

## Review Articles

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# Neurodevelopmental Disorders (NDDs) in Children: Role of Maternal Factors

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### Abstract:

*Neurodevelopmental disorders (NDDs) are disabilities affecting normal brain development and function. The early stages of brain development are critical, and disruption of this process results in neurodevelopmental disorders (NDDs) in children. Common neurodevelopmental disorders in children include autism spectrum disease (ASD), attention deficit hyperactivity disorder (ADHD), cerebral palsy (CP), intellectual disability (ID), epilepsy, learning disability, schizophrenia etc. Though the causes of NDDs are multifactorial, epidemiological studies have shown that a number of maternal factors such as, diabetes, hypertension, obesity, maternal immune activation, infection, diet, genetics, lifestyle etc. also influence the development of NDDs. In this review, we focus on some common NDDs in children and the mechanism by which different maternal factors may contribute to the development of NDDs. With the increasing incidence of NDDs, it is urgent to mitigate the risk and severity of these conditions through both preventive measures in pregnancy and developing treatment strategies.*

**Keywords:** Neurodevelopmental Disorders (NDDs), autism spectrum disease (ASD), attention deficit hyperactivity disorder (ADHD), cerebral palsy (CP), intellectual disability (ID), Maternal factors.

### Introduction:

Neurodevelopmental disorders (NDD) are a group of disorders that typically manifest early in development and are characterized by developmental deficits that produce impairments in personal, social, academic, or occupational functioning.<sup>1</sup> Neurodevelopmental deficits range on a broad continuum from rare and very severe disorders to more frequent and less disabling conditions, like cerebral palsy, intellectual disability, autism spectrum disorders (ASD), attention deficit-hyperactivity disorder (ADHD), tic disorders, schizophrenia, speech disorders, dyslexia and learning disabilities. The common characteristic of these disorders is that they are believed to be the outcome of some abnormal developmental processes of the brain, in the unborn or very young child.<sup>2</sup>

Brain development in the fetus starts within a few weeks of conception, with proliferation of glia and neurons and their migration, followed by programmed cell death, formation of synapses, myelination, and the establishment of complex neuronal circuits.<sup>3</sup> Dynamic interactions of genetic, epigenetic and environmental factors play a crucial role in guiding, shaping and supporting the complex neural networks in the brain throughout life.<sup>4</sup> The brain is however, thought to be particularly vulnerable while the child is still within the womb because of the immense growth. Although their etiology is multifactorial, in utero disruption of the environment by maternal infection, psychosocial stress, maternal psychopathology, high body mass index, neurotropic, and metabolic factors has been shown to affect fetal neurodevelopment, leading to neurodevelopmental disorders.<sup>3</sup>

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**Neurodevelopmental disorders in children:****Autism Spectrum Disorders**

Autism spectrum disorders (ASDs) are a group of neurodevelopmental disorders characterized by a deficit in socialization and communication, with restricted repetitive patterns of behaviors.<sup>1</sup> The onset of ASD occurs early in the first 36 months of life, with the expression of symptoms ranging from mild to severe.<sup>5</sup> Worldwide, 1 in 100 children has been identified with ASD.<sup>6</sup> ASD is a disease of complex interaction between genetics and the environment, with heritability ranging from 40 to 80%.<sup>7</sup> Among monozygotic twins, the concordance rate was about 60–91%.<sup>8</sup> Large-scale genetic studies have identified hundreds of risk gene on ASD patients

and majority of them are related to synapse formation, transcriptional regulation and chromatin-remodeling pathways.<sup>9</sup> Prematurity, environmental mutagen such as mercury, trichloroethylene, cadmium, vinyl chloride, advanced parental age, maternal autoimmune disease, infection etc. also contribute to the pathogenesis of ASD.<sup>10</sup>

**Attention deficit- hyperactivity Disorder (ADHD)**

ADHD is a neurobehavioral disorder defined by impairing levels of inattention, disorganization, and/or hyperactivity-impulsivity.<sup>1</sup> Inattention or disorganization is characterized by failure to pay close attention to details, inability to stay on task, not listening when spoken to, losing materials. Hyperactivity-impulsivity entails over activity, fidgeting, inability to stay seated, often intruding into other people's activities, and inability to wait for their turn. The symptoms should have persisted for at least 6 months, inconsistent with age or developmental level.<sup>1</sup> Several symptoms are present before 12 years of age. ADHD is a disorder of executive function which is attributable to abnormal dopamine transmission in the frontal lobe and frontostriatal circuit.<sup>11</sup>

