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Review Article

Maternal Gestational Diabetes and Autism Spectrum Disorder in Offspring: Risk Factors, Mechanisms, and Pediatric Implications

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Abstract

Introduction: Gestational diabetes (GDM) complicates around 14% of pregnancies globally. While GDM's physiological effects are often transient, its long-lasting effects on the mother and the child are significant. Studies show a heightened chance of autism occurring in offspring subjected to gestational diabetes in utero.

Methods: A thorough search of literature was performed across PubMed, SCOPUS, and ProQuest, identifying 35 relevant studies published between 2012 and 2024. This review focuses on exploring the impact of GDM on the offspring's chances of developing autism. It aims to explore the factors influencing this relationship, such as the timing of GDM onset, the presence of coexisting complications, and the condition's underlying mechanisms.

Results: The findings demonstrate that gestational diabetes can significantly increase the risk of autism. Key factors influencing this relationship include the timing of diagnosis, maternal glucose management, and treatment strategies during pregnancy. Potential mechanisms include increased fetal exposure to inflammation, oxidative stress, and immune dysregulation.

Conclusion: The findings highlight the importance of early and effective GDM management and its pediatric implications for improving neurodevelopmental outcomes in offspring during early childhood.

Keywords: autistic spectrum disorder (ASD), endocrinology, gestational diabetes (GDM), neurodevelopmental disorders (NDD), psychiatry

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1. Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder marked by repetitive and seemingly purposeless behaviors, limited areas of interest, and varying degrees of communication difficulties [1]. Globally, ASD is recognized as a significant pediatric concern, with approximately 1 in 100 children diagnosed [2]. The disorder often persists throughout the individuals' lives, profoundly affecting the life quality of both them and their family [3]. Among the various prenatal risk factors, maternal metabolic conditions—particularly Gestational Diabetes Mellitus (GDM)—have drawn increasing attention due to their potential role in fetal neurodevelopmental disruption. Understanding the link between GDM and the pathogenesis of ASD is critical, particularly for pediatricians responsible for early screening and intervention in affected children.

Based on the 2021 estimates from the International Diabetes Federation (IDF), GDM complicates around 14% of pregnancies globally [4]. Although the metabolic disturbances associated with GDM often resolve post-delivery, the long-term implications for both maternal and offspring health remain significant [5]. The timing of GDM onset, typically during the second and third trimesters, overlaps with critical periods of rapid fetal brain development. Emerging evidence points to a link between GDM and adverse neurodevelopmental outcomes in children, including an increased ASD risk [6].

This review aims to explore the underlying mechanisms by which GDM can affect fetal brain development, potentially increasing ASD risk. Additionally, it will examine the clinical factors influencing this association and discuss its pediatric implications, particularly for screenings and early intervention.

2. Methods

This narrative review synthesizes the literature on the influence of GDM on the development of ASD in offspring. An electronic literature search was conducted on March 31, 2024, across PubMed, SCOPUS, and ProQuest. The search encompassed studies published between January 1, 2012, and March 31, 2024. Medical Subject Headings (MeSH) terms used included: "Gestational diabetes", "Gestational diabetes mellitus", "Autism Spectrum Disorder", and "Autistic disorder", along with free-text keywords such as "Diabetes", "Gestational Diabetes", "Autism", "Autism Spectrum Disorder", and "Neurodevelopment".

Inclusion criteria restricted the search to studies that specifically addressed the association between GDM and the offspring's risk of autism. Studies were excluded if they focused on chronic diabetes mellitus and ASD; combined chronic diabetes and GDM as a single entity, unless it was feasible to obtain specifically related to GDM; investigated the relationship between GDM and neurodevelopmental disorders without specifically focusing on ASD; explored associations between prenatal metabolic syndrome and ASD in offspring; were duplicates or published in languages other than English and the English translation was not available.

The search yielded a total of 3830 articles (1822 from ProQuest, 1282 from PubMed, and 726 from SCOPUS) after removing the duplicates. Following screening and application of the exclusion criteria, 35 articles were included. Figure **1** illustrates the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).
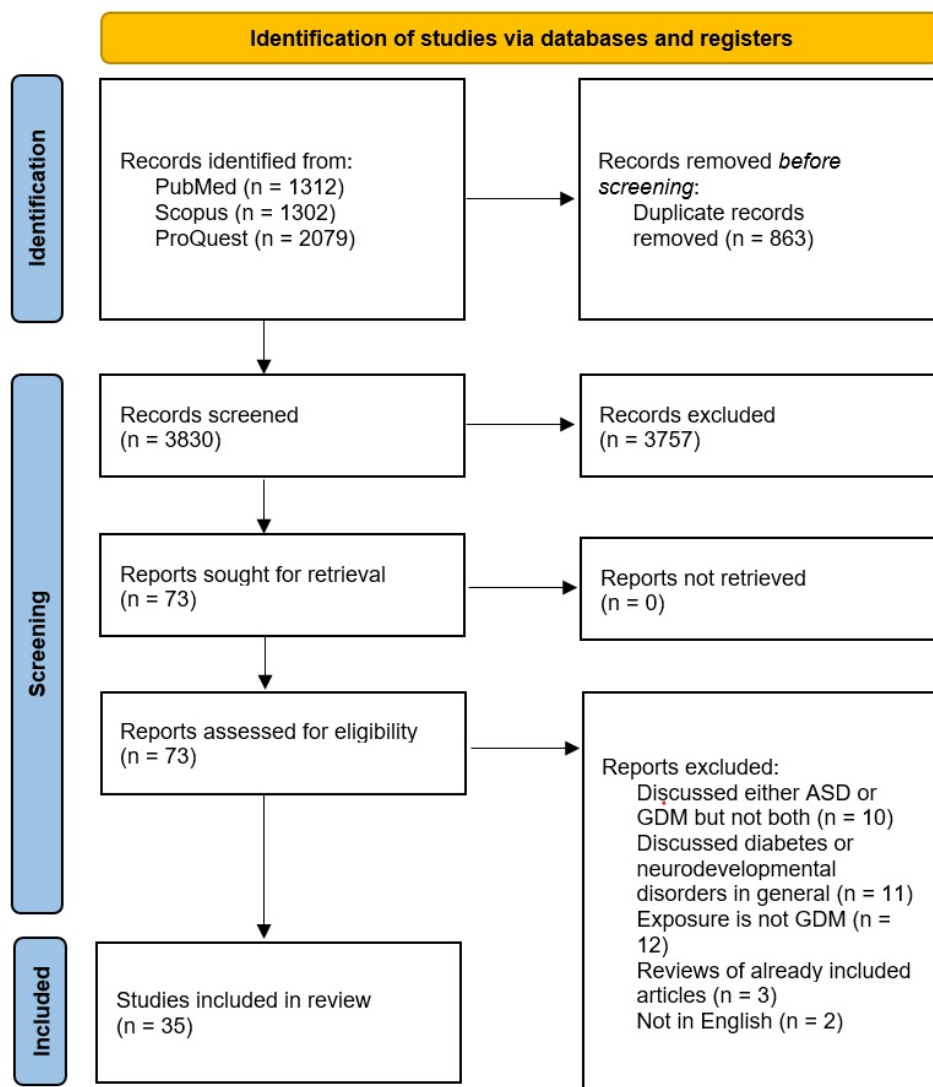
Figure 1: The preferred reporting items 126 for systematic reviews and meta-analysis (PRISMA). (ASD = Autism spectrum disorder, GDM = Gestational diabetes).

3. Results

A comprehensive literature search identified a total of 35 studies. Among these, 11 studies specifically measured the association between GDM and ASD. Most studies, including two meta-analyses, suggest that GDM is linked to a heightened chance of ASD in offspring [7-12], with the calculated Odds Ratio (OR) ranging from 1.10 to 1.43 [7, 8]. Rowland et al. conducted a meta-analysis of 18 studies, concluding that pregnancies complicated by GDM were associated with a pooled OR of 1.42 (95% confidence interval

(CI) [1.22, 1.65]) [8]. However, a few studies reported no significant associations, possibly due to limited sample sizes [13, 14].

Other studies provided additional insights into the role of maternal factors. Kong et al. reported that the likelihood of ASD increased with higher body mass index (BMI) among diabetic mothers, with greater risk observed for children of overweight and obese mothers [7]. Xiang et al. found that the timing of GDM diagnosis influenced the risk of ASD, with an increased risk observed for GDM diagnosed before the 26th week of pregnancy (OR = 1.62, 95% CI [1.44, 1.82]), while no significant association was noted for diagnoses occurring later in pregnancy [15]. Gender differences were also noted as male offspring showed a notably larger risk of ASD in the presence of in-utero GDM exposure [9].

Several other studies discussed potential pathogenic mechanisms underlying the association. Key mechanisms identified include oxidative stress, inflammation, and epigenetic changes, which may alter neurodevelopment [16-18]. Oxidative stress associated with hyperglycemia can adversely affect fetal brain development [16]. Furthermore, maternal inflammation and immune dysregulation have been identified as significant factors that could contribute to neurodevelopment in children whose mothers experienced GDM [17, 18].

