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# Impact of Intrauterine Exposure on Fetal Brain Development and Brain Injury

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**ABSTRACT**

Intrauterine exposures to environmental factors influence fetal brain development. During early development of fetal brain, billions of cells differentiate into neurons and form connections. Synaptic activity affects the strength and number of synapses that form between neurons. The intrauterine environment plays an essential role in the mechanisms of fetal brain development and injury. Various intrauterine insults that impact the process of brain development, including genetic, traumatic, infectious, maternal stress, and environmental etiologies, can result in abnormal development or neurological injuries. Perinatal brain injury can cause lifetime neurologic disability. Understanding of the relationship between the intrauterine environment and fetal brain development remains limited and is needed to shed light on effective strategies to predict and prevent the risk of brain injury during intrauterine fetal development. This review focuses on intrauterine exposure to various environmental factors, their impact on brain development, and resultant brain injury among premature and term infants.

## Introduction

Human prenatal brain development after fertilization is usually classified into four periods: 0–7 gestational weeks (GW) and neuronal proliferation during 8–15 GW, 16–25 GW, and > 26 GW [1]. In humans, neurons are mostly produced in the first trimester of gestation. The rapid development of the fetus's cerebral cortex from the day of fertilization occurs for a period lasting from 8 to 15 weeks, and by 16 weeks, the number of neurons in the cerebral cortex reaches the adult level [2,3]. Abnormal brain growth may result from an unsuitable intrauterine environment. Adverse intrauterine environments that may have a negative effect on the fetal brain include maternal diabetes, undernutrition, infection, hypoxia, stress, alcohol, smoking, toxins, and anemia; hypertensive disorders in pregnancy; high-altitude pregnancies; and placental insufficiency. These adverse environmental factors may trigger epigenetic alteration and have a significant impact on fetal brain development through genome-wide changes of epigenetic regulation. The common epigenetic modifications include acetylation of histone and methylation of DNA, in addition to non-coding RNA epigenetic regulations [4,5] and chromatin modification [6,7], which are vulnerable to the maternal environment [8]. The purpose of this review is to summarize articles on the deleterious effects of some types of intrauterine exposure on fetal brain development and brain injury. The hope is to provide the impetus for further studies to delineate the function of the intrauterine environment on fetal brain development, through evidence from premature and term infants, as well as the role of the intrauterine environment in lifelong brain injuries and the pathologic mechanisms by which these injuries occur.

### Fetal Brain Development

**Synapse Development:** Synapses connect billions of neurons during intrauterine fetal brain development, which is important in all functional neuronal circuits [9]. Synaptic plasticity is characterized by the removal and insertion of amino-3-hydroxy-5-methy1-4-isoxazolepropinic receptors (AMPARs) into the

postsynaptic membrane, and by the shrinkage or enlargement of dendritic spines, where the majority of excitatory synapses are positioned [9,10]. Synapse formation exceeds elimination, leading to a surplus of immature excitatory synapses during early brain development. Subsequently, synapse elimination and destabilization diminish the number of synapses, thus refining neural circuits that generate cognition and behavior [11]. Cell surface receptors such as metabotropic glutamate receptors (mGluRs), NMDA-type glutamate receptors (NMDARs), and tyrosine kinase (TRK) receptors activate mTOR signaling through the AKT pathway and the phosphoinositide-3 (PI3K) pathway, and MAPK via the ERK pathway. The ERK/MAPK pathway plays a key role in synaptic plasticity, consolidation of memory, and the transition from pluripotent stem cells to neuronal progenitors [12]. The myocyte enhancer factor (MEF2) family of transcription factors can regulate synapse elimination during brain development [13,14]. Synaptic strength is mainly influenced by changes in synaptic structure that depend on instruction of local protein synthesis, structural remodeling of the cytoskeleton, and receptor signaling [15,16]. Glutamate serves as both as a key neuromodulator to control synape and cirruit function and the mammalian brain's primary excitatory neurotransmitter over a wide range of temporal scales and spatial.The group metabotropic GluRs (mGluRs) are abundant at excitatory synapses throughout the brain, where they are speculated sited to adjust to glutamatergic signaling [17]. They are vital to synaptogenesis and the shape of neural circuitry during the period of brain development [17]. Some evidence has demonstrated the important function of signaling lipids in mediating signal transduction and membrane traffic at pre-and post-synapses. For example, phosphoinositides can conduct ion channels, regulate exocytosis and endocytosis of synaptic vesicles and postsynaptic receptors, and signal from activated neuroreceptors such as NMDARs and mGluRs to allow plastic adjusted function of synapse [18,19].