Along with genetics, other possible causes and risk factors such as brain injury, exposure to environmental risks (e.g., lead, tobacco, alcohol) during pregnancy or at a young age, prematurity and low birth weight may contribute to the development of ADHD.<sup>12</sup>

**Cerebral palsy**

Cerebral palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-

progressive disturbances that occurred in the developing fetal or infant brain.<sup>13</sup> In approximately 6% of individuals with CP, brain injury was acquired during an event more than 28 days after birth; and in the remaining 94% of individuals, brain injury occurred during pregnancy, at birth, or over the first 28 days of life. About 40% of individuals with CP are born preterm and more than half of all individuals with CP are born at term.<sup>14</sup> The maternal immune system, maternal infections, or factors related to maternal immune function play a role for the development of cerebral diseases in the offspring.<sup>15</sup>

**Epilepsy**

The International League Against Epilepsy (ILAE) defined epilepsy as a disease of the brain with any of the following conditions:<sup>16</sup>

1. At least two unprovoked (or reflex) seizures occurring > 24 h apart
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
3. Diagnosis of an epilepsy syndrome.

Epilepsy affects around 50 million people worldwide and most of the cases begin in childhood or adolescence.<sup>17</sup> Approximately 102/100,000 new cases of epilepsy are reported each year in children under the age of one.<sup>18</sup> Children who are exposed to maternal infection during prenatal period were more likely to develop epilepsy.<sup>19</sup> Cystitis, pyelonephritis, vaginal yeast infection, diarrhoea, urinary infection, coughs have all been linked to epilepsy.<sup>3</sup>

**Intellectual disability**

Intellectual disability is characterized by deficits in both general mental functioning and adaptive behavior. The individual has a deficit in conceptual, social, practical, academic or occupational functioning and this deficit originated before the age of 18 years.<sup>1</sup> Prevalence in the general population has been estimated at more than 1/100 and has both genetic and non-genetic etiology.<sup>20,21</sup> Several studies have shown that advanced maternal age, multiple gestation, maternal alcohol use, maternal tobacco use, maternal diabetes, maternal hypertension, maternal epilepsy, maternal asthma, preterm birth, male sex, and low birth weight are associated with an increased risk of ID.<sup>21</sup>

## Schizophrenia

Schizophrenia is a complex brain disorder with a worldwide lifetime prevalence of 4 per 1,000 people.<sup>22</sup> Schizophrenia is characterized by positive, negative and cognitive symptoms and the onset is typically in late adolescence or early adulthood.<sup>1</sup> Positive symptoms include delusions and hallucinations; disorganized speech; catatonic behavior; negative symptoms include alterations in drive and volition, including lack of motivation, blunted affect, social withdrawal, reduction in spontaneous speech and alterations in neurocognition, including difficulties in memory, attention and executive functioning are the cognitive symptoms.<sup>1</sup> Maternal inflammatory responses triggered by infection with additional genetic and environmental risk factors play a role in the development of schizophrenia.<sup>3</sup>

### Maternal factors:

Maternal diabetes with neurodevelopmental disorders

Worldwide about 15% of pregnancies are complicated by diabetes which may manifest as gestational diabetes mellitus (GDM) or as preexisting type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM).<sup>23</sup> The highest prevalence of diabetes was found in the South-East Asia Region about 25.0%. Of the cases of maternal diabetes, approximately 87.5% are GDM, 7.5% are pre-pregnancy type 1 diabetes mellitus (T1DM), and 5% are T2DM.<sup>24, 25</sup>

Diabetes is characterized by elevated blood glucose levels, impaired insulin secretion, and/or peripheral resistance to insulin action.<sup>26</sup> Several studies suggest an association between maternal diabetes and an increased risk of NDDs in offspring, such as ASD, ADHD, ID, language abnormality, depression, anxiety and psychosis.<sup>27</sup> Recent studies showed that pre-gestational diabetes mellitus (PGDM) was associated with a greater risk of NDDs in offspring compared with GDM and may have a greater influence on the gross development of the brain in the first trimester. GDM usually occurs during the second half of pregnancy when the major developmental events for the cerebral cortex occur and may thus have a greater influence on the development of higher cognitive function.<sup>27</sup>

