Review

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Oxidative Stress and Potential Fetal Programming of Neuronal Dysfunction in Newborns Following Maternal COVID-19

Miljana Z Jovandaric[1,*], Srboljub Milicevic[2,3], Bojana Petrovic[3]

[1]Department of Neonatology, Clinic for Gynecology and Obstetrics, University Clinical Center of Serbia, 11000 Belgrade, Serbia
[2]Faculty of Medicine, University of Belgrade, 11000 Belgrade, Serbia
[3]Clinic for Gynecology and Obstetrics, University Clinical Center of Serbia, 11000 Belgrade, Serbia
*Correspondence: rrebecca080@gmail.com (Miljana Z Jovandaric)
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Maternal coronavirus disease 2019 (COVID-19) has been associated with systemic inflammation, endothelial dysfunction, placental injury, and increased production of reactive oxygen species (ROS), all of which may influence fetal development. Oxidative stress has emerged as a potential mechanistic link between maternal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and adverse maternal, placental, fetal, and neonatal outcomes. This narrative review summarizes current evidence regarding the role of oxidative stress in pregnancies complicated by COVID-19, with particular emphasis on placental dysfunction, fetal programming of neuronal injury, neonatal vulnerability, and molecular mechanisms that may contribute to long-term neurodevelopmental consequences. SARS-CoV-2 infection promotes oxidative imbalance through inflammatory activation, mitochondrial dysfunction, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase stimulation, hypoxia-related pathways, and dysregulation of the renin–angiotensin system. These processes may contribute to endothelial injury, placental vascular malperfusion, impaired maternal–fetal exchange, fetal hypoxia, and activation of pathways involved in fetal programming. Maternal immune activation and elevated proinflammatory cytokines may further influence fetal brain development through neuroinflammation, microglial activation, oxidative damage, mitochondrial dysfunction, and altered neuronal signaling. Emerging evidence also suggests that prenatal exposure to maternal SARS-CoV-2 infection may be associated with alterations in gene expression, immune signaling pathways, DNA methylation patterns, and microRNA regulation, providing biologically plausible mechanisms linking maternal infection with developmental programming. Newborns, particularly preterm infants, are highly susceptible to oxidative injury because of immature antioxidant defenses, potentially increasing vulnerability to respiratory, neurological, retinal, and gastrointestinal complications. While these findings establish biological plausibility, it is essential to distinguish between these indirect mechanistic pathways and direct clinical evidence of neurodevelopmental impairment in offspring. As current evidence remains heterogeneous and insufficient to establish definitive causal relationships, available findings support a potential role for oxidative stress in mediating the effects of maternal COVID-19 on fetal and neonatal health, necessitating further prospective, mechanistic, and longitudinal studies to clarify long-term outcomes.

Keywords: SARS-CoV-2; oxidative stress; placental dysfunction; fetal programming; neuroinflammation; epigenetic alterations; neurodevelopment; neonatal outcomes

Introduction

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1], was declared a global pandemic by the World Health Organization on March 11, 2020. Since the beginning of the pandemic, COVID-19 has been recognized not only as a respiratory disease but also as a multisystem disorder associated with immune dysregulation, endothelial injury, coagulation abnormalities, and prolonged inflammatory complications [2].

The mechanism of SARS-CoV-2 infection involves the binding of the viral spike glycoprotein to the membrane-bound angiotensin-converting enzyme 2 (ACE2) receptor [3]. ACE2 receptors are expressed in pulmonary alveolar epithelial cells, vascular endothelial cells, enterocytes, renal tubular cells, placental tissue, and other organs, which explains the broad systemic manifestations of COVID-19 [4]. Following viral entry, SARS-CoV-2 disrupts the physiological balance of the renin-angiotensin system (RAS). Under normal conditions, ACE2 converts angiotensin II into angiotensin-(1–7), thereby maintaining physiological homeostasis. However, after viral internalization, ACE2 activity becomes reduced, resulting in accumulation of angiotensin II and dysregulation of the ACE2/angiotensin-(1–7)/Mas receptor axis [5].

This imbalance contributes to vasoconstriction, endothelial dysfunction, increased vascular permeability, inflammatory cell recruitment, thrombosis, and tissue fibrosis [6]. SARS-CoV-2-mediated endothelial injury may lead to systemic vasculitis, disseminated intravascular coagulation, thromboembolic events, and multiorgan dysfunction [4]. In addition, prolonged inflammatory activation and immune dysregulation contribute to persistent systemic complications observed after acute infection [7].

