

## A REVIEW ON 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.

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

### 1. 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>[1]</sup>

#### 1. Nutrition:

Both maternal under- and overnutrition may have consequences for fetal neurodevelopment. Maternal obesity is also associated with impaired neurodevelopment and executive functioning and with adverse neuropsychiatric outcomes in children including Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD). Studies in mouse models of maternal obesity suggest that there are adverse effects on brain development and behaviour and in non-human primates, exposure to a high fat diet during pregnancy is associated with an increase in offspring anxiety-like and repetitive behaviours. Some of these effects may be mediated by epigenetic alterations, for example in mice, exposure to excess dietary  $\omega$ -6 polyunsaturated fatty acids (used to model a western high fat diet) has been associated with altered DNA methylation and chromatin architecture in the offspring cortex.

#### 2. Infection:

Pregnant women are more susceptible to infection and display an increased inflammatory response to some pathogens, but the mechanisms behind this are largely unknown. Maternal viral infections during pregnancy may increase the risk of psychiatric disease in the offspring, with the time of infection being particularly important. For instance, a large

Danish study found a significant association between maternal hospitalisation for influenza during the first trimester and ASD in her offspring. Maternal exposure to measles, rubella and polio been associated with an increased risk of schizophrenia in offspring. Other maternal infections (for example untreated genital herpes) may affect neurodevelopment increasing the risk for preterm birth, which is independently associated with adverse neurodevelopment..

### 3. Maternal stress:

While stress during pregnancy affects women worldwide, pregnancy-related stress in lower and middle income countries appears to be associated with a greater risk of adverse outcome Offspring exposed to high levels of prenatal maternal stress or anxiety are at a higher risk of developing depression , ASD, schizophrenia and ADHD as well as various emotional and behavioural problems; with the timing of stress and the sex of the fetus playing important roles in the outcome of these studies. There is also evidence to suggest that maternal antenatal depression and socioeconomic status can interact with a polygenic score for major depressive disorder to modulate risk . Moreover, good maternal mental health during pregnancy is positively associated with cognitive abilities in the offspring at 2 years of age.

### 4. Transgenerational effects:

The transmission of programmed effects on neurodevelopment through the maternal line could occur through a number of mechanisms including

- Continued exposure to an adverse environment;
- Re-exposure via programmed alterations in maternal physiology which impact on the development of the next generation e.g. through increased maternal glucocorticoid levels; or
- Changes in maternal behaviour leading to the development of similar behavioural phenotypes in her own children.<sup>[2]</sup>

## 2. NEURODEVELOPMENTAL DISORDERS

Neurodevelopmental disorders represent a group of heterogeneous conditions with onset during the developmental age, characterized by an alteration of communication and social skills, learning, adaptive behavior, executive functions, and psychomotor skills. These deficits lead to an impairment of personal, social, scholastic, or work-related functioning. This new diagnostic category of the DSM-5 in fact, compared with the previous category “Childhood and Adolescent Disorders” of the DSM-IV , underlines how these disorders are not limited to these age groups but tend to persist for a long time throughout life, changing according to the evolutionary trajectory.

These disorders often occur in comorbidity, representing a “constellation” of conditions that show overlapping clinical manifestations, probably because of common risk factors and shared pathogenetic mechanisms, defining a continuum between different pathologies (hypothesis of a genetic spectrum of neurodevelopmental disorders).

Neurodevelopmental disorders (DSM) include the following pathologies:

- Intellectual disability (intellectual development disorder);
- Communication disorders;
- Autism spectrum disorder;
- Attention deficit/hyperactivity disorder;
- Specific learning disorder;
- Movement disorders;
- Other neurodevelopmental disorders.<sup>[3]</sup>

### NEURODEVELOPMENTAL DISORDERS IN CHILDREN:

#### 1. Autism spectrum disorders:

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication and the presence of restricted interests and repetitive behaviors (1). In 2013, the Diagnostic and Statistical Manual of Mental Disorders—5th edition (DSM-5) was published, updating the diagnostic criteria for ASD from the previous 4th edition (DSM-IV). In DSM-5, the concept of a “spectrum” ASD diagnosis was created, combining the DSM-IV’s separate pervasive developmental disorder (PDD) diagnoses: autistic disorder, Asperger’s disorder, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified (PDD-NOS), into one. Rett syndrome is no longer included under ASD in DSM-5 as it is considered a discrete neurological disorder. A separate social (pragmatic) communication disorder (SPCD) was established for those with disabilities in social communication, but lacking repetitive, restricted behaviors. Additionally, severity level descriptors were added to help categorize the level of support needed by an individual with ASD.<sup>[4]</sup>