During pregnancy, insulin resistance is gradually elevated causing increased plasma insulin levels. It is linked to elevated levels of TNF- $\alpha$  and proinflammatory cytokines in GDM. When glucose passes through the placenta, the fetus develops

hyperglycemia and also insulin resistance. Hyperglycaemia induces oxidative stress and increased peripheral insulin levels have large effects on brain development that adversely affect neurobehavioural outcomes.<sup>28</sup> Hyperglycemia also influences epigenetic changes in the offspring. For example, DNA methylation is reduced in neurodevelopmental disorders such as ASD.<sup>29</sup>

Hyperglycaemia can lead to systemic inflammation and pro-inflammatory cytokines are able to cross the placenta and the fetal blood-brain barrier, which may affect neurodevelopment.<sup>30</sup>

Furthermore, ASD and ADHD are complex NDDs with high estimated heritabilities, and T1DM and T2DM are both polygenic disorders. A genetic investigation discovered an association of genes linked to higher risks of both types of diabetes and may also play a role in the etiology of NDDs.<sup>27</sup>

### Maternal hypertensive disorders and neuro-developmental disorders in offspring

Hypertensive disorders of pregnancy (HDPs) are estimated to affect approximately 5%–15% of all pregnancies.<sup>31</sup> HDP was classified by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy as chronic hypertension, preeclampsia, preeclampsia superimposed on chronic hypertension, and gestational hypertension.<sup>32</sup> Along with affecting maternal health and pregnancy outcomes, HDP may also increase the risk of neurobehavioral abnormalities in the offspring later in life by having an effect on the fetal brain.<sup>33</sup> HDP exposure has been linked to an increased risk of autism spectrum disorder, attention-deficit/hyperactivity disorder, developmental delay, intellectual disability, CP, epilepsy, and cognitive disorders in children.<sup>34</sup> Mothers with pre-eclampsia have a 1.3-fold risk of ASD and a 1.2-fold risk of ADHD in offspring.<sup>35</sup> The Childhood Autism Risks from Genetics and Environment cohort in the US showed that offspring exposed to preeclampsia had a 2.3-fold risk of ASD and a 1.4-fold risk of developmental delay.<sup>36</sup>

Maternal HDP may involve a decreased oxygen and nutrient supply to the fetus due to uteroplacental under-perfusion and hypoxia.<sup>33</sup> Thus, hypoxia/placental ischemia, oxidative stress, angiogenic and growth factor changes, inflammation, and interactions between these mechanisms may impair fetal brain

development and thus contribute to a greater risk of neurodevelopmental disorders.<sup>32</sup>

### **Maternal obesity and gestational weight gain**

Globally, the prevalence of maternal obesity is increasing day by day. In the United States, nearly 27% of women of childbearing age are overweight (body mass index (BMI)  $\geq$  25 and  $<$ 30 kg/m<sup>2</sup>), 37% are obese (BMI  $\geq$  30 kg/m<sup>2</sup>).<sup>37</sup> Gestational weight gain (GWG) is another prenatal complication and it is the amount of weight gained by mothers during the period between conception and delivery.<sup>38</sup> Maternal obesity and excessive gestational weight gain (GWG) during critical periods of prenatal development have been linked to negative fetal outcomes such as prematurity, congenital anomaly, fetal adiposity, and an increased risk of neuropsychiatric disorders.<sup>28</sup> Several studies have demonstrated an association between maternal obesity and neurodevelopmental and psychiatric morbidities in offspring, including intellectual disability and cognitive deficits; autism spectrum disorders (ASDs); attention deficit hyperactivity disorder (ADHD); cerebral palsy (CP); anxiety and depression; schizophrenia; and eating disorders, including food addiction, anorexia and bulimia.<sup>37</sup>

A systematic review and meta-analysis reported that maternal overweight and obesity were associated with a 36% higher risk for ASD than normal weight during pre-pregnancy or pregnancy.<sup>39</sup> Maternal obesity is associated with a 1.6 to 2.8-fold increased risk of offspring ADHD and a 1.3 to 3.6-fold increase in the risk of intellectual disability or cognitive impairment in offspring.<sup>37</sup> The risk of CP increased by 7% with each one-unit increase in maternal BMI, and each kilogram of additional weight at 34 weeks increased the risk of offspring CP by 2%.<sup>40</sup> The primary mechanisms that have been proposed to underlie the risk of neurodevelopmental morbidity in the offspring of obese women include:<sup>37</sup>

1. Oxidative stress and inflammation-induced malprogramming.
2. Dysregulation of insulin, glucose, and leptin signaling in the developing brain.
3. Dysregulation of dopaminergic and serotonergic signaling.
4. Perturbations in brain-derived neurotrophic factor-mediated synaptic plasticity.

### **Maternal immune activation (mIA) and NDDs**

Several human and animal studies indicate that maternal immune activation (mIA) can program the fetal brain and immune system through inflammatory and epigenetic mechanisms during critical developmental periods of central nervous system, microglial, immune system and gut microbiome.<sup>41</sup> This can be responsible for the development of neurodevelopmental and psychiatric disorders in children including ASD, ADHD, Schizophrenia, Tourette syndrome (TS), Epilepsy, Cerebral palsy, Alzheimer's disease (AD), Parkinson's disease (PD) etc.<sup>3, 42</sup>

Maternal inflammatory states play a key role in immune activation during pregnancy and exposure to dysregulated maternal immune milieu in utero affects fetal neurodevelopment.<sup>43</sup> Maternal immune activation can be triggered by acute and systemic chronic inflammation (SCI). Systemic chronic inflammation is a persistent, sterile, non-resolving inflammation that increases with age. Maternal environmental and lifestyle factors including obesity, unhealthy diet, psychosocial stress, physical inactivity, disturbed sleep, microbial dysbiosis, and exposure to toxicants like smoke and pollution, collectively known as exposome, contribute to SCI, whereas acute inflammations are usually provoked by acute infection and cause short-term, high-grade inflammation.<sup>43</sup> During maternal immune activation, levels of inflammatory markers exceed the normal range or levels of these markers in the higher normal range.<sup>42</sup> Heterogeneous infectious and non-infectious maternal inflammatory factors induce the release of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), which activate Toll-like receptors on maternal peripheral innate immune cells and placental cells, leading to cytokine production. Interleukin 6 (IL-6), IL-1 $\alpha$ , IL-10, tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), C-reactive protein (CRP) or the complement system has been suggested to play a major role.<sup>42</sup> During the critical period of fetal brain development, passive transport and active placental production of immune mediators induce long-lasting epigenetic memory on fetal microglia and immune cells. Interactions among offspring aberrant immune programming, epigenetic factor and second immune 'hits' in life result in a state of chronic inflammation in both the brain and periphery, which manifest with a spectrum of diverse neurodevelopmental outcomes with varied expression and progression.<sup>41</sup>

### Maternal infection

Maternal infection during pregnancy has been linked with the occurrence of some neurodevelopmental disorders in the offspring. There is well-established evidence concerning neurodevelopmental impairment in children following maternal exposure in pregnancy to infections belonging to the TORCH complex.<sup>44</sup> The TORCH infections are a group of teratogenic infections and were originally referred to as *Toxoplasma Gondii*, Rubella, Cytomegalovirus, and Herpes Simplex Viruses. Today, the acronym is used more broadly and encompasses infections such as Parvovirus B19, Varicella Zoster, Syphilis, Human Papillomavirus and many more as well.<sup>45</sup> TORCH infection produces neurological manifestations such as microcephaly, hydrocephalous, periventricular leucomalaciae, brain calcification, brain malformation, migration defect, cortical dysplasia and many more. It also causes eye abnormalities and sensory neuronal deafness. Cerebral palsy, epilepsy, intellectual disability, schizophrenia, ASD, ADHD as long-term sequelae.<sup>45</sup> Recently, maternal Zika virus infection has been found to be associated with microcephaly alone or with congenital anomalies that lead to poor neurocognitive outcomes in offspring. Zika virus may cause acute neurological lesions (including septal and colossal disruption, abnormal neuronal migration, cerebellar hypoplasia), brain calcifications, degenerative changes in neuronal and glial cells, gliosis, necrosis, white matter and decline axonal rarefaction.<sup>46</sup> It is estimated that around 60% of all pregnant women experience at least one infection while pregnant. However, infections such as influenza, urinary tract infections, vaginal infections, upper respiratory tract infections, and diarrhea are all very common during pregnancy.<sup>47</sup> Maternal infection during pregnancy increases the risk of autism and depression in childhood and adulthood among the exposed offspring.<sup>48</sup>

