Review Article

Maternal obesity and autism spectrum disorders in offspring

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ABSTRACT

There is a growing body of evidence from both human epidemiologic and animal studies that maternal obesity and a high-fat diet are associated with autism spectrum disorders (ASDs). They also include cognitive impairment, attention deficit hyperactivity disorder, cerebral palsy, anxiety and depression, schizophrenia, and eating disorders. This review synthesizes the role of the maternal immune activation hypothesis and the other possible mechanism underlying abnormal fetal brain development, including neuroinflammation; increased oxidative stress, dysregulated insulin, glucose, and leptin signaling; dysregulated serotonergic and dopaminergic signaling; and perturbations in synaptic plasticity and neurodevelopmental and psychiatric morbidity in offspring. Finally, this review summarizes the available targeted strategies that can be designed to curb maternal obesity and the subsequent development of ASDs.

Key words: Autism spectrum disorders, Maternal obesity, Neuroinflammation, Prenatal

Obesity is the most witnessed medical condition among women in the reproductive age group. It is a common problem that affects both the mother and the child. Obesity during pregnancy is associated with both long-term and short-term health consequences which includes gestational diabetes and pre-eclampsia [1]. Pregnancy is a crucial phase in a woman's life. Experiences and exposures during this phase have a strong impact on the child's well-being. Optimized care before and during pregnancy has special implications for later health outcomes. Healthy lifestyle habits from before conception to postpartum can help achieve successful pregnancies with the lower rates of gestational diseases. The World Health Organization has also established healthy diet, nutrition, weight management and planned pregnancy as the few preconception priorities. Therefore, all these maternal diets have a strong influence on increasing the risk of weight gain during pregnancy [2-4]. In early pregnancy maternal obesity can lead to spontaneous abortion and congenital anomalies. Similarly, children born to obese mothers can also develop components of metabolic syndrome later in their life. And in the long term, the risk of morbidity and mortality associated with maternal obesity is reinforced. In a recent meta-analysis conducted to examine the role of maternal body mass index (BMI) and its effect on pregnancy outcomes, it was evidenced that a slight increase in maternal BMI can result in fetal death, still birth, perinatal, and infant death [5].

Management options for obesity in the non-pregnant population include lifestyle interventions, anti-obesity drugs, and bariatric bypass surgery. However, anti-obesity drugs and bariatric surgery are not options among pregnant women [6]. Therefore, instituting correct and effective methods to curb the threat of obesity among pregnant women is highly needed. In the United States, it is estimated that around 27% of women in the reproductive age group are overweight and 37% are obese. In alliance with the findings of the United States, in the United Kingdom data suggests rates of maternal obesity to be more than 25%. Similarly, maternal obesity is also rising in developing countries, particularly in urban settings [7-9]. Studies have implicated the growing trends of psychotropic medication usage among youths and children. In comparison to the mental healthcare of adults, those of youth have increased significantly in the past two decades, this has strong implications for the role of rising maternal obesity [10]. Furthermore, in the United States, it was found that developmental disabilities are becoming increasingly common and one in every six children in the United States in 2006–2008 had a developmental disability. In particular autism, attention deficit hyperkinetic disorder and other developmental delays have increased in the past two decades [11]. Therefore, maternal health during pregnancy is of utmost importance for the growth and well-being of their offspring.

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MATERNAL IMMUNE ACTIVATION HYPOTHESIS

Autism spectrum disorder (ASDs) is a neurodevelopmental disorder characterized by reduced social interactions and communication, along with repetitive and restrictive behaviors. Studies have implicated the role of maternal immune activation in the development of common neurodevelopment disorders. Experimental animal and human research have proliferated in recent years, and there is now a sizable research base for the role of maternal immune activation in the development of neuropathologies [12]. Pieces of evidence have also suggested that there is an important role in immune dysregulation and/or inflammation in the development of ASD. According to the maternal immune activation hypothesis, maternal immune activation induces microglial activation, oxidative stress, and mitochondrial dysfunction, a highly dangerous trio in the brain and this leads to subsequent neuroinflammation and neurodevelopmental pathologies in offspring. Maternal cytokines can directly cross the placenta and enter the fetal circulation which in turn activates the fetal immune system. This sets in a neuroinflammation cascade starting with the activation of microglia [13]. Exposure to inflammatory cytokines at the prenatal stage, in-utero and post-natal stages can influence the epigenetic architecture of the brain and the peripheral immune system. This culminates in modulating individual susceptibility to the development of neurodevelopment disorders. Maternal immune activation is mediated by acute and chronic inflammatory pathways that are transferred to the developing fetus through multiple inflammatory pathways and epigenetic mechanisms [14]. Obesity, stress, depression, pollution and disease states such as autoimmunity, asthma, and infection increasingly cause a state of chronic inflammation. Defining preventable risk factors in high-risk pregnancies could mitigate the expression and severity of neurodevelopmental disorders [15].

POSSIBLE UNDERLYING MECHANISMS

There are certain possible mechanisms that underlie obese pregnant mothers which increases the threat of neurodevelopmental disorders in the offspring, particularly ASD. A few of them have been described in the following sections (Fig. 1).

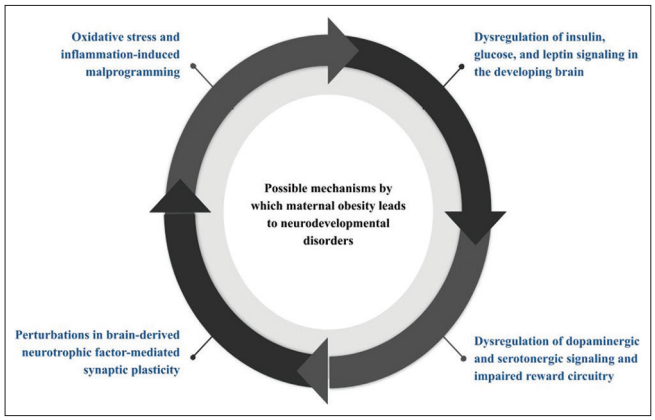

Figure 1: Possible mechanisms that lead to neurodevelopmental disorders due to maternal obesity

Oxidative Stress and Inflammation-Induced Programming

Chronic inflammation is a characteristic feature of pregnancy and maternal obesity [16]. The amount of circulating free fatty acids increases in obese women due to increased lipolysis and elevated dietary intake, and these fatty acids can cross the placenta [17]. As the amount of free fatty acids increases, it leads to increased oxidative stress on the developing fetus. Animal models of maternal obesity have also documented persistent changes in offspring behavior and impairments in critical neural circuitry among offspring born to obese mothers [18]. Fetal exposure to excess lipids can activate the pro-inflammatory pathways that can affect organ development and post-natal growth. Since fetal and neonatal life is characterized by tremendous plasticity and the ability to respond to environmental factors, preventing the onset of maternal obesity is crucial [19,20].

Studies with RNA-sequence analysis conducted among obese and lean pregnant women have found that there is greater lipotoxicity and oxidative stress among the placentas of obese pregnant women in comparison to lean women. Therefore, maternal obesity is associated with an elevated fetal lipotoxic environment coupled with decreased regulators of angiogenesis [21]. In alliance with the above findings, maternal BMI has been highly correlated with maternal pro-inflammatory concentrations and activation of placental pro-inflammatory pathways. Thus, the placenta develops an exaggerated inflammatory response to obesity [22]. With increasing maternal weight, studies have corroborated an increase in developmental delay particularly ASDs [23]. The placental inflammatory response is associated with an increased burden of fetal neuronal damage and neonatal brain gene expression [24,25]. Furthermore, evidence from epidemiological studies and animal models has documented the dysregulation in dopamine and serotonin secretion as a possible mechanism underlying the neuropathology in pregnant women [17].

Dysregulation of Insulin, Glucose, and Leptin Signaling in the Developing Fetal Brain

The developing fetus is exposed to a glucose-rich environment that predisposes the fetus to insulin resistance. The fetal pancreas also overproduces insulin thereby resulting in peripheral fetal insulin resistance. Peripheral insulin resistance has wider implications for the proper functioning of the central nervous system. Evidence suggests that synaptic insulin signaling has a key role to play in the development of learning and memory in children [26-30].

Similarly elevated leptin resistance is a common finding in obese women. Studies have shown that a maternal high-fat diet decreases the hippocampal gene expression of leptin receptors in the offspring [22]. Furthermore, leptin signaling is crucial for hippocampal-dependent learning through synaptic plasticity and neurotransmitter receptor trafficking [29]. Furthermore, the deficit in leptin concentrations is associated with a decrease in neuronal stem cell differentiation and growth [31]. Therefore, a dysregulation in leptin signaling in obese women could lead to neurodevelopmental disorders in the newborn.

Dysregulation of Serotonergic and Dopaminergic Signaling

Impaired serotonergic and dopaminergic signaling are associated with a wide variety of neurodevelopmental and neuropsychiatry disorders including anxiety, depression, schizophrenia, eating disorders, food addiction, post-traumatic stress disorder, ASD, and attention deficit hyperkinetic disorder. Serotonin also has a role to play in neuronal migration, cortical neurogenesis, and synaptogenesis during fetal brain development [26]. Maternal obesity also affects dopamine signaling which has a strong correlation with eating and behavior disorders. Hence, it is imperative to ensure adequate weight management during pregnancy to avoid adverse fetal outcomes [32]. Table 1 represents recent studies in the field of maternal obesity and the impending threat of autism in offspring.

EXPLORATORY PRENATAL THERAPIES

Studies from animal models and humans have shown that a modification in the lifestyle and dietary habits of the mother can have a positive impact on the neurodevelopment of the child [41]. Furthermore, maternal metformin treatment, supplementation of poly-unsaturated fatty acids and antiobesity medications can have a protective effect on the developing fetus [42]. Therefore, targeted strategies can be designed to curb maternal obesity.