**Oligodendroglial Cells:** Oligodendroglial cells in the central nervous system (CNS) synthesize myelin, transform from progenitor to the mature oligodendrocyte, and play a key role in salutatory conduction of action potentials [20-22]. After 20 GW, oligodendrocyte progenitor cells (OPCs) are shaped in the ventricular zone [23]. OPCs are generated in the brain and spinal cord from multipotent stem cells, and then they proliferate and differentiate. Neurogenesis and oligodendrogliogenesis progress at different rates in the human brain. OPCs first emerge in the ganglionic eminence at approximately 9 GW in pregnant women [24,25]. In humans, cortical oligodendrogenesis begins at around 10 GW, but it progresses well into adulthood [26]. Olig2-positive stem cells from early fetal development exist in the germinal matrix of the brain and transfer from the original regions in the brain to the axon-dense zones of the neocortex, spinal cord, diencephalon, and brainstem.

**Gliogenesis:** Gliogenesis is often generated during the last trimester of gestation in humans [27]. As mentioned above, the timing of an insult in pregnancy is critical to compare and estimate the neurodevelopmental response of offspring. While early insult in pregnancy is related to structural brain abnormalities such as neural tube defects, late-gestation insults may disturb the migration progression of postmitotic neurons and cause deviant cortical development [28]. Later insults have been demonstrated to be associated with more with behavioral, cognitive, and psychiatric disorders, such as autism, obsessive compulsive disorders, and schizophrenia [29,30]. The regulation of oligodendrocyte differentiation and myelination in the fetal brain involves negative and positive regulators [23]. There are three negative regulatory pathways for oligodendrocyte differentiation, including the BMP signaling, Notch signaling, and Wnt/β-catenin pathways. These and Wnt pathways are involved in oligodendrocyte maturation. Some studies showed that white matter disorders are associated with dysregulation of the BMP and Wnt/β-catenin signaling pathways [31,32]. The maturation of oligodendrocytes relies on ATP through oxidative phosphorylation in mitochondria [33]. Mitochondria support oligodendrocyte differentiation and survival [34]. It is commonly found that after hypoxia-ischemia, mitochondrial dysfunction occurs in the developing brain [35]. Studies have demonstrated that microglia have an effect on the maturation of oligodendrocytes during normal brain development. Activated microglia discharge high levels of pro-inflammatory cytokines, including interleukin (IL)-1β, IL-2, and IL-17; tumor necrosis factor-alpha (TNFα); and excitotoxic factors such as glutamate, nitric oxide, and hyaluronan, or endothelial growth factor, which impair immature oligodendrocyte differentiation and proliferation and assist in decreasing the number of oligodendrocytes [36-39]. Mitochondria are very important in the developing brain and throughout life in energy phosphate tasks such as regulating the cellular redox state, maintaining organelle function, cellular proliferation, mediating the DNA or protein responsible for transcription, excitotoxic injury, translation and assembly of the enzyme complexes of the respiratory chain, and apoptosis. These mitochondrial functions in cellular proliferation rely on mitochondrial dynamics. Mitochondria are extremely plastic and mobile, altering their shape through fission and fusion to reach sites of high energy demand in cells [40]. Mitochondrial impairment results in deregulation of calcium homeostasis, bioenergetic failure, mitochondrial permeabilization with release of proapoptotic proteins, and production of reactive oxygen species (ROS), leading to cell death [41].

**Myelination:** The myelination of mature oligodendrocytes continues especially in late gestation and is susceptible to excitotoxic and damage associated with premature exposure to the extrauterine environment without neuroprotection. Neonatal or fetal brain injury may occur as a result of thrombosis, infection,

hemorrhage, trauma, or hypoxia and can lead to lifelong cognitive, sensory, or motor dysfunction. Defining the type and range of brain damage is not as simple as it would seem. Magnetic resonance imaging (which requires dangerous ionizing radiation) and transcranial ultrasound (which has limited sensitivity) can only be used to examine the damaged fetal brain, not to predict function.

**Placenta and Fetal Brain Development:** The placenta is the maternal-fetal interface that has an essential role in the transfer of nutrients and oxygen to the fetus and provides and secretes growth-regulating factors to ensure the neurodevelopment of fetal brain. In addition, the placenta functions as an immuno-defender to protect the fetus from maternal infection and inflammation. The placenta, which controls the intrauterine environment, is of fetomaternal organ. It is well-known to secrete neurotransmitters, which are associated with abnormal neurodevelopment and normal fetal brain development. The maternal component of the placenta is the decidua. The fetal placental tissues include the umbilical cord, chorionic villi, amniotic membrane, and chorionic membrane [42,43]. Placental metabolism, placental hormone production, and substrate transport are all essential for fetal development. Normal development of the placenta includes two concurrent and complex processes: the cytotrophoblast (CT) cells invade the endothelium of the maternal spiral artery and then the fetal vascular tree develops. Endothelial cell invasion initially leads to the formation of a trophoblast "plug," resulting in a hypoxic milieu environment within the intervillous space (oxygen partial pressure [$PaO_2$] < 20 mm Hg) [44]. After 10 GW, the CT plug dissipates, which results in increased placental blood flow and $PaO_2$ [45,46]. Several mechanisms affect placental function. The sustained high-pressure flow through the intervillous space (2–3 m/s, while normal dilated vessels are 10 cm /s) leads to increased shear stress and damage to the trophoblast cells of the chorionic villus, thereby damaging the capacity of the villi for nutrient and gas exchange [46,47]. Unsuccessful spiral arterial conversion makes these vessels prone to adrenergic stimulation and vasoconstriction, which leads to intervillous $PaO_2$ fluctuations and placental hypoxic perfusion injury [48]. Dysregulation of angiogenesis and anti-angiogenic factors in the placental interface results in abnormal development of the fetal vascular tree in the placenta [49], subsequently impairing the function of the placenta, and has been relevant in the development of preeclampsia, gestational diabetes-related pregnancy, fetal growth restriction (FGR), placenta early exfoliation, intrapartum fetal compromise (IFC), and preterm birth [50-52].

Risk factors of arterial disruption involve trauma, preeclamptic arteriopathy, uterine rupture, abruption placenta, and vasoactive drugs, such as nicotine or cocaine. Marginal retroplacental hemorrhages mostly occur at the margin of venous drainage of the placenta [53,54]. Many other events, such as malnutrition, genetic abnormalities, and infection can also disturb placental function and alter the fetal brain's environment. The failure function of placenta can directly injure the developing brain or raise its vulnerability to injury, result in lasting neurological disabilities [55,56].

## Fetal Brain Injury

**Intrauterine Fetal Brain Injury:** Chorioamnionitis, hypoxia, fetal inflammatory response, and preterm birth can contribute to brain injury and progression of the subsequent neurological deficits [57]. Hypoxia and inflammation mediate neuropathology, acting to induce neuroinflammation and breakdown of the blood brain barrier (BBB), resulting in oligodendrocyte cell damage [58]. The activated immune cells such as mast cells, microglia, and neutrophils release the key cytokines IL-1α, IL-1β, IL-6, and IL-18, which sequentially stimulate the discharge of TNF, ROS, and excitatory amino acid agonists, including glutamate, which work together to initiate neural cell apoptosis [59,60]. The substances above can also directly influence the differentiation of neurons and OPCs by inducing apoptosis and can cause mitochondrial failure [61,62]. Neighboring reactive astrocytes, by releasing TNF-α and IL-1β, cause proliferative inhibition of oligodendrocytes and downstream activation of apoptotic pathways [63].

**Impact of Intrauterine Infection:** Many microorganisms, which include certain viruses, bacteria, and protozoa, have been linked to intrauterine infection. These infections can result in clinical syndromes, including TORCH infections, referring to infections caused by toxoplasma, other microorganisms, rubella virus, cytomegalovirus (CMV), and herpes simplex viruses (HSV) [64]. Other common infections in women are caused by aerobes, such as group B streptococcus (GBS) (15%); and gram-negative rods, including Escherichia coli (8%), anaerobes, including Bacteroides sp. (30%) and Gardnerella vaginalis (25%) [65]. These microorganisms are associated with preterm birth [66]. Further studies demonstrated that a persistent intrauterine inflammatory exposure may also result in fetal brain injury [67]. The characterization of chorioamnionitis is an intra-amniotic infection in which bacteria invaded the amniotic cavity, resulting in acute inflammation of the fetal membranes and/or the placenta [65]. Chorioamnionitis, which results in spontaneous preterm birth and premature rupture of membranes (PROM), is defined as a feto-placental environment of acute inflammation [68]. Chorioamnionitis often leads to fetal inflammation and damage to the immature brain, raising the possibility of diffuse white matter injury and intraventricular hemorrhage [69]. Fetal inflammatory response syndrome (FIRS), resulting from systemic immune activation, is characterized as inflammation of multiple fetal organs in utero [70]. Infections can trigger inflammatory pathways, causing the discharge of diverse proinflammatory biomarkers, such as interleukins, cytokines, and other molecules. Proinflammatory cytokines such as IL-1β, IL-6, and tumor necrosis factor-alpha