Overall, the evidence supports a mild to moderate increase in ASD risk associated with GDM, influenced by various factors including the time of diagnosis, maternal BMI, and underlying pathogenic mechanisms.

4. Discussion

4.1. Association Between GDM and ASD Risk

Studies indicate a notable connection between GDM and an elevated risk of autism in offspring [7, 8]. This relationship is supported by multiple studies, though variability in study design and methodology leads to differing conclusions. The pooled estimates from meta-analyses indicate that GDM is associated with a moderate elevation in the risk of autism. Rowland et al. reported a pooled OR of 1.42 (95% CI [1.22, 1.65]) [8], while Xu et al. reported the pooled Relative Risk (RR) as 1.43 (95% CI [1.13, 1.79]) [9]. These findings suggest that children exposed to GDM during their intrauterine lives have a 42% to 43% higher risk of developing ASD in comparison to those not exposed. In addition, Liu et al. reported a significantly higher risk of ASD [10], while Vui et al. observed a strong association with an OR of 7.7 (95% CI [3.5, 16.9]) in a cross-sectional study [11]. These differences may reflect specific population or methodological characteristics such as varying diagnostic criteria or inclusion of additional risk factors.

Conversely, Cordero et al. calculated an adjusted OR of 1.1 (95% CI [0.77, 1.53]), suggesting the absence of a significant association between any form of diabetes during pregnancy and ASD [13]. The relatively small number of GDM cases within the sample might have limited their ability to detect a significant association. Similarly, Chen et al. observed that while high glucose levels early in pregnancy were initially

associated with ASD, the association lost its significance after statistical adjustments were applied [14]. The study's small number of GDM cases (n=219) may have resulted in insufficient statistical power to sustain significant findings after correction for multiple comparisons. Additionally, the focus on early glucose levels rather than comprehensive measures of glycemic control may have affected the outcome.

Overall, the majority of studies support a moderate increase in ASD risk associated with GDM, with RRs reported around 1.43 in the available literature. These measures, while reflecting different aspects of the association, collectively suggest that GDM elevates the chances of autism in offspring, though the strength of the association may vary depending on study design and population characteristics [19, 20]. Table **1** and Figure **2** display a summary of studies assessing the association of GDM with ASD, while additional factors influencing this association are discussed in subsequent sections of this review.

Table 1: Summary of studies assessing the association between GDM and ASD.

No.	Author and year	Study design	Country	Sample size	Ascertainment of GDM diagnosis	Ascertainment of ASD diagnosis	Findings
1.	Kong et al., 2020 [7]	Retrospective cohort study	Finland	GDM cases = 98,242 Control = 541,133	Diagnosis from medical records (HILMO): ICD-10 code O24.4	Diagnosis from medical records (HILMO): ICD-F84	HR of ASD separated by BMI of diabetic mothers: - Overweight: 1.28 (95% CI [1.07, 1.53]) - Obese: 1.57 (95% CI [1.26, 1.95]
2.	Rowland et al., 2021 [8]	Systematic review and meta-analysis	Countries in North America, Europe, MENA, South Asia, and East Asia	Total participants = 932,655 (GDM = 51,370; ASD = 512)	Self-report, report from medical professionals or medical records	Self-report, report from medical professionals or medical records	GDM is associated with increased risk of ASD in offspring, pooled OR = 1.42 (95% CI [1.22; 1.65]
3.	Xu et al., 2014 [9]	Systematic review and meta-analysis	China/United States	Total participants = 784,056 (ASD = 5885)	The diagnosis of maternal diabetes was made based on ICD codes in six studies. In the remaining studies, the diagnostic criteria were not specified	The ICD-9 or ICD-10 criteria were used in five studies; ADI-R and ADOS in four studies; DSM-IV-R and CARS in three studies	Maternal diabetes is associated with increased risk of ASD, pooled RR = 1.43 (95% CI [1.13, 1.79])
4.	Liu et al., 2024 [10]	Retrospective cohort study	United States	GDM cases = 1417 Control = 13,063	Diagnosis from medical records: ICD-9: 648.8x and ICD-10: O24.4x	Diagnosis from medical records: ICD-10: F84.x except F84.2x, F84.3x and ICD-9: 299.x except 299.1x	GDM is associated with increased risk of ASD in offspring, adjusted HR = 3.16 (95% CI [1.36, 7.37])
5.	Vui et al., 2023 [11]	Cross-sectional study	Vietnam	Total participants = 42,551 (ASD = 302)	Face-to-face interviews with mother/father or caregiver	Children were screened using M-CHAT, then diagnosis confirmed using DSM-IV criteria by pediatric neurologist	Having GDM, or high blood pressure or pre-eclampsia during pregnancy were consistently associated with ASD, OR = 7.7 (95% [CI 3.5, 16.9])

Table 1: Continued.