COVID-19 is characterized by increased production of reactive oxygen species (ROS), particularly in predisposed individuals such as obese patients, diabetics, and patients with cardiovascular diseases [8]. Persistent inflammatory processes further contribute to the formation of a microenvironment rich in ROS, including superoxide, nitric oxide, hydrogen peroxide, and other free radicals [9]. Although ROS participate in elimination of infected cells, prolonged exposure to oxidative stress may contribute to DNA damage, cellular injury, and chronic inflammatory changes.

Pregnancy itself represents a condition associated with altered immune responses and increased susceptibility to infections. An important aspect that may increase vulnerability of pregnant women to SARS-CoV-2 infection is the expression of ACE2 receptors within placental tissue and fetal circulation [10]. A study investigating placental tissue demonstrated the presence and localization of SARS-CoV-2 spike glycoprotein within placental villi in pregnancies affected by COVID-19 [11].

SARS-CoV-2 placental infection has been documented during pregnancy, while placental blood vessels and placental tissue show similarities to pulmonary tissue regarding ACE2 receptor expression. Viral RNA has also been identified in placental and fetal tissues in early pregnancies complicated by miscarriage [12]. Histopathological analyses demonstrated syncytiotrophoblast damage, trophoblast necrosis, intervillous inflammation, perivillous fibrin deposition, and collapse of the intervillous space in placentas from SARS-CoV-2-positive pregnancies [13,14].

Placental injury and inflammatory changes may impair maternal-fetal exchange and contribute to fetal complications. Furthermore, prolonged inflammatory activation and endothelial dysfunction may participate in the development of persistent post-COVID manifestations. Some patients recovering from SARS-CoV-2 infection experience chronic fatigue, dyspnea, palpitations, headaches, visual disturbances, anxiety, depression, and reduced functional capacity long after acute infection [15]. Long COVID and chronic post-COVID syndrome are therefore considered multisystem disorders requiring multidisciplinary management [16].

Overall, current evidence suggests that SARS-CoV-2 infection induces systemic inflammation, endothelial dysfunction, oxidative stress, and placental injury, which may contribute to maternal complications and adverse fetal outcomes during pregnancy.

Literature Search Strategy

This structured narrative review was conducted by systematically searching the PubMed, Scopus, and Google Scholar databases for literature published in English from January 2020 through March 2026. The search strategy employed specific combinations of the following keywords: “COVID-19”, “SARS-CoV-2”, “pregnancy”, “oxidative stress”, “placenta”, “fetal programming”, and “neurodevelopment”. To ensure reproducibility, we utilized standardized Boolean operators to combine terms related to the virus, the maternal-fetal environment, and oxidative stress pathways. The screening process was performed in two stages: an initial review of titles and abstracts to exclude irrelevant studies, followed by a full-text assessment of eligible articles. We included only full-text articles published in English; studies were excluded if they were not available in full-text or were published in languages other than English. We prioritized original research, systematic reviews, and meta-analyses that provided mechanistic insights into placental or fetal oxidative injury. This structured approach provided the framework for selecting the evidence presented, ensuring a transparent and reproducible basis for our synthesis.

Oxidative Stress in COVID-19

Mechanisms of ROS Production

Oxidative stress represents a condition in which excessive production of ROS overwhelms the antioxidant defense capacity of the organism, leading to numerous pathophysiological disturbances and tissue injury. ROS affect structural and functional cellular components either directly or indirectly. In addition to causing genetic abnormalities, excessive ROS may induce oxidative modification of proteins and lipids, thereby affecting apoptosis, migration, differentiation, and cellular proliferation [17,18].

During COVID-19 infection, several reactive oxygen and nitrogen species are generated, including superoxide anions, hydroxyl radicals, nitric oxide (NO), hydrogen peroxide, and peroxynitrite. These molecules interact with lipid and protein components of cellular membranes, leading to cellular injury, organ dysfunction, and cell death. SARS-CoV-2 infection is also associated with activation of inflammatory pathways and excessive cytokine production, contributing to the development of cytokine storm syndrome. Proinflammatory cytokines stimulate recruitment of neutrophils and activation of macrophages at sites of inflammation, thereby promoting vascular leakage, exudation, and further ROS production [19,20].