(TNF-α) from microglia and astrocytes may directly insult neurons and oligodendrocytes. The injection of IL-1β in neonatal rats leads to delayed myelination and neuronal death [71]. TNF-α induces apoptosis in developing oligodendrocytes and cell death in mature oligodendrocytes [72].

**Toxoplasma:** Primary infection of congenital toxoplasmosis in pregnant women is uncommon, but it remains as a latent, chronic, cryptic brain infection throughout the life of the host, often with severe consequences [73]. Some studies have demonstrated that infection of the toxoplasma may alter cognitive functions and human behavior and may cause headaches, the onset of schizophrenia, and cryptogenic epilepsy [74]. Chronic, adult-acquired Toxoplasma gondii infection in outbred mice can cause behavioral and neurologic abnormalities secondary to the loss of brain parenchyma and inflammation [74]. There is also improved expression of message for synaptic remodeling and markers of neuronal cell death and mediators of inflammation in brains of chronically infected mice, comparing to uninfected control mice [74]. Synaptic transmission underlies vastly complicated instruction by protein networks assembled at the presynaptic location of neurotransmitter discharge and the postsynaptic device for neurotransmitter reception. Haroon and colleagues have indentified that T. gondii––activated cytokines disturb synaptic signaling [75]. Chronic T. gondii infection brings dissimilar changes in synaptic protein composition, which downregulate a huge number of proteins occupied in synaptic plasticity and pose a danger for neuropsychiatric disorders [75].

**Rubella:** During the Rubella epidemic in the U.S, in 1964-1965, thousands of infants were infected and subsequently suffered lifelong problems. During this epidemic, 8–13% of cases were congenital rubella syndrome (CRS) occurring in early pregnancy. Rubella virus has a particular affinity for the central nervous system, resulting in mental retardation, encephalitis, cataracts, central auditory imperceptions, glaucoma, and cochlear atrophy [76]. Fetal damage associated with rubella is inclined to occur only when an infection occurs in the first 16 weeks of pregnancy. In general, the earlier the infection begins, the more severe the malformation that is observed [77]. The later sequelae of rubella in early pregnancy include diabetes and autism [78-81].

**Cytomegalovirus:** Human cytomegalovirus (HCMV) infection is the main cause of congenital viral infection and brain disease in developed countries. HCMV is also a major pathogen in congenital illness and can lead to permanent disabilities, including hearing loss, mental retardation, and vision loss. It was reported that 50% of children with congenital HCMV infection in Japan developed hearing loss 6 months after their diagnoses [82]. HCMV in fibroblasts acquires its covering by budding into exosome-like vesicles, which subsequently combine with the plasma membrane to discharge mature virions from the cell. Compared to the infected cells, the glycerophospholipid component of HCMV virions is strikingly different. The liposome of virions has been found to be similar to that of synaptic vesicles via comparing Monica the published results [83]. These similarities showed that HCMV in fibroblasts obtains its envelope by budding into vesicles, which can fuse at the plasma membrane to discharge mature versions of this cell. Synaptosomal-associated protein of 25 kDa (SNAP-25), a constituent of the SNARE complex, which mediates exocytosis of synaptic vesicles in exocrine cells and neurons, has been found to be involved in the exit of HSV-1 from neurons [83,84].

**Herpes Simplex Viruses:** The rate of neonatal herpes simplex virus (HSV) infection ranges from 1 in 2,500 to 1 in 20,000 live births. Manifestations of congenital HSV include hydranencephaly, chorioretinitis, skin lesions, scars, and microcephaly. The condition of neonates who have HSV infection can deteriorate rapidly due to encephalitis, disseminated intravascular coagulopathy, shock, or respiratory distress. Infants who survive neonatal HSV encephalitis have high rates of neurological sequelae, including mental retardation, visual or motor deficits, Alzheimer's disease (AD), and seizure disorders [85]. HSV-1–infected neurons also have shown considerably reduced expression of the presynaptic proteins synaptophysin and syanpsin-1 and depressed synaptic transmission. In mice, these effects rely on intraneuronal accumulation of Aβ and GSK-3 activation [86].

**Bacterial Infection:** Group B Streptococcus and E. Coli: GBS is the leading reason for congenital bacterial infection in developed nations. The incidence of transmission to newborns in GBS-positive women is about 21% [87]. No direct evidence has shown that GBS infection plays a function in cerebral palsy (CP), but nearly 50% of infants who survive GBS meningitis experience long-term neurodevelopmental sequelae [88]. In addition, mediation of extensive cortical neuronal injury through reactive oxygen intermediates was observed in GBS-infected neonatal rats [89]. The association of cellular response of the fetal brain with perinatal inflammatory or infectious damage reflects activation of astrocytes and microglia with oligodendrocyte dysfunction and neuronal loss. In developing countries, E. coli is one of the major pathogens leading to early-onset infections in preterm neonates. In human newborn infants, cerebral white matter injury has been observed by MRI following an episode of E. coli meningitis [90].

## Hypoxic-Ischemic Injury

Unpredictable and severe events that involve placental abruption, cord prolapse, uterine rupture, or eclampsia are strongly associated with a high risk of catastrophic fetal hypoxia [91]. Hypoxic-ischemic injury that leads to mental retardation, motor impairment (CP), hypoxic ischemic encephalopathy (HIE), and seizures is a considerable contributor to morbidity and

mortality in infants [92]. The fetal brain of prematurity before 32 GW is immature, and the white matter is especially susceptible [93]. The susceptibility of the immature CNS to hypoxia-ischemia is mainly dependent on regional status and the timing of decisive developmental processes, for example, proliferation, differentiation, migration, programmed cell death, and myelination, as well as on the instruction of metabolism and cerebral blood flow. The fetal brain is hypersensitive to hypoxic damage and oxidative stress because of its high oxygen consumption, lack of glucose stores, high lipid content [94,95], and considerably low concentrations and activity of antioxidant enzymes [96,97]. The upregulation of IL-1 and TNF-R1 can result from periods of hypoxia in the brain. Pro-inflammatory cytokines mediate the immune response to inflammation and infection and influence a wide range of physiological action that involves cell survival, fever, acute-phase response gene expression, glial activation, hypotension, T- and B-lymphocyte stimulation, and leukopenia [98-101]. Hypoxia, which damages OPCs by activating the enzymes caspase-3 and caspase-9, leading to cell death, is also related to calcium influx after inflammation-induced glutamate discharge from immune cells, which causes excitotoxicity and results in bax translocation to the mitochondria on OPCs and release of cytochrome-c [102]. The exact mechanisms underlying hypoxic cerebral damage are multifarious and are not totally mediated by the initial hypoxic injury, but instead are compounded by insults happening during the reperfusion stage [103] because of toxicity from ROS and activation of N-methyl-D-aspartate-type glutamate receptors [104]. In fact, the severity of the secondary injury happening during the reperfusion phase associates best with the severity of neurodevelopmental disability at 1 and 4 years of age [105]. There is a strong connection between hypoxia and hypotension with fetal injury, mainly fetal death and neuronal damage. During hypoxia, the blood flow of cerebral hemispheres is reduced, whereas perfusion to the thalamus, brainstem, and basal ganglia is increased [106]. Cerebral ischemia has a dramatic and rapid effect on synaptic function and structure [107].

## Seizures

Seizures are one of the most common neurological emergencies in newborns. A reduction in the normal environment of fetal neurosteroids is associated with undesirable outcomes, such as episodes of potentially destructive seizures, which can cause destructive and permanent conversion in neurodevelopment [108,109]. Premature birth is related to an increased rate of seizure disorders [110]. Neonatal seizures create a long-term increase in seizure susceptibility and change in inhibition/excitation balance of synaptic transmission in layer II/III neurons of the somatosensory cortex [111]. In summary, neonatal seizures have enduring effects on synaptic plasticity in the somatosensory cortex [112].