Maternal Dietary and Lifestyle Modifications

Animal studies have highlighted the benefits of changing from a high-fat diet to a low-fat diet during the pre-pregnancy and lactation periods. It is most often associated with decreased offspring adiposity, circulating leptin, and anxiety behaviors [42]. Similarly, in another animal-based study (mice) conducted by Kang *et al.,* it was concluded that maternal insults have a huge impact on the offspring's sociability, a key feature in ASD. As per their findings, a maternal high-fat diet is associated with a greater incidence of decreased sociability in the female offspring. They also exhibited increased brain IL-1β and TNFα and microglial activation [43].

Studies have emphasized the role of maternal exercise in improving the learning efficiency of the offspring. In a study conducted by Molteni *et al.,* they have illustrated that a maternal high-fat diet reduces the levels of brain-derived neurotrophic factor (BDNF), a key player of synaptic plasticity that is a common predictor of learning efficiency. Similarly, they have implicated that exercise reduces the levels of reactive oxygen species increased due to maternal high fat diet. Furthermore, exercise reversed the decrease in BDNF, and its downstream effectors on plasticity such as synapsin I and the transcription factor cyclic AMP response element binding protein, both of which are important for learning and memory [44]. Maternal exercise during pregnancy can also improve object recognition memory in adult male offspring [45].

Table 1: Human epidemiologic studies examining the effects of maternal obesity on offspring particularly the development of autism

Sample	Study design	Outcome	Reference
Maternal/infant dyads (n=62) born ≤30 weeks gestation	Prospective cohort study	Maternal obesity was associated with a positive screen for autism (p=0.002) and lower composite language scores (p=0.002) at age 2	Reynolds *et al*., 2014 [33]
Infants born to mothers with pre-pregnancy BMI of 30 kg/m^2 or more and non-obese patients	Population-based cohort study	Offspring of obese mothers had higher rates of ASDs and psychiatric disorders (p<0.05)	Neuhaus *et al*., 2020 [34]
Children from a subset of the Boston Birth Cohort who completed at least 1 postnatal study visit diagnosed with ASDs and other developmental disorders	Epidemiologic study	Maternal prepregnancy obesity and maternal diabetes in combination were associated with increased risk for ASDs and intellectual disability	Li *et al*., 2016 [35]
Eligible children were 2–5-years-old at enrollment, born between September 2003 and August 2006	Case-control study	Maternal obesity class 2/3 was associated with ASDs and developmental delays	Matias *et al*., 2021 [36]
Mother-child dyads enrolled in the Boston Birth Cohort	Nested case-control study	Lower maternal postpartum plasma LDL concentration was associated with increased odds of ASD in offspring among children born to overweight and obese mothers	Park *et al*., 2021 [37]
Children diagnosed with ASDs in the ages 4–13 years	Norwegian Mother and Child Cohort Study	Paternal obesity is an independent risk factor for ASDs in children	Suren *et al*., 2014 [38]
Mother-child dyads from the Finish pregnancy and drugs registry	Record linkage study	Severely obese mothers had a 67% to 88% increased risk of having a child with mild neurodevelopmental disorders (including ASDs, attention deficit hyperkinetic disorder, and psychotic, mood and stress-related disorders)	Kong *et al*., 2018 [39]
Children with a diagnosis of autism spectrum disorders from birth to 2010	Population-based case-control study	Extremes in maternal BMI may be associated with modest increases in the risk for ASDs among offspring	Getz *et al*., 2016 [40]

Medical Therapies and Prenatal Supplementation

Metformin therapy among women without diabetes who had a BMI of more than 35, the antenatal administration of metformin reduces maternal weight gain [46]. In a study conducted in mice-model it was found that diet-induced-obesity/metabolic syndrome during pregnancy significantly enhanced fetal and placental cytokine production and metformin supplementation reduces the fetal cytokine levels [47]. Similarly, as obesity is associated with an inflammatory state with an increased concentration of reactive oxygen species, supplementation of antioxidants can ameliorate maternal and fetal morbidity. The drugs resveratrol and luteolin have been recently implicated in exerting neuroprotective effects on the developing child. Furthermore, studies conducted in mice models have also explored the improvement in memory performance when supplemented with luteolin [48-50]. These results indicate a previously unrecognized potential of antioxidants in alleviating obesity-induced cognitive impairment among the offspring of obese women.

CONCLUSION

Maternal obesity is increasing worldwide with a parallel increase in neurodevelopmental and psychiatric disorders in the offspring. Epidemiologic studies from developed and developing nations have provided ample evidence of an association between maternal obesity and adverse neurodevelopmental and psychiatric outcomes in offspring, particularly ASDs. Although there is the mounting level of evidence for this link, there are only few promising therapies to overcome neuroinflammation and mal-programming among the offspring. Furthermore, data on its safety and efficacy are still questionable. The best possible precaution is to control maternal weight during pregnancy. Future studies are warranted for stronger evidence and possible implications in the clinical setting.

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