Several cytokines play an important role in oxidative stress during COVID-19 infection, particularly interferon gamma (IFN-γ), interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-2 (IL-2), and tumor necrosis factor alpha (TNF-α). These inflammatory mediators contribute to en-

dothelial dysfunction, vascular permeability, and amplification of the inflammatory response. Moreover, excessive production of reactive oxygen species activates redox-sensitive signaling pathways, including NF-κB, further promoting cytokine production and establishing a vicious cycle between inflammation and oxidative stress [19,21].

After viral entry into host cells, SARS-CoV-2 induces activation of CD4+ T lymphocytes, which stimulate B cells to produce virus-specific antibodies, while CD8+ T lymphocytes participate in the elimination of infected cells. However, SARS-CoV-2 infection is characterized by the ability to evade the host immune response and to sustain the production of proinflammatory cytokines and ROS, leading to persistent inflammation and a cytokine storm [22,23].

Accumulating evidence indicates that mitochondrial dysfunction and activation of NADPH oxidase contribute to ROS generation during COVID-19 infection. Virally induced mitochondrial injury may exacerbate oxidative imbalance and promote inflammatory signaling pathways, while activation of NADPH oxidase in neutrophils and macrophages further amplifies oxidative damage and endothelial dysfunction through excessive production of reactive oxygen species [20,24,25,26].

Hypoxia and reperfusion injury observed in severe COVID-19 may additionally increase ROS production and aggravate tissue damage. Excessive oxidative stress contributes to endothelial dysfunction, vascular injury, thrombosis, and multiorgan complications associated with severe forms of the disease [21,27].

Pregnancy represents a physiological condition associated with increased sensitivity to oxidative stress, primarily due to increased oxygen demand and mitochondrial activity within the placenta. Several stages of pregnancy, including embryogenesis, implantation, fetoplacental development, fetal growth, and labor, are accompanied by physiological ROS generation. When the balance between ROS production and antioxidant defense mechanisms becomes disturbed, excessive oxidative stress may lead to severe cellular injury and pathological changes affecting both maternal and fetal tissues [28,29].

Oxidative stress, therefore, plays an important role in the pathogenesis of numerous pregnancy complications and may significantly influence fetal development. Increased oxidative stress during maternal SARS-CoV-2 infection may additionally contribute to placental dysfunction, endothelial injury, inflammation, and adverse neonatal outcomes.

Biomarkers of Oxidative Stress

Several biomarkers have been used to assess oxidative stress in patients with COVID-19. Biomarkers of lipid, DNA, and protein oxidative damage, including malondialdehyde (MDA), 8-hydroxy-2′-deoxyguanosine (8-OHdG), and advanced oxidation protein products (AOPP), have been reported to be elevated, indicating enhanced oxidative injury to cellular macromolecules [30,31]. In addition, alterations in antioxidant defense systems have been observed, including reduced antioxidant capacity and disturbances in the activity of key antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione reductase (GR) [31,32]. Increased levels of thiobarbituric acid-reactive substances (TBARS) together with decreased antioxidant capacity further support the presence of pronounced oxidative stress in COVID-19 patients [31,32]. A previous study reported reduced total antioxidant capacity (TAC), accompanied by alterations in NO concentrations and antioxidant enzyme activities, suggesting impaired antioxidant defenses, particularly in patients with severe disease [32]. Altered oxidative stress biomarkers have been associated with increased inflammatory response, endothelial dysfunction, tissue injury, and disease severity in COVID-19 patients [30,31,32]. Furthermore, reduced glutathione availability may contribute to persistent inflammation, dysregulation of redox homeostasis, and impaired cellular defense against oxidative damage [31,33].

Oxidative Stress in Pregnancy with COVID-19

Placental Dysfunction

The placenta is particularly vulnerable to oxidative stress because of its high metabolic activity and substantial oxygen requirements. During maternal SARS-CoV-2 infection, excessive production of ROS and inflammatory mediators may contribute to placental injury and impaired placental function. Histopathological studies have demonstrated features of maternal vascular malperfusion, including abnormal maternal vessels, intervillous thrombi, delayed villous maturation, and chorangiosis, suggesting impaired maternal blood flow and placental hypoperfusion in pregnancies complicated by COVID-19 [34,35].

Endothelial dysfunction represents another important mechanism involved in placental injury during COVID-19. SARS-CoV-2-associated inflammation promotes endothelial activation, vascular damage, and a prothrombotic state, increasing the risk of placental thrombosis and microvascular impairment. Oxidative stress may further exacerbate endothelial injury through disruption of redox homeostasis and amplification of inflammatory signaling pathