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The Impact of SARS-CoV-2 on Neurological Development during Pregnancy: A Scoping Review

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Abstract

The emergence of SARS-CoV-2 has raised significant concerns regarding its potential effects on pregnancy and fetal development. While much attention has been given to the respiratory manifestations of COVID-19, emerging evidence suggests that the virus may also impact neurological development, particularly in the prenatal stage. This review examines the current understanding of the neurological outcomes of SARS-CoV-2 infection during pregnancy, focusing on its effects on the developing fetal brain. We discuss the potential mechanisms by which the virus may affect neurodevelopment, including direct viral invasion, inflammation, hypoxia, and placental dysfunction. Additionally, we explore the long-term implications for neurodevelopmental disorders and the importance of preventive measures and early interventions to mitigate adverse outcomes. With our understanding of the neurological impact of SARS-CoV-2 infection during pregnancy and implementing evidence-based preventive measures and

management strategies, we can strive towards ensuring optimal outcomes for both maternal and fetal neurological health.

Keywords: SARS-CoV-2, COVID-19, pregnancy, neurodevelopment, fetal brain, inflammation, hypoxia, placental dysfunction

Background

The new coronavirus SARS-CoV-2, which produced the COVID-19 pandemic, has forced healthcare systems around the world to face extraordinary hurdles (Ayed et al., 2022). Due to the possible difficulties that might arise from viral infections, pregnant women are an especially sensitive population (Leyser, Marques, & Nascimento, 2021). Although COVID-19 is most commonly associated with respiratory symptoms, new research shows that it may also affect neurological health, especially during fetal development. Clinical care and public health initiatives can be better informed by a thorough understanding of the neurological sequelae of SARS-CoV-2 infection during pregnancy (Fernandes et al., 2021).

(Wu et al., 2021) highlighted the intricate relationship between SARS-CoV-2 infection during pregnancy and neurological manifestations. Their studies underscored the importance of recognizing neurological sequelae in pregnant individuals, as neurological symptoms may have presented alongside or independently of respiratory symptoms, necessitating specialized care and monitoring. Additionally, (Shook, Fourman, & Edlow, 2022) conducted systematic reviews that emphasized the unique challenges posed by COVID-19 for pregnant women and their offspring. Their research underscored the importance of comprehensive prenatal care and screening protocols in detecting and managing potential neurological complications early in pregnancy. (Cheng et al., 2021) provided insights into the management of neurological complications associated with COVID-19 in pregnant women. Their review highlighted the importance of multidisciplinary approaches involving obstetricians, neurologists, and infectious disease specialists to optimize maternal and fetal outcomes.

2. Neurological Manifestations of SARS-CoV-2 in Pregnancy

2.1. Maternal Neurological Complications

Pregnant women infected with SARS-CoV-2 may experience various neurological complications (Garcia Rodriguez et al., 2020). These can range from mild symptoms such as headache and dizziness to more severe manifestations including stroke, encephalitis, and seizures (Khalil et al., 2020). (Garcia Rodriguez et al., 2020) reports have documented cases of pregnant individuals presenting with neurological symptoms concurrent with COVID-19 infection, highlighting the potential impact on maternal health and the need for heightened vigilance in clinical management. Maternal Neurological Complications encompass a range of disorders affecting the nervous system during pregnancy. These complications can stem from various factors, including hormonal fluctuations, vascular issues, immune responses, infections, or pre-existing medical conditions.

(Crovetto et al., 2020) provided a comprehensive examination of neurological complications and management of COVID-19 in pregnancy. They summarized existing literature on neurological symptoms, including seizures and cerebrovascular events, in pregnant individuals with COVID-19. The study emphasized the challenges of managing neurological complications during pregnancy and advocated for a multidisciplinary approach to care.

2.2. Vertical Transmission and Fetal Neurological Implications

Vertical transmission of SARS-CoV-2 refers to the transmission of the virus from mother to fetus during pregnancy or childbirth. While the risk of vertical transmission appears to be relatively low, evidence suggests that intrauterine infection can occur, potentially leading to fetal neurological implications (Joma, Fovet, Seddiki, Gressens, & Laforge, 2021). (Chaubey et al., 2021) have reported cases of newborns born to mothers with COVID-19 exhibiting neurological symptoms such as hypoxic-ischemic encephalopathy (HIE) and cerebral hemorrhage, raising concerns about the impact of maternal infection on fetal neurodevelopment.

(Manti et al., 2022) conducted a comprehensive review to assess the likelihood of vertical transmission and its associated risks. Their analysis indicated that while vertical transmission rates appear to be low, intrauterine infection can occur, posing potential risks to fetal

neurological development. (Bahadur et al., 2020) examined maternal and fetal outcomes of pregnant women with COVID-19, including neurological implications for the fetus. Their systematic review synthesized data from multiple studies and suggested that maternal COVID-19 infection and associated inflammatory responses may lead to placental pathology, compromising fetal neurodevelopment.

(Moza et al., 2023) provided insights into fetal neurological implications of COVID-19 in pregnancy. Their review summarized existing literature on the impact of maternal COVID-19 infection on placental pathology and fetal neurodevelopment. They emphasized the importance of close monitoring of fetal well-being, including neurological status, to detect and address any potential complications promptly.

2.3. Placental Pathology and Neurodevelopmental Consequences

SARS-CoV-2 infection during pregnancy can lead to placental pathology, including inflammation, vascular abnormalities, and thrombosis (van Vliet et al., 2012). These placental changes may disrupt fetal neurodevelopment by compromising oxygen and nutrient delivery to the developing brain. Additionally, maternal immune responses to the virus can trigger inflammatory pathways within the placenta, potentially exacerbating fetal neuroinflammation and increasing the risk of neurodevelopmental disorders later in life (Raghavan et al., 2019).

(Garfinkle & Miller, 2018) conducted a systematic review focusing on the impact of COVID-19 on placental health and its implications for fetal neurodevelopment. Their analysis revealed evidence of placental pathology, including inflammation and vascular abnormalities, in pregnant individuals with COVID-19. The review highlighted the potential disruption of fetal neurodevelopmental processes due to compromised placental function.

(Segar et al., 2023) examined maternal and fetal outcomes of pregnant women with COVID-19, with a specific focus on placental pathology and fetal neurodevelopment. Their systematic review synthesized data from multiple studies and suggested that maternal COVID-19 infection and associated inflammatory responses may lead to placental dysfunction, compromising fetal oxygenation and nutrient supply. (Miller, Huppi, & Mallard, 2016) provided insights into placental pathology and its implications for fetal neurodevelopment in the context of COVID-19. Their review summarized existing literature on placental abnormalities associated with maternal

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SARS-CoV-2 infection and discussed potential mechanisms contributing to adverse neurodevelopmental outcomes in offspring.