No.	Author and year	Study design	Country	Sample size	Ascertainment of GDM diagnosis	Ascertainment of ASD diagnosis	Findings
6.	Chen et al., 2022 [12]	Retrospective cohort study	Taiwan	GDM cases = 90,200 Control = 787,033	Diagnosis from medical records: ICD-9 codes 648.0 (diagnosis is based on 50-g oral glucose tolerance test between 24-28 weeks)	Diagnosis from medical records: ICD-9: 299	Calculated OR = 1.30 (95% CI [1.24, 1.37])
7.	Cordero et al., 2019 [13]	Case-control study	United States	ASD cases = 698 Non-ASD DD = 887 Control = 979	Prenatal medical record or maternal self-report	Screened using the Social Communication Questionnaire, assessment by ADOS, caregivers completed ADI-R	Any diabetes during pregnancy was not associated with ASD. AOR = 1.10 (95% CI [0.77, 1.56])
8.	Chen et al., 2023 [14]	Retrospective cohort study	Sweden	GDM cases = 219 No GDM = 76,009	Not specified	Diagnosis from medical records and ICD-10 code F84	High glucose levels in early pregnancy were associated with Autism and ADHD, though these associations did not remain significant after adjusting for FDR correction due to small sample size
9.	Xiang et al., 2018 [15]	Retrospective cohort study	United States	GDM cases (<26 weeks) = 11,922 GDM cases (>26 weeks) = 24,505 Control = 372,924	Not specified	Not specified	GDM diagnosed by 26 weeks of gestation had risk of ASD in offspring, Calculated OR = 1.62 (95% CI [1.44, 1.82])
10.	Liu et al., 2023 [26]	Case-control study	China	ASD cases = 221 Control = 400	Maternal self-report	Diagnosed by senior doctors in neurology department using DSM-5 criteria	GDM is associated with increased risk of ASD in offspring, OR = 2.18 (95% CI [1.04, 4.54])
11.	Mahboub et al., 2023 [47]	Case-control study	Saudi Arabia	ASD cases = 103 Control = 567	Questionnaire	Interview with mothers	GDM increases the risk of developing ASD by three times with p<0.05, OR = 3.1 (95%CI [1.7–5.4])

GDM = Gestational diabetes mellitus, ASD = Autism spectrum disorder, DD = Developmental delay, ICD = International classification of diseases, OR = Odds ratio, ADOS = Autism diagnostic observation schedule, ADI-R = Autism diagnostic interview-revised, HILMO: Finnish care registers for health care, CI = Confidence interval, MENA = Middle East and North Africa, HR = Hazard ratio, BMI = Body mass index, aOR = Adjusted odds ratio, RR = Risk ratio, M-CHAT= Modified checklist for autism in toddlers, DSM = Diagnostic and statistical manual of mental disorders, ADHD = Attention deficit hyperactivity disorder, FDR = False discovery rate.
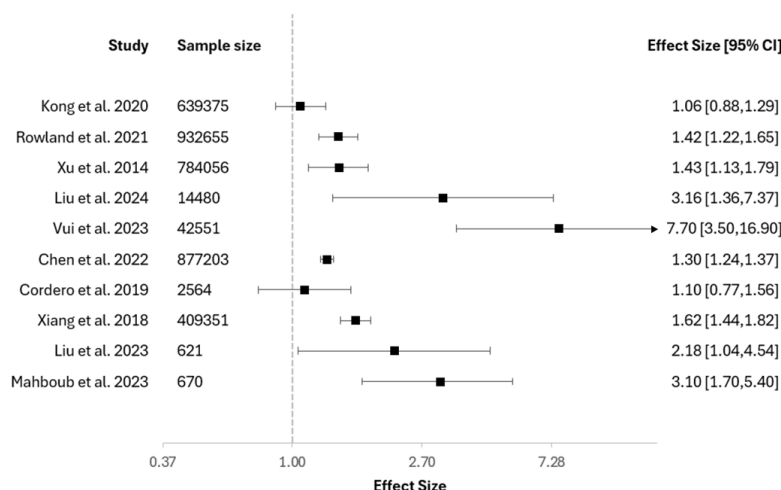
Figure 2: Comparison of study effect sizes (CI = Confidence interval).