## Cerebral Palsy

CP is defined as a disorder of posture and movement that includes abnormalities in reflexes, tone, movement, and coordination, and delays or aberration in primitive reflexes and in motor milestone achievement that is enduring, and is caused by a lesion, nonprogressive interference, immature brain, or abnormality of the developing fetal and infant brain [113,114]. CP is also defined by type (dyskinetic, dystonic, or spastic), topography (limb involvement), and descriptors of the extent and pattern of involvement (quadriplegia, hemiplegia, diplegia, and monoplegia) [114]. Autopsy of the brain of a preterm child with CP showed white matter atrophy, dysmyelination, ventriculomegaly, and reactive gliosis [115].

## Autism Spectrum Disorders

Autism spectrum disorders (ASDs) are characterized by a complex and strong genetic component with broad familial inheritance patterns and have been found to be related to mutations in as many as 1,000 genes [116]. Environmental factors, including maternal diabetes, prenatal infections, prenatal and perinatal stress, zinc deficiency, and toxins, can also contribute to the risk of autism during early life [117,118]. Some evidence shows that the placenta plays a key role in ASD pathogenesis [119]. That the architecture of placenta from ASD patients consists of smaller branch angles than in population-based counterparts, fewer branch points, better extension to the surface boundary, and thicker and less tortuous arteries may indicate that both environmental and genetic factors have an impact on vascular branching morphogenesis in pregnant women [120,121]. A recent study of the placenta from patients with ASD demonstrated considerably higher incidences of fetal inflammation, maternal vascular mal-perfusion, and acute generalized inflammation, suggesting that these conditions are deleterious to fetal brain development [119]. Some forms of intellectual disabilities and syndromic autism are linked to mutations in genes that regulate protein synthesis and influence transmission, plasticity, and structure of synapses [12]. Failures to sustain RNA-binding protein levels and the accurate number of mRNA molecules are critical access points of synaptopathies [122].

## Schizophrenia

Schizophrenia is a greatly polygenic disorder, involving hundreds of genes. Genes implicated in synaptic plasticity and glutamatergic function figure prominently among genes associated with schizophrenia [123]. A deficit in glutamatergic synapses can provoke schizophrenia [124]. Both neurochemical alterations and structural changes may lead to defective neuronal transmission in schizophrenia [123]. The uterine environment may have a significant influence on later development of schizophrenia [125-127]. Influenza infection during early gestation that has

a strong correlation with schizophrenia in offspring can result in overexpression of tumor necrosis factor-α (TNF-α) and IL-6, probably through changing either epigenetic modification or gene expression [128]. Schizophrenia has been associated with exposure that may happen in early life and might be linked to pregnancy (hyperglycemic conditions, hemorrhage, or preeclampsia), labor (uterine rupture, birth asphyxia), or fetal conditions (genetic anomalies or intrauterine growth restriction) [56,129].

## Stress Or Mood Disorders

Many maternal stressors such as trauma, depression, and malnutrition can have an effect on the placenta and change maternal glucocorticoid levels, which play a major role in programmed cell death and neuronal maturation and to which the developing brain is extremely susceptible [130]. 11βHSD2 is expressed at very high levels in the placenta, which protects the fetus from the normal increase in maternal cortisol occurring during gestation. Maternal mood disorders have a relationship with disruption of the placental barrier, in part through suppressing 11βHSD2 expression, resulting in abnormal neurodevelopment in the offspring [131]. Human placental lactogen expression was considerably decreased in placentas from women diagnosed with depression and who had high depression scores [131].

## Premature Birth and Fetal Brain Development

**Preterm And Fetal Brain Development:** Steroid precursors generate from the placenta that maintain the neuroprotective and trophic functions of neuroactive steroids in the fetal brain [132]. In preterm birth, the loss of neuroactive steroid precursors leads to disruption of the normal track of fetal brain development and delays the progress of myelination [133]. The GABAA receptors that play a key role in late gestation are vital to interaction with the placenta-derived neuroactive steroids [134,135]. Research studies showed that tobacco smoke during pregnancy may result in chronic hypoxia and be associated with increased placenta resistance and carboxyhemoglobin and decreased uterine blood flow [136]. Some scientists have also found the connection between elevated levels of serotonin and altered oligodendrocyte development and myelination [137]. Recent studies showed that extracellular vehicles (EVs) including proteins, nucleic acids, and lipids are a mechanism for communication between fetus and mother [138]. How EVs influence the maternal response to pregnancy and fetal development is currently an area of vigorous exploration [139,140].