## 2. Attention deficit- hyperactivity Disorder (ADHD):

Attention deficit hyperactivity disorder (ADHD) is characterised by a pattern of behaviour, present in multiple settings (e.g., school and home) that can result in performance issues in social, educational, or work settings. Symptoms are divided into two categories: inattention; and hyperactivity and impulsivity, which include behaviours such as failure to pay close attention to details, difficulty organising tasks and activities, excessive talking, fidgeting, or an inability to remain seated in appropriate situations. Children must have at least six symptoms from either (or both) the inattention group of criteria and the hyperactivity and impulsivity criteria, while older adolescents and adults (aged >17 years) must present with five. The definition of ADHD has been updated in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) to more accurately characterise the experience of affected adults. Using DSM-5, several of the individual's ADHD symptoms must be present prior to age 12 years, compared with 7 years as the age of onset in DSM-IV. DSM-5 includes no exclusion criteria for people with autism spectrum disorder, because symptoms of both disorders co-occur. However, ADHD symptoms must not occur exclusively during the course of schizophrenia or another psychotic disorder and must not be better explained by another mental disorder, such as a depressive or bipolar disorder, anxiety disorder, dissociative disorder, personality disorder, or substance intoxication or withdrawal. The ICD-10 uses the term 'hyperkinetic disorder' for a more restricted diagnosis. It differs from the DSM-5 classification in that: all three problems of attention, hyperactivity, and impulsiveness must be present; more stringent criteria for 'pervasiveness' across situations must be met; and the presence of another disorder is an exclusion criterion. However, in clinical practice, the co-existence of anxiety and mood and autistic spectrum disorders is generally recognised. Formal diagnostic criteria are most applicable to boys aged 6 to 12 years, and most research data relate to this group.<sup>[5]</sup>

## 3. 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. 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. 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.

## 4. Epilepsy:

Epilepsy one must fully grasp the official terminology and nomenclature used to describe seizures and epilepsy. According to the International League Against Epilepsy (ILAE), the main governing body responsible for terminology and nomenclature as it pertains to seizures and epilepsy, a seizure is defined as an abnormal electrical perturbation resulting from a network of neurons. In the year 2014, an ILAE task force revised the definition of epilepsy. A person is considered to have epilepsy if they meet any of the following conditions: 1. At least two unprovoked or reflex seizures occurring .24 hours apart. 2. One unprovoked or reflex seizure and a probability of further seizures similar to the general recurrence risk of at least 60% after two unprovoked seizures occurring over the next 10 years. 3. A diagnosis of an epilepsy.<sup>[6]</sup>

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

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. Approximately 102/100,000 new cases of epilepsy are reported each year in children under the age of one. Children who are exposed to maternal infection during prenatal period were more likely to develop epilepsy. Cystitis, pyelonephritis, vaginal yeast infection, diarrhoea, urinary infection, coughs have all been linked to epilepsy.

## 5. 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.1 Prevalence in the general population has been estimated at more than 1/100 and has both genetic and non-genetic etiology. 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.

## 6. Schizophrenia:

Schizophrenia is a chronic mental illness characterized by two categories of symptoms: positive and negative. Positive symptoms include hallucinations, delusions, disorganized thinking and speech patterns and abnormal motor behaviour, which may include bizarre movements or catatonia (American Psychiatric Association, 2013; Coghill, Bonnar, Duke, Graham, & Seth, 2009). Negative symptoms include blunt or flat affect, lack of motivation, absence or diminished speech patterns, diminished interest in social interaction and anhedonia (American Psychiatric Association, 2013; Coghill et al., 2009). Schizophrenia most commonly emerges during early adulthood between the ages of 16 and 30, but it can also be diagnosed during childhood (The National Institute of Mental Health, 2009). A diagnosis of childhood-onset schizophrenia (COS) is given when the onset of the illness occurs prior to age 13. COS is a very rare illness and as such is poorly understood. This lack of understanding makes it difficult to accurately diagnose and, as a result, children with schizophrenia are often misdiagnosed. It is important that clinicians have an in-depth understanding of the manifestation and prognosis of COS in order to better recognize and treat it.<sup>[7]</sup>

Schizophrenia is a complex brain disorder with a worldwide lifetime prevalence of 4 per 1,000 people. Schizophrenia is characterized by positive, negative and cognitive symptoms and the onset is typically in late adolescence or early adulthood. 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. Maternal inflammatory responses triggered by infection with additional genetic and environmental risk factors play a role in the development of schizophrenia.