4.1.1. Timing of GDM Diagnosis and ASD Risk

The timing of GDM diagnosis plays a crucial role in ASD risk. Studies indicate that the risk of ASD decreases with a later diagnosis of GDM [21]. Women diagnosed with GDM by the 26th week of pregnancy exhibit 1.42 times higher chance of having children with ASD [1]. Elevated hemoglobin A1c levels (>6.5%) in early gestation further correlates with an increased autism risk [10]. This suggests that early and more severe hyperglycemia during pregnancy has a larger impact on fetal brain development. Population-based studies consistently show that maternal diabetes, whether type 1, type 2, or GDM diagnosed by the 26th week of pregnancy, is linked to an elevated risk of ASD in offspring [1, 22, 23]. However, diabetes diagnosed after the 26th week of pregnancy does not significantly increase autism risk. This suggests that the severity of the disease and its timing of onset during pregnancy are important determinants of this relationship [24]. The interaction of these factors with maternal glycemia, autoimmune conditions, genetic predispositions, prematurity, and neonatal hypoglycemia requires further investigation [13]. A meta-analysis reinforced the significant association between maternal diabetes and increased ASD risk [25]. A cross-sectional study in Vietnam identified GDM as one of the five perinatal factors associated with an autism RR of 1.48 (95% CI [1.26, 1.75]) [11, 15]. Another study revealed that the combination of obesity and chronic diabetes resulted in a significantly higher risk of offspring ASD [17], emphasizing the compounded impact of these maternal health conditions [17].

4.1.2. Co-existing Complications

Maternal body mass index (BMI) is another critical factor that exacerbates the ASD risk in children with prenatal exposure to GDM [17]. Severe obesity combined with diabetes during pregnancy creates a notably higher risk of ASD than either condition alone [26]. This increased risk is likely due to the enhanced

exposure of neurons to oxidative stress, lipotoxicity, increased blood glucose, and insulin resistance, as well as inflammation in cases of severe obesity with concurrent diabetes [14]. Resistance to insulin increases progressively during gestation to ensure that the growing fetus receives enough carbohydrates. This process is associated with increased post-meal glucose levels, greater secretion of insulin both at rest and in response to food intake, and increased glucose production by the liver [27]. These metabolic changes are exacerbated if the pregnant woman is diabetic, obese, or both. This results in increased placental glucose transfer, cytokine release, and fetal insulin secretion, potentially leading to adverse outcomes for the fetus [28]. Women with GDM exhibit elevated risks for other obstetric complications, including pre-eclampsia, preterm delivery, fetal macrosomia, cesarean delivery, and perinatal mortality [28-30]. These complications can further influence the offspring's neurodevelopmental outcome [8]. It has been demonstrated that prenatal and perinatal factors significantly influence the clinical manifestation of ASD [31]. A prospective national cohort study from the Nurses' Health Study II found that females who developed pregnancy complications, particularly toxemia and GDM, were more prone to have their children diagnosed with ASD [32]. These findings emphasize the importance of early and effective management of GDM to mitigate long-term neurodevelopmental risks [33].

4.1.3. Gender-specific Susceptibility to ASD

The gender of the offspring also interacts with GDM exposure in influencing ASD risk [34]. A case-control study concluded that male children of mothers with GDM exhibited a notably elevated ASD risk (OR=3.67, 95% CI [1.16, 11.65], p-value (probability value) =0.028) [35]. The gender-specific susceptibility underscores the need for more nuanced research into how maternal metabolic conditions impact male and female fetuses differently [9].

4.1.4. Impact on Fetal Neurodevelopment

The developmental impact of GDM on ASD is a critical area of research, as maternal glucose intolerance in pregnancy is linked to alterations in fetal brain development and subsequent neurobehavioral outcomes. GDM onset, typically during the latter half of pregnancy, coincides with critical periods of fetal cerebral cortex development and postnatal development [36, 37]. GDM diagnosed before the 26th week of pregnancy has been associated with an increased ASD risk, while diagnosis after the 26th week shows no such association [1, 31, 32, 38]. This finding indicates that hyperglycemia during this critical developmental period can adversely affect the development of the nervous system. A study assessed the influence of diabetes on mice offspring by inducing diabetes with streptozotocin injections and compared the results to a control group. Male offspring from diabetic mothers showed reduced mobility, increased repetitive behaviors, and fear-related freezing, while females did not exhibit these signs. Maternal glucose levels correlated positively with these behaviors in males. Additionally, specific genes were dysregulated in

their cortices and striatums such as *bhlhe22* (*basic helix-loop-helix family member E22*) and *Nde1* (*nudE neurodevelopment protein 1*) [34]. *Bhlhe22* is known to play a role in cortical development and the establishment of neuronal circuits [34]. These findings suggest that maternal GDM may contribute to specific behavioral alterations in offspring, particularly in males, with the severity potentially linked to maternal glucose levels.