### Maternal diet and neurodevelopment

A diet with adequate quantity and quality is essential for the mother's health and the healthy development of the offspring during pregnancy. A healthy maternal diet rich in macro and micronutrients influences the mother's regulatory systems, such as the immune, endocrine, and nervous systems, which in turn influence the offspring's overall development. Maternal dietary imbalance can lead to diet-induced maternal immune activation (MIA) and neuroinflammation, which have potential long-term impacts on neurodevelopment

in the progeny and may be associated with neurodevelopmental disorders like autism spectrum disorders, attention-deficit-hyperactivity disorder, cognitive impairment and schizophrenia etc.<sup>49</sup>

Vitamin B12 or cobalamin acts as a cofactor with folate in DNA methylation and their deficits are associated with neural tube defects and neurodevelopmental disorders like ASD, ADHD, intellectual disability and schizophrenia.<sup>50</sup> Supplementation of vitamin B reduces neuroinflammation and oxidative stress by increasing oxidative metabolism, which may promote energy storage and developmental processes.<sup>51</sup> Vitamin D helps in neuronal differentiation, metabolism of neurotrophic factors and neurotoxins, gives protection from brain inflammation, and thereby influences fetal brain growth.<sup>52</sup> Iodine deficiency has been associated with a developmental condition called cretinism.<sup>53</sup> Zinc is also important for neuronal development.<sup>54</sup> Macronutrients such as protein have long been associated with brain growth and also have neurocognitive effects.<sup>55</sup> Supplementation of omega-6 and omega-3 fatty acids (PUFAs) during pregnancy improved neurocognitive performance in the children<sup>56</sup> whereas diets with high saturated fat have deleterious consequences on brain development, including decreased hippocampal size.<sup>57</sup> So dietary recommendations have been made for certain essential fatty acids,  $\alpha$ -linolenic acid (n-6 PUFA) and linoleic acid (n-3 PUFA) in pregnancy.<sup>58</sup>

Iron deficiency anemia is frequent during pregnancy and the worldwide estimated prevalence is between 15% to 20%.<sup>59</sup> Maternal iron deficiency can lead to fetal and neonatal iron deficiency.<sup>60</sup> Iron is necessary for normal neuronal and glial energy metabolism and helps in myelination and dendrite arborization. It is also necessary for the synthesis of monoamine neurotransmitters and its deficiency causes alteration of dopamine metabolism, hippocampal structure and function, and also long-term genomic changes. All of these have a negative effect on brain function with concurrent behavioral abnormalities that even persist long after treatment.<sup>61</sup> A recent study demonstrated that the prevalence of ASD, ADHD, and ID was higher among children born to mothers diagnosed with anemia within the first 30 weeks of pregnancy compared with mothers with anemia diagnosed later in pregnancy.<sup>62</sup> So, the WHO recommends that 30–60 mg of elemental iron should be started daily as early as possible during pregnancy.<sup>63</sup>

Genetic Factors: NDDs are multifactorial and have heterogeneous origins. Many genes and mutations as well as environmental factors influence the outcome, causing difficulties in genotype–phenotype correlations.<sup>64</sup> Different types of mutations have been associated with NDDs, including chromosomal rearrangements, copy number variations, small indels, and point mutations. There are a number of maternal factors influencing epigenetic pathways such as infections, obesity, gestational diabetes mellitus (GDM), lifestyle, including diet, alcohol consumption, and smoking thereby contributing to neurodevelopmental disorders.<sup>65</sup> But there are few studies about the inherent impact of maternal genetics on in-utero inflammation and fetal neurodevelopment in the absence of strong external inflammatory exposures. By changing IL-10 mediated materno-fetal immunosuppression, maternal genetics alone can modulate fetal neurodevelopment and ASD-related phenotypes in the offspring.<sup>64</sup>

#### Conclusion:

Many of the maternal factors reviewed here have been associated with neurodevelopmental disorders in children. Diabetes, obesity, nutrient intake, hypertension, maternal inflammatory status, infection, lifestyle, psychological stress, and genetics are all linked to an increased risk of NDDs in offspring. So, comprehensive assessment of maternal factors, the child's postnatal exposome, immunological factors with early intervention can reduce the incidence of NDDs in offspring. Future research should also improve our understanding of the disease pathway and help us find more specific and curative treatments.

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