### Neuroscience of the environmental impact on child's development:

Neurodevelopment begins at the embryonic stage and continues through adulthood. The brain is the primary organ of stress and adaptation, responsible for interpreting and regulating behavioral, neuroendocrine, autonomic, and immunological responses to the events (adverse or protective), changing structurally and functionally in response to significant adversity or to positive experiences. The interconnection between these experiences and the individual responses to them during the first years of life will be the foundation for all the future developmental processes. The early childhood brain is extremely plastic, but this enhanced plasticity also provides an enhanced vulnerability to all types of experiences. The nature and timing of these experiences influence the course of the developing brain in many ways, especially if they occur during the "sensitive or critical periods". Sensitive periods may be defined as restricted windows of development when experiences have strong influences on the neural circuit formation.<sup>[8]</sup>

### ETIOLOGY AND RISK FACTORS:

Neurodevelopmental disorders are characterized by multifactorial etiology, consequent to a complex interaction between genetic and environmental factors (especially pre and perinatal ones). Examples of environmental factors in utero include exposure to alcohol, drugs, or other toxic substances during pregnancy, maternal stress, maternal infections, prematurity, and prenatal nutrition.

The genetic etiology has been widely confirmed: for example, as regards autism, the concordance of the pathology in homozygous twins is 60–90% and 5–40% in heterozygous twins. The genetic factors include copy number variations (CNVs), single nucleotide variations (SNVs), and chromosomal abnormalities. The interaction between these factors determines alterations in cortical migration and synaptic and neuronal networks, chromatin remodeling, regulation of transcription, and immunological regulation, constituting a trio of mutually interactive domains, therefore, environment, genes, and brain.

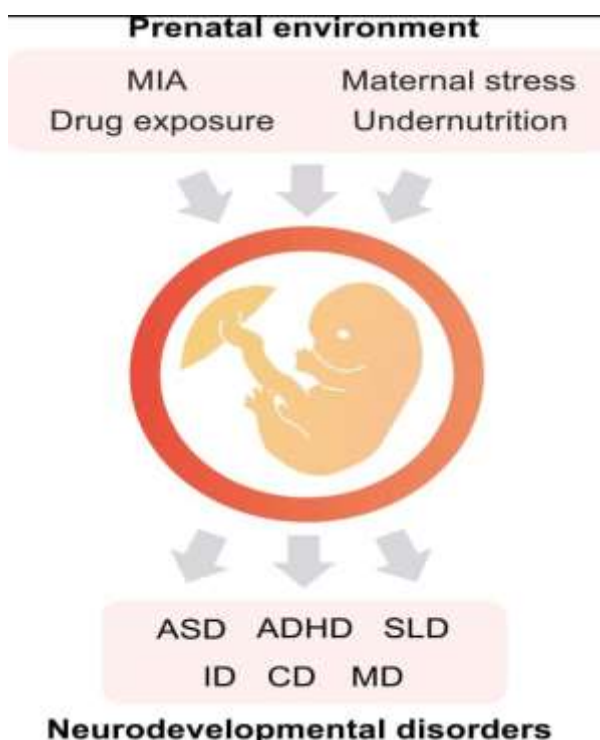
### RISK FACTORS:

The main risk factors for neurodevelopmental disorders, specifically for ASD, are as follow;

- Complications of pregnancy and childbirth;
- Prematurity;
- Low birth weight;
- Exposure to alcohol, drugs, or other toxic substances during pregnancy;
- Low socio-economic level of parents;
- Situation of early emotional deficiency