4.2. GDM and Its Pathophysiological Impact on ASD

GDM has been associated with alterations in neurological development, impairments in fine and gross motor skills and cognitive function, and increased learning difficulties. The underlying mechanisms are complex, involving epigenetic changes, increased oxidative stress in the fetus, and chronic neuroin-flammation [6]. Figure **3** summarizes the possible mechanisms during the prenatal period that may be implicated in the development of autism in children born to diabetic mothers.
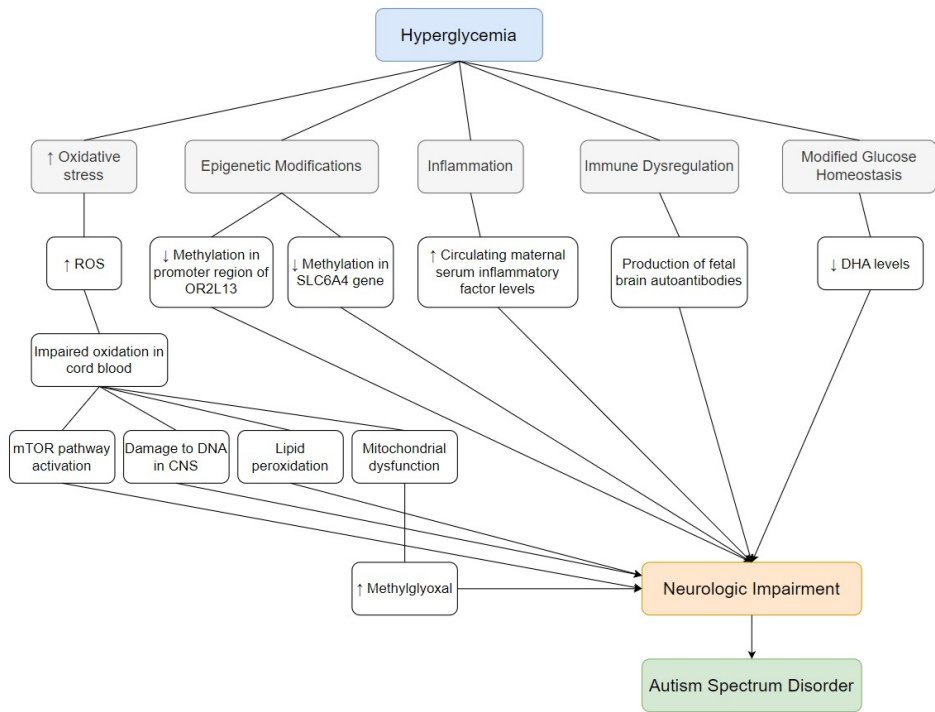
Figure 3: Diagrammatic representation of the possible mechanisms during the perinatal period that may lead to the development of autism in the offspring of diabetic mothers (ROS = Reactive oxygen species, mTOR = mammalian Target of rapamycin, DNA = Deoxyribonucleic acid, CNS = Central nervous system, *OR2L13 = Olfactory receptor family 2 subfamily L member 13 (OR2L13)*, *SLC6A4 = Solute carrier family 6 member 4,* DHA = Docosahexaenoic acid).

4.2.1. Oxidative Stress

Some studies indicate that oxidative stress, a common feature of GDM, may contribute to neurodevel-opmental disorders like ASD [16]. Hyperglycemia triggers a series of chemical reactions that produce an

excess of reactive oxygen species (ROS). Excessive ROS can overwhelm the body's antioxidation capacity, resulting in oxidative stress as they interact with various body tissues [30]. Maternal hyperglycemia can compromise antioxidant defense mechanisms and enhance the production of free radicals [16]. These changes may contribute to an increased oxidative stress burden in both cord blood and placental tissue [16]. In embryos, oxidative stress can damage DNA (deoxyribonucleic acid) across various cell types, including those in the central nervous system, potentially leading to long-lasting neurodevelopmental impairments [30].

Oxidative stress not only increases lipid peroxidation but also alters the regulation of genes linked to perinatal complications [39]. Additionally, it disrupts methylation processes, which can contribute to neurological issues by reducing the capacity for methylation [39]. Research has identified elevated levels of oxidative stress markers, such as 3-nitrotyrosine (3-NT) and neurotrophin-3 (NT-3), in specific brain regions, particularly the cerebellum, in patients with ASD [37, 39].

Oxidative stress also disrupts pathways responsible for breaking down harmful metabolic byproducts, potentially causing mitochondrial dysfunction and impacting fetal brain development [30]. One critical pathway affected is the Glo1-methylglyoxal pathway, essential for metabolizing methylglyoxal, a byproduct of glucose metabolism associated with diabetes. When oxidative stress impairs Glo1 enzyme's ability to neutralize methylglyoxal, elevated levels of this compound can damage neural progenitor cells (NPCs) during embryonic development, leading to alterations in the structure and function of the brain [39]. Experimental studies have demonstrated that increasing Glo1 expression can mitigate the harmful effects of elevated methylglyoxal on NPCs. These disruptions in embryonic NPC development may result in premature neurogenesis and depletion of NPC pools, potentially affecting brain development through-out adulthood [33]. Understanding this pathway could lead to interventions to improve outcomes for individuals affected by maternal metabolic disorders.

The mammalian Target of Rapamycin (mTOR) pathway might also be implicated in the pathogenesis of neurodevelopmental disorders through oxidative stress [16]. mTOR is a crucial serine-threonine kinase which regulates essential cellular functions. Besides its role in regulating carbohydrate and lipid metabolism, mTOR also plays a vital role in synaptic plasticity and autophagy inhibition [16]. Dysregulation of mTOR has been identified in various neurodevelopmental diseases such as ASD [37, 40-45]. Activation of mTOR was observed in ASD patients, leading to the inhibition of autophagy and failure to eliminate the redundant synapses in the central nervous system [37, 44].

4.2.2. Epigenetic Modifications

Hyperglycemia can affect epigenetic modifications in offspring, including decreased DNA methylation, commonly observed in neurodevelopmental diseases such as ASD, however the current evidence is still sparse [9]. A meta-analysis of epigenome-wide association studies (EWAS) uncovered distinct methylation

patterns linked to GDM particularly in two genomic regions: the promoter region of the *OR2L13* gene (*olfactory receptor family 2 subfamily L member 13*) and the gene body of *CYP2E1* (*cytochrome p450 family 2 subfamily E member 1*) [18]. Lower methylation levels were observed in these regions among newborns exposed to GDM. The *OR2L13* gene, responsible for encoding an olfactory receptor, exhibited differential methylation of the same CpG site in both blood and buccal cells from individuals with ASD [18]. Although the exact mechanism remains unknown, research suggests a correlation between olfactory dysfunction and more severe social impairments in ASD individuals [45, 46]. Further investigation is needed to explore the potential role of *OR2L13* in mediating the relationship between GDM and neurodevelopment.

Serotonin, also known as 5-hydroxyptamine or 5HT, contributes significantly to the embryonic development through the regulation of various pathways, including the formation of the serotonergic system [47]. Disruptions in serotonin balance during prenatal or early postnatal stages can increase the infant's vulnerability to conditions like autism, depressive disorders, and other mental health disorders later in life [46]. Before the fetal brain starts synthesizing serotonin, the placenta serves as an important producer of this neurotransmitter [48]. A study investigated the relationship between maternal glucose metabolism during pregnancy, placental serotonin transporter *SLC6A4* (*solute carrier family 6 member 4*) gene methylation, and gene expression [49]. The research revealed that glucose variations associated with GDM impact fetal *SLC6A4* gene methylation, resulting in lower methylation levels and higher gene expression in placentas from GDM pregnancies [49]. This suggests that maternal glucose dysregulation influences serotonin transport in the placenta through alterations in *SLC6A4* methylation, indicating a significant role of epigenetic mechanisms in regulating the expression of placental *SLC6A4*.

4.2.3. Inflammation

ASD often exhibits elevated concentrations of proinflammatory cytokines in the peripheral blood which suggests a connection between inflammation and ASD [29]. Epidemiological studies found that individuals with GDM have increased circulating serum inflammatory factor levels compared to women without GDM [29]. GDM can induce a state of chronic hypoxic stress and inflammation in the placenta. Excessive adipose tissue, often observed in Type 2 Diabetes Mellitus (T2DM) and GDM, is recognized for its role in inducing chronic inflammation [9]. A study performed in 2018 presented neurophysiological evidence indicating that exposure to GDM during pregnancy is linked to reduced cortical excitability and neuroplasticity in offspring at 11–13 years old. Interestingly, maternal perinatal factors, particularly insulin resistance and inflammation, were strongly associated with these neurophysiological outcomes [17]. In another study, elevated cortisol levels seen in pregnant women with impaired glucose tolerance or GDM were shown to increase serotonin transporter (SERT) levels, disrupting serotonin signalling [22].

4.2.4. Immune Dysregulation

Specific autoantibodies targeting fetal brain proteins were detected in approximately 23% of women with children diagnosed with ASD, compared to 1% of those with neurotypical offspring [50]. These autoantibodies were connected to more severe forms of stereotyped behaviors and expressive language deficits in ASD children [51]. Research has shown that mothers of children with ASD, particularly those who faced metabolic complications during pregnancy, may produce autoantibodies targeting fetal brain proteins, given that these antigens have been detected in maternal blood [21]. Mothers diagnosed with diabetes during pregnancy were almost three times more likely to develop these autoantibodies than non-diabetic mothers. The association was stronger between diabetes and positive antibodies when women with chronic conditions like T2DM were excluded [21]. This suggests that GDM may alter maternal immune tolerance, resulting in the production of autoantibodies that target fetal brain proteins [21]. The anti-fetal brain autoantibodies were found to be associated with a functional polymorphism in the *mesenchymal epithelial transition factor (MET)* gene. The associated polymorphism is linked to reduced expression of the *MET* receptor tyrosine kinase, which may induce susceptibility to immune dysregulation [52, 53]. Additionally, several animal studies have linked disruptions in *MET* signaling to GDM [54, 55].

4.2.5. Modified Glucose Homeostasis

Docosahexaenoic acid (DHA) plays an essential role in fetal growth and development [56]. Its selective transfer across the placenta may be altered in GDM due to disrupted glucose metabolism [56]. An in-vitro study demonstrated that exposure of trophoblasts to increased glucose and insulin, mimicking insulin resistance, was associated with suppressed expression of Sirtuin 1 (SIRT1), a regulator of lipid metabolism, and subsequently a decreased DHA transfer across trophoblasts [57]. A prospective study revealed that cord DHA levels of offspring of GDM mothers were significantly lower than those of the control group. Additionally, these offspring exhibited significantly lower psycho-motor and mental scores when assessed using the Bayley Scale of Infant Development II (BSID II) compared to controls [58]. In conclusion, while there is growing evidence linking GDM to an increased risk of ASD in offspring, the exact mechanisms involved are complex and multifactorial [16].

4.3. Pediatric Implications

The association between GDM and ASD has important implications for pediatric practice. Recognizing that children born to GDM mothers may be at an elevated risk for ASD underscores the significance of integrating early developmental screening into routine pediatric check-up. Pediatricians should consider using screening tools such as the Modified Checklist for Autism in Toddlers (M-CHAT) to identify potential developmental delays early [59]. Early detection allows for timely and targeted interventions, which are

crucial for optimizing developmental outcomes. Interventions tailored to the unique needs of children with prenatal GDM exposure might involve early behavioral therapies, speech and language interventions, and occupational therapy [60]. Additionally, educating parents about the potential risks and signs of ASD and providing resources for support may significantly benefit families. Understanding the broader context of maternal health and ensuring effective management of GDM during pregnancy might reduce the risks of ASD [10]. Public health initiatives should focus on early screening and education for expectant mothers and promote optimal GDM management to mitigate potential developmental issues. Overall, integrating these practices into pediatric care may potentially improve outcomes for children at risk of ASD due to prenatal GDM exposure, highlighting the need for continued research and interdisciplinary collaboration to address these challenges effectively.

4.4. Limitations

While this review offers a thorough examination of the association between GDM and ASD, several limitations should be considered. The review's reliance on diverse study designs and differing statistical metrics to report effect sizes may limit direct comparability. Additionally, the unavailability of raw data in some studies prevented the calculation of a single standardized effect size metric across all studies. Many of the included studies used retrospective cohort or case-control designs which, while valuable, are susceptible to biases and may not capture the full complexity of the association between GDM and ASD. Additionally, the variability in the diagnostic criteria for both GDM and ASD across studies can affect the consistency and generalizability of the results. Some studies had small sample sizes or limited data on glycemic control, which may have influenced the observed associations. Despite these challenges, this review provides a comprehensive narrative that highlights key trends and potential mechanisms.

5. Conclusion

In conclusion, evidence indicates that GDM may heighten the chance of an offspring developing autism and is influenced by factors such as the timing of GDM diagnosis, its management strategies, and maternal health conditions during pregnancy. Early diagnosis of GDM (before the 26th week) and medication-treated GDM particularly appear to be associated with higher ASD risks, suggesting a potential impact of prolonged hyper-glycemic exposure and pharmacological interventions on early fetal neurodevelopment. Maternal obesity, pre-eclampsia, and gender-specific susceptibility further increase these risks. Understanding the pathogenetic pathways involving epigenetic modifications and mitochondrial dysfunction provides critical insights into how metabolic disorders in pregnancy can disrupt fetal neurodevelopment.

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Since the research is exclusively based on published literature, ethical approval is not required.

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Conflict of Interest

Authors declare that there is no conflict of interest.

Author Contribution

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