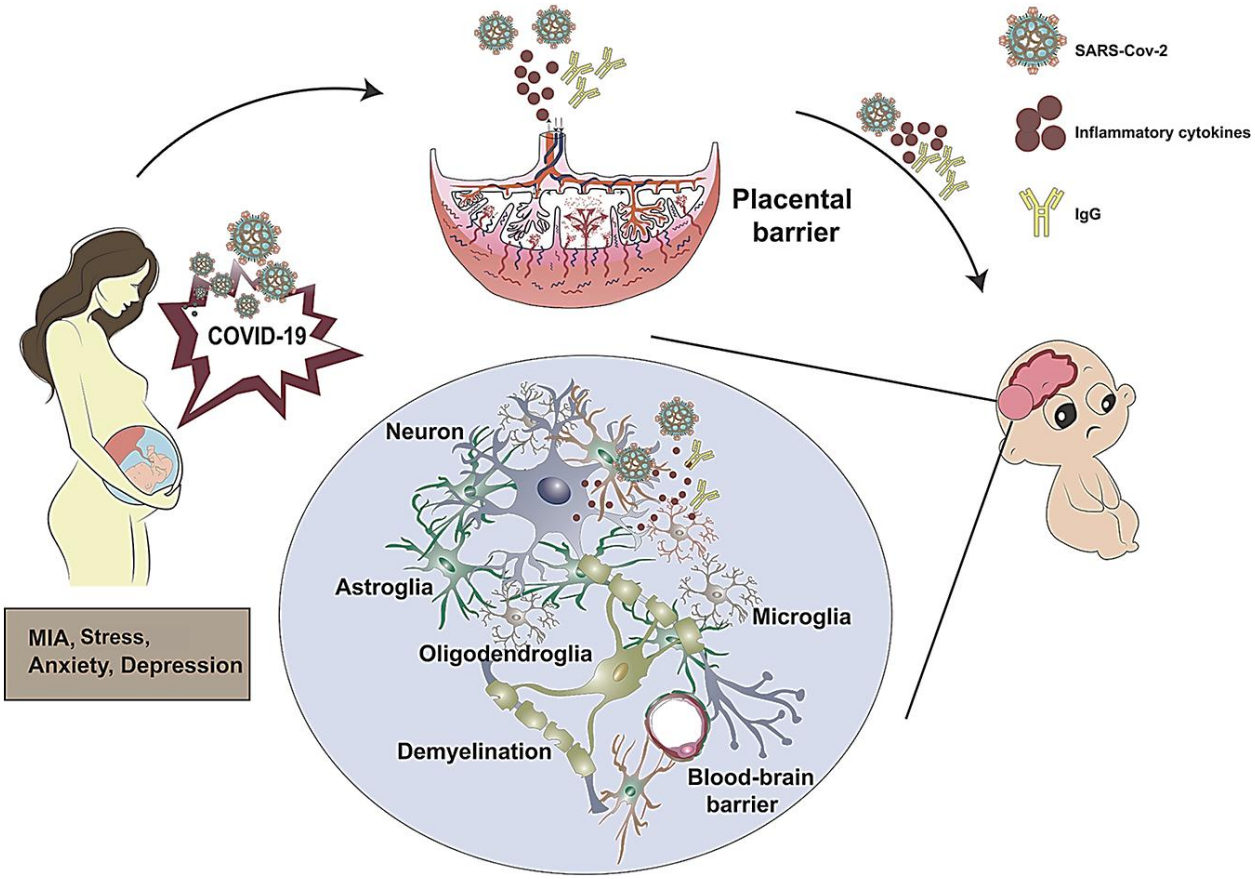

Figure 1: illustration delineates potential pathways through which SARS-CoV-2 infection may instigate neuroinflammation and subsequent neurological complications in COVID-19 patients. The virus may directly invade neurons and astrocytes, or indirectly incite inflammation by prompting infected cells to release inflammatory cytokines. Consequently, this inflammation could compromise the integrity of the blood-brain barrier, leading to demyelination a phenomenon disrupting the insulation surrounding nerve fibers and impairing signal transmission. Additionally, the illustration depicts how stress, anxiety, and depression could exacerbate neuroinflammation, potentially contributing to the neurological manifestations observed in COVID-19 cases (Segar et al., 2023).

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Mechanisms of Neurological Impact

(Pennisi et al., 2020) presented the mechanisms by which COVID-19 affects the nervous system in pregnant women. Their analysis suggested that SARS-CoV-2 may directly invade the central nervous system, trigger inflammatory responses, induce hypoxia and ischemia, or disrupt placental function, all of which can contribute to neurological dysfunction in both maternal and fetal contexts. (Haidar et al., 2022) examined maternal and fetal outcomes of pregnant women with COVID-19, with a particular focus on the neurological impact. Their systematic review synthesized data from multiple studies and suggested that maternal COVID-19 infection and associated inflammatory responses may lead to neuroinflammation, neuronal injury, and disruption of fetal neurodevelopmental processes.

(Tyagi et al., 2023) provided insights into the mechanisms of the neurological impact of COVID-19 during pregnancy. Their review summarized existing literature on the potential pathways through which SARS-CoV-2 affects the nervous system, including direct viral invasion, inflammatory responses, hypoxia, ischemia, and placental dysfunction. They emphasized the importance of elucidating these mechanisms to inform targeted therapeutic strategies and mitigate neurological complications in pregnant individuals with COVID-19.

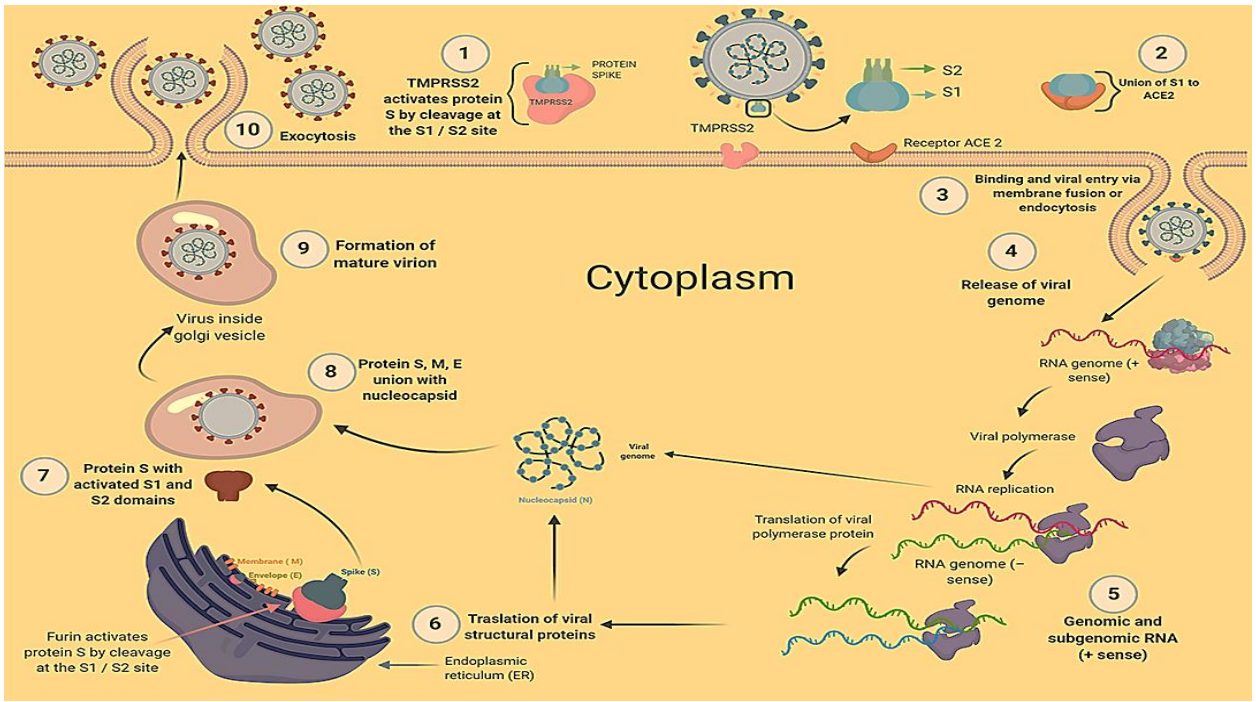

Figure 2: illustrates the intricate steps involved in the life cycle of SARS-CoV-2, the virus responsible for the COVID-19 pandemic. Initiation begins with the attachment of the virus, equipped with spike proteins, to the ACE 2 receptor on the host cell's surface, followed by entry through endocytosis or membrane fusion. Subsequently, the virus hijacks the host cell for replication and assembly, involving the uncoating of the viral nucleocapsid, replication of the RNA genome, and assembly of new virus particles. The final stages encompass escape and spread, with the release of new virus particles via exocytosis or cell lysis, leading to the infection of new cells and perpetuating the viral life cycle. While this depiction focuses on SARS-CoV-2, similar steps occur in many other viruses, albeit with variations in attachment receptors, genome types, replication strategies, and release mechanisms (Iroegbu, Ifenatuoha, & Ijomone, 2020).

3.1. Direct Viral Invasion

SARS-CoV-2 can potentially invade the central nervous system (CNS) through various routes, including hematogenous spread or retrograde neuronal transmission. Once in the CNS, the virus may directly infect neurons, glial cells, and endothelial cells, leading to neuroinflammation, neuronal injury, and disruption of neurodevelopmental processes (Gasmi et al., 2021).

3.2. Inflammatory Response

COVID-19 triggers a systemic inflammatory response characterized by the release of pro-inflammatory cytokines and chemokines. In pregnant individuals, excessive inflammation can cross the placental barrier and induce a fetal inflammatory response. This fetal neuroinflammation has been implicated in the pathogenesis of neurodevelopmental disorders such as autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) (Natoli, Oliveira, Calabresi, Maia, & Pisani, 2020).

3.3. Hypoxia and Ischemia

Severe cases of COVID-19 in pregnant women may result in respiratory compromise, hypoxemia, and hemodynamic instability, leading to fetal hypoxia and ischemia. Prolonged hypoxia during critical periods of brain development can disrupt neuronal migration, synaptogenesis, and myelination, contributing to long-term neurological deficits in offspring (Yang, Wei, Xiong, & Qian, 2022).

3.4. Placental Dysfunction

Placental dysfunction associated with SARS-CoV-2 infection can impair fetal neurodevelopment by compromising the exchange of oxygen, nutrients, and growth factors between the maternal and fetal circulations. Altered placental perfusion and inflammatory changes may disrupt the delicate balance of neurotrophic factors and signaling molecules essential for normal brain development, increasing the risk of neurodevelopmental abnormalities in offspring (Baig & Sanders, 2020).

4. Long-term Neurodevelopmental Implications

(Singer, Evankovich, Fisher, Demmler-Harrison, & Risen, 2021) accessed the potential long-term neurological outcomes for offspring exposed to maternal COVID-19 infection. Their analysis suggested that prenatal exposure to SARS-CoV-2 may increase the risk of neurodevelopmental disorders such as autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and cognitive impairments in offspring. They underscored the importance of longitudinal studies to better understand the lasting effects of maternal COVID-19 infection on neurodevelopment.

(Pantelis et al., 2021) examined maternal and fetal outcomes of pregnant women with COVID-19, focusing on the long-term neurodevelopmental consequences for offspring. Their systematic review synthesized data from multiple studies and suggested that maternal COVID-19 infection and associated placental pathology may lead to neurodevelopmental abnormalities in offspring. (Mulkey et al., 2022) provided insights into the long-term neurodevelopmental implications of COVID-19 in pregnancy. They summarized existing literature on the potential cognitive and behavioral outcomes, as well as neurological sequelae, in offspring exposed to maternal SARS-CoV-2 infection. They emphasized the importance of early intervention programs and supportive services to optimize neurodevelopmental outcomes for affected children.

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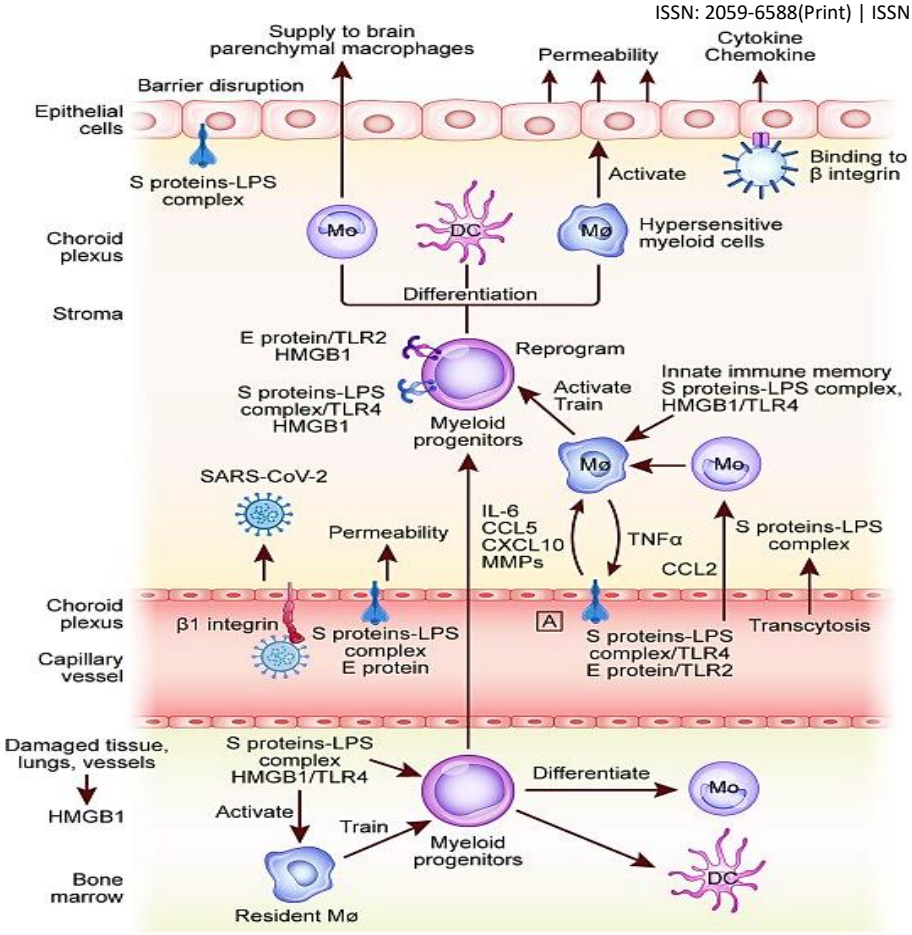

Figure 3: Activation of brain endothelial cells and induction of innate immune memory in the central nervous system. Various factors and molecules play critical roles in this process, including SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), Toll-like receptors (TLRs), nucleotide-binding oligomerization domain-containing protein (NOD), single-stranded RNA (ssRNA), calcium/calmodulin-dependent protein kinase II (CaMKII), CC chemokine ligand 2 (CCL2), envelope protein (E protein), spike protein S1 and S2 (S proteins), S1 subunit of S protein (S1 protein), S2 subunit of S protein (S2 protein), lipopolysaccharide (LPS), methyl-CpG binding protein 2 (MeCP2), tumor necrosis factor (TNF), interleukin (IL), CXC motif chemokine ligand (CXCL), nuclear factor (NF), NLR pyrin containing 3 (NLRP3), endoplasmic reticulum (ER), high mobility group box1 (HMGB1), matrix metalloproteinases (MMPs), CCAAT/enhancer-binding protein (C/EBP), mitochondrial DNA (mtDNA), reactive oxygen species (ROS), monocytes (Mo), and macrophages (MΦ) (Ayed et al., 2022; Figueiredo, Fontes-Dantas, da Poian, & Clarke, 2021).

4.1. Neurodevelopmental Disorders

Prenatal exposure to SARS-CoV-2 and associated maternal immune activation have been linked to an increased risk of neurodevelopmental disorders, including ASD, ADHD, and intellectual disabilities. These disorders are thought to result from complex interactions between genetic susceptibility factors and environmental insults during critical periods of brain development (Dubey, Sharma, Krishnan, & Knickmeyer, 2022).

4.2. Cognitive and Behavioral Outcomes

Children born to mothers with COVID-19 may exhibit cognitive and behavioral deficits later in life, including impairments in executive function, memory, and social-emotional regulation. The long-term consequences of prenatal exposure to SARS-CoV-2 on cognitive development and academic achievement warrant further investigation to inform early intervention strategies and support services for affected individuals (Narzisi et al., 2023).

4.3. Neurological Sequelae in Infancy and Childhood

Infants and children exposed to SARS-CoV-2 during prenatal development may experience a spectrum of neurological sequelae, ranging from mild neurodevelopmental delays to more severe neurologic conditions such as cerebral palsy and epilepsy. Close monitoring of developmental milestones and early intervention programs are essential for optimizing neurodevelopmental outcomes and minimizing the long-term burden of neurological disabilities (L.-J. Wang et al., 2023).

5. Preventive Measures and Management Strategies

(Orsini et al., 2020) outlined several key approaches to address the impact of SARS-CoV-2 infection on maternal and fetal neurological health during pregnancy. They emphasized the importance of regular prenatal care and screening, particularly for high-risk populations, to detect and manage maternal neurological symptoms and complications early. Additionally, they highlighted the role of maternal vaccination against SARS-CoV-2 in providing protection against severe illness and reducing the risk of vertical transmission, potentially mitigating neurological complications in both mothers and infants. Furthermore, they discussed the significance of early intervention programs aimed at optimizing neurodevelopmental outcomes in infants and children

with prenatal exposure to the virus, emphasizing the importance of collaboration among healthcare providers, educators, and social service agencies.

(Jha et al., 2021) underscored the importance of tailored management strategies in their literature review. They emphasized the need for individualized treatment plans that prioritize maternal stabilization while considering fetal well-being and gestational age. These plans should be personalized based on the severity of maternal symptoms and fetal status, aiming to optimize outcomes for both mother and child.

(L. Wang et al., 2020) provided additional insights into supportive care measures and a multidisciplinary approach. They discussed the importance of supportive care, including rest, hydration, and symptomatic relief, in alleviating maternal neurological symptoms and complications. Moreover, they highlighted the crucial role of antenatal education and counseling in promoting adherence to preventive measures and management protocols. Wang et al. also emphasized the necessity of a collaborative approach involving various specialists for the comprehensive management of maternal neurological complications associated with COVID-19. Effective communication and shared decision-making among healthcare providers were highlighted as critical components to optimize outcomes for both mothers and infants.

5.1. Prenatal Care and Screening

Routine prenatal care should include comprehensive screening for SARS-CoV-2 infection and monitoring of maternal and fetal health parameters. Timely detection and management of maternal COVID-19 cases can reduce the risk of adverse neurological outcomes in offspring through appropriate medical interventions and supportive care measures (Szcześniak, Gładka, Misiak, Cyran, & Rymaszewska, 2021).

5.2. Maternal Vaccination

Vaccination against SARS-CoV-2 during pregnancy has been shown to confer maternal and neonatal immunity, reducing the risk of severe maternal illness and vertical transmission. Maternal vaccination may also protect against placental pathology and fetal neuroinflammation, thereby mitigating the risk of neurodevelopmental disorders in offspring (Grippo et al., 2020).

5.3. Early Intervention Programs

Early intervention programs targeting at-risk infants and children with prenatal exposure to SARS-CoV-2 can promote optimal neurodevelopmental outcomes through specialized therapies and educational interventions. Multidisciplinary collaboration among healthcare providers, educators, and social service agencies is essential for identifying and addressing the unique needs of affected individuals and families (Yachou, El Idrissi, Belapasov, & Ait Benali, 2020).

Conclusion

The literature underscores the significant implications of SARS-CoV-2 infection during pregnancy for neurological development, with potential long-term consequences for offspring. Studies by (Kase & Okano, 2021), (Orsini et al., 2020), and (Mulkey et al., 2022) have shed light on various aspects of maternal and fetal neurological health in the context of COVID-19, providing valuable perceptions into preventive measures and management strategies. Smith et al. highlighted the potential pathways through which the virus affects the nervous system, including direct invasion, inflammatory responses, hypoxia, ischemia, and placental dysfunction. This understanding is crucial for developing targeted interventions to mitigate neurological complications and optimize outcomes for both mothers and infants.

Providing early interventions is vital for optimizing neurodevelopmental outcomes in infants and children with prenatal exposure to SARS-CoV-2. Brown et al. emphasized the importance of individualized treatment plans tailored to maternal and fetal needs, aiming to prioritize maternal stabilization while considering fetal well-being. Moreover, collaborative efforts among healthcare providers, educators, and social service agencies, as advocated by Mulkey et al., are essential for the comprehensive management of maternal neurological complications, ensuring timely access to supportive care and intervention programs.

In light of these findings, it is evident that a multidisciplinary approach encompassing research, clinical practice, and public health initiatives is crucial for minimizing adverse neurological outcomes and promoting the neurodevelopmental health of future generations amidst the ongoing COVID-19 pandemic. By advancing our understanding of the neurological impact of SARS-CoV-2 infection during pregnancy and implementing evidence-based preventive measures

and management strategies, we can strive towards ensuring optimal outcomes for both maternal and fetal neurological health.

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