diabetic complications is hyperglycemia induced overproduction of superoxide by the mitochondrial electron transport chain.[56] Exposure of the prenatal brain to excess superoxide and other free radicals may contribute to impaired neurodevelopment.

Epigenetics

Epigenetics is one mechanism suggested to explain the widely divergent concordance rates of autism for MZ and DZ twins. Epigenetics are defined as heritable changes in gene expression that do not involve the underlying genetic sequence. Several lines of evidence suggest that epigenetic changes may be involved in the development of ASD. First, ASD share phenotypic traits with two disorders in which epigenetics underlie the pathogenesis, including Rett syndrome and fragile X syndrome.[57] Imprinting is a classic example of an epigenetic mechanism and chromosomal regions, including 15q11-13 as well as genes, such as UBE3A, that are associated with ASD, also demonstrate parent-of-origin effects.[57] Finally, genes that are not imprinted, but themselves are regulated by DNA methylation have been implicated in autism.[58]

It has also been postulated that the intrauterine environment of a pregnancy affected by GDM could in turn affect epigenomes of the offspring.[59] While this model has been used to describe the association between in utero exposures and future development of metabolic disorders such as T2DM,[60] it may be expanded to include potential effects on neurodevelopment. However, empiric evidence of epigenetic mechanism contributing or resulting from GDM is sparse.

Additional Pathways

Several additional pathways may also contribute to the significant link between autism and obesity and diabetes. For example, copy number variation has been identified (a 1.4Mb deletion) in a greater proportion of autism cases versus ethnically matched controls in the region (7q12) which contains HNF1B, the gene responsible for renal cysts and diabetes syndrome.[61] In addition, autism was found in 3 of 53 children with the 7q12 deletion.[62] Another pathway implicated with both T2DM and autism is the melatonin pathway.[63] Melatonin is a hormone that is both an antioxidant and important in regulating sleep, circadian rhythm regulation and immune response.[64] Finally, the gene for the β2-adrenergic receptor (ADRB2), a G protein-coupled receptor, is involved in the muscular, circulatory and digestive systems. Polymorphisms in ADRB2 have been associated to multiple diseases states including autism,[65] obesity,[66] insulin resistance,[67] and T2DM.[68] Certainly, more research is warranted to decipher the underlying molecular mechanisms for the links between maternal obesity and hyperglycemia and ASD in offspring.

CONCLUSION

Obesity and gestational diabetes are common conditions that are increasing among women of reproductive age. We presented epidemiologic evidence as well as plausible biologic mechanisms suggesting that impaired neurodevelopment and specifically autism spectrum disorders may be an additional adverse health consequence of maternal obesity and diabetes in pregnancy. Considering the concurrent rise in obesity and diabetes in pregnancy, as well as the modifiable nature of these disorders, their associations with ASD and the underlying molecular mechanisms should be explored further, which may shed light on the prevention of ASD.

Current public health efforts aiming to alleviate the epidemic of obesity and diabetes may also help reduce risks of autism spectrum disorders in offspring.

DISCLOSURE

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CONFLICT OF INTEREST

None.

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