**Premature Birth and Neurodevelopmental Disorders:** Preterm birth can result from maternal/fetal inflammatory responses and intrauterine infection and result in fetal brain damage with a negative effect on the function and structure of the entire brain [141]. Serial MRI examinations have shown that the gray and white matter volume of premature infants is reduced compared to full-term control groups [142,143]. Loss of neurons as a result of apoptosis may partly explain the reduction in gray matter volume of the basal ganglia and cortex in both humans and mice. This loss of neurons is the most common form of cerebral abnormalities in premature infants, which include hippocampus and gray matter abnormalities and diffuse white matter injury [144,145]. However, focal necrotic lesions of cystic ventricular leukocyte softening are seldom seen in preterm infants [146]. Prematurity can also result in CP and visual and hearing impairments [147]. The common forms of white matter injuries in preterm birth occur as diffuse white matter injury, periventriclular leukomalacia (PVL), and germinal matrix hemorrhage [148]. The less frequent forms of injury are cerebral sinus vein thrombosis, primary intraparenchymal hemorrhage, hyperbilirubinemia-induced kernicterus, and infectious meningitis/encephalitis [149]. PVL lesions have been demonstrated that have a relationship with the loss of pre-oligodendrocytes and OPCs [150].

**Prospective:** Extracellular vesicles provide a promising strategy for early prediction of intrauterine brain development EVs, including microvesicles and exosomes, participate in signal transmission between neurons, play a fundamental role in activity of the nervous system, and facilitate communication of the CNS with all body systems [151]. EVs may be produced in almost all cells of the body, function to transport biologically active molecules to target cells, and provide intercellular communications [152,153]. EVs are secreted by numerous cell types in the brain, including microglia, astrocytes, oligodendrocytes, and neurons [154-158]. Neuronal communications with glial cells are mediated via EVs by the transport of mRNAs, miRNAs, and proteins, where vesicles' discharge into the extracellular space is taken up through recipient cells [154,159-161]. Synaptic pruning was performed through neuronal EVs via neuron-specific signal transduction between microglia and neurons; it was not improved via non-neuronal EVs [162]. Some evidence indicates that synaptic dysfunction is an essential role in the pathophysiology of neurodegenerative disorders. Exosomal miRNAs have also been demonstrated to play a latently neuroprotective function in subsequent ischemic brain injury. Exosomes from multipotent mesenchymal stem cells (MSCs) mediate miR-133b transfer to neurons and astrocytes, which modify gene expression in charge of functional recovery and neurite remodeling after stroke [163]. EVs provide an apparatus of communication not only between glial cells and nerves, but also permitting the interconnection of the CNS with all body systems [151,164]. The pathology of neurodegenerative disorders is a result of intercellular spreading and aggregation of proteins in the brain [165]. In recent years, the decrease of EV production through an nSMase-ceramide pathway resulted in the alleviation of AD in a mouse model of this disease [166]. α-synuclein of the Parkinson's disease gene encapsulated in neuron-derived EVs is present not

only in the membranes, but also in the extracellular space of EVs and are secreted from neurons [167,168].

## Conclusion

This review has addressed the dysregulated synaptic function and plasticity, receptors, molecular signaling cascades, and spine architecture that underlie cognitive deficits and the behaviors associated with other forms of syndromic ASDs. Synapse dysfunction is linked to the pathophysiology of diverse neurodevelopmental disorders such as intellectual disability, schizophrenia, and autism [12,169]. EVs are membrane-bound nanoparticles discharged into the extracellular space through most types of cells. Many CNS cells can release EVs, including exosomes, which may play a key role in the spread of pathogenic agents in various diseases. EVs have been studied extensively in pathologies including neurodegenerative disorders, such as prion protein in prion diseases, α-synuclein protein in Parkinson's disease, tau and amyloid-β peptide in AD, mutant huntingtin in Huntington's disease, and superoxide dismutase-1 and transactive response DNA-binding protein 43 kDa (TDP-43) in amyotrophic lateral sclerosis [166,170-175]. MSCs show homing abilities, which make it possible for them to travel to sites of inflammation or brain injury and to be used in treatments of various neurological disorders [176]. It may be difficult for clinicians to detect subtle injuries in the fetal brain. With the recognition of novel vesicle biomarkers, we hopefully will develop the ability to use EVs as a tool in clinical practice for treatment of nervous system diseases in the future.

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## Declaration

The authors declare that there is no conflict of interest regarding the publication of this paper.

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