**MATERNAL IMMUNE ACTIVATION:**

MIA is an inflammatory response triggered by pathogenic infection and autoimmune diseases in the mother. According to the previous epidemiological studies, MIA is known to be a risk factor for NDDs and psychiatric disorders such as ASD and schizophrenia. Toxoplasma, rubella, cytomegalovirus, herpes simplex virus, and Zika virus are vertically transmitted to the fetus, affecting its development and resulting in severe complications such as miscarriage and malformations. However, the infections with non-vertically transmitted pathogens such as influenza during pregnancy can cause NDDs in the offspring. Inflammatory cytokines produced in the mother because of infection directly damage the fetal brain via the placenta. In a mouse model of MIA induced by poly(I:C), it was demonstrated that interleukin (IL)-17 produced from T-helper (Th)-17 cells in the mother’s body reach the fetal brain via the placenta and induce cell death via IL-17 receptors expressed in the fetal brain, resulting in ASD-like behavioral and morphological brain abnormalities . In MIA-induced ASD model mice, the decreases of synaptic density and expression levels of synapse formation associated proteins were also reported. Such synaptic dysfunction is well known in pathophysiology of ASD. For example, mutations of neuroligin encoding genes NLGN3 and NLGN4 related with synapse formation have been reported in ASD patients.<sup>[9]</sup>



**GENETIC AND EPIGENETIC FACTOR:**

The most recent studies show that CNVs and SNVs should be responsible for approximately 15% and 7% of ASD cases, respectively. Despite considerable progress, most ASD cases (>75%) still have unknown causes. Genetic and epigenetic factors can act at various levels of the neuronal cell body through nuclear and cytoplasmic mechanisms, for example, chromatin remodeling, gene transcription, DNA methylation, post-transcriptional regulation by miRNAs, and many others. The main genes involved in the etiopathogenesis of ASD code for molecular adhesion cells, scaffold proteins, proteins involved in neuronal communication, and voltage-gated ion channels, for example RELN, MET, GABRB3, SLC6A4, Neuroligins 3 and 4 (NL), Neurexins (NRX) 1 and 3, SHANK3, Cadherin (CDH) 9 and 10 (probably causing approximately 15% of ASD), and Contactin (CNTN) 2, 3, and 4. These mutations lead to impaired neuronal maturation and migration, reduction of apoptosis or increase in cell proliferation, alteration of cellular differentiation, reduction of dendritic spines and synaptogenesis (causing synaptopathies), resulting in alteration of brain morphology, functionality, and connectivity (reduced long-distance connectivity and excessive local connectivity) and excess excitability compared with neuronal inhibition.<sup>[10]</sup>

**Mechanism:**

Epigenetic mechanisms have the peculiar characteristic of modulating gene expression without altering the DNA sequence and represent the mediators of the gene/environment interface. They can lead to modulation of susceptibility genes, causing alterations of brain morphology, functionality, and connectivity involved in neurodevelopment. In fact, epigenetic changes could be implicated in the stress susceptibility and pathogenesis of psychiatric disorders such as depression and schizophrenia, as well as neurodevelopmental disorders.

The main epigenetic mechanisms are as follows:

- DNA methylation.
- miRNAs or microRNAs, small sequences of 20–25 RNA nucleotides, organized as a single strand, not coding for any protein but having the function of regulating the translation of target genes through down regulation mechanisms. They induce gene silencing through binding to complementary sequences on target mRNA molecules, resulting in repression of translation or degradation of the target molecule.

#### Environmental Factors:

Environmental factors play a fundamental role in the pathogenesis of neurodevelopmental disorders. According to many recent studies, environmental factors should be responsible for approximately 40–50% of ASD and include exposure to drugs or toxic agents, high parental age, nutrition, fetal environment, and many other factors. High parental age is one of the most studied factors, although recently downsized, and would seem to be related to ASD, ADHD [16], bipolar disorder, and schizophrenia. A meta-analysis of 27 studies showed that a 10-year increase in maternal and paternal age was associated with a 20% greater risk of developing ASD, probably also due to age related methylation changes in sperm. High parental age also appears to be associated with a reduction in the cortical thickness of the right posterior cingulate cortex in offspring with ASD.

Environmental factors, especially heavy metals, can affect neurodevelopment through various mechanisms:

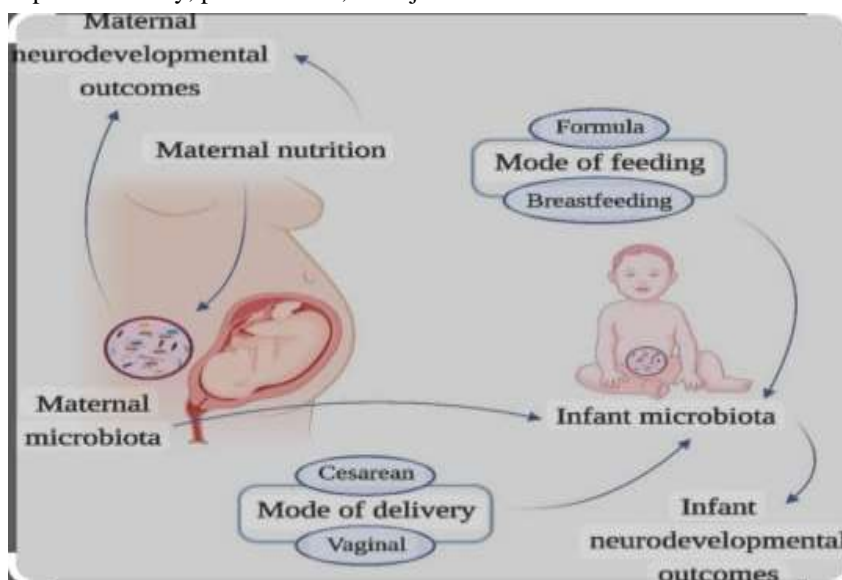
- Epigenetic/genetic mechanisms (discussed previously).
- Immune dysregulation and neuro inflammation—in fact, the interaction between the immune system and nerve cells is essential for neurodevelopment. For example, IL-6 and INF- $\gamma$  regulate dendritic growth and synaptogenesis through signal transduction mechanisms and the MAPK pathway.
- Oxidative stress and mitochondrial dysfunction through an imbalance between free radicals and antioxidants leading to the alteration of ATP levels in nervous cells.
- Endocrine alterations, such as hormonal imbalances.
- Alterations of neurotransmitters (such as serotonin, glutamate, and GABA) and cell signaling pathways.<sup>[11]</sup>

#### Prenatal factors:

Prenatal factors Our findings report of only the mother’s opinion on her subjective health to be considered affected by the NDD group vis-a-vis TD group. This is consistent with many studies where no prenatal factors have emerged (Sharma et al., 2020; Chattopadhyay & Mitra, 2015). Some research points to increased duration of labor, psychological stress, exposure to toxic substances, and poor nutrition as risk factors to ASD. One meta-analytic review on various conditions of NDD from low-middle income nations such as ours, have pointed to parental smoking and a history of febrile illness to be a risk factor.

#### Perinatal factors:

All the children have been in hospital-births in our study. Apart from this, all the rest of the perinatal factors have emerged significantly differently for the two groups in our study. Many studies concur with our findings, both Indian and western. In a study of children with ASD, Mamidala et al. (2013b) obtained significant differences between their control and ASD groups on birth cry, preterm birth, birth jaundice.



**Postnatal factors:** The number of males being affected with NDD is more in our study, being in line with the prevalence rates from previous studies. Many studies both from India and abroad concur on neonatal events as a major risk factor. Though our study only points to the presence of neonatal illness such as pneumonia/common cold/meningitis in children with NDD, many studies have enumerated numerous postnatal factors. In a study on 350 children with risk for ASD from south India, factors such as resuscitation at birth, 12 hours, and more in neonatal intensive care unit (NICU), seizures at infancy, radiation, not immediately breastfed have been found to be significantly different from the non-risk children. Later in their development, increased crying, banging and breath-holding spells were noted. Chattopadhyay and Mitra (2015) found jaundice, convulsions apart from other neonatal infections in 134 children with developmental delay in comparison with 293 children of TD from a north Indian city. Moreover, Geetha, Sukumar, Dhivyadeepa, Reddy & Balachandar (2019) found parents having mood changes, sleeping disorders, gastrointestinal upset postnatally in parents of children with ASD. Golmirzaei et al. (2013) concur with postnatal factors such as seizures and childhood head trauma emerging significantly in ADHD children of 4 to 11 years than the control group of TD children.<sup>[12]</sup>

**Potential risk factor:** Potential risk factor for ASD is fetal exposure to sex hormones (in fact, the fetal testosterone theory was one of the theories proposed to explain the major prevalence of ASD in males, a very controversial hypothesis) [25]. Some studies have detected high levels of sex hormones and cortisol in amniotic fluid samples from male autistic patients compared with controls [26]. The same authors reported an association between fetal levels of estrogens, important for synaptogenesis, and the risk of autism. Other studies have found post-mortem reduced levels of estrogen beta receptors and aromatase in the frontal gyrus in ASD patients compared with controls. Furthermore, several SNPs of protein-coding genes involved in the synthesis or transport of sex hormones appear to be associated with autistic traits. Maternal health conditions have a high impact on the risk of ASD.

## 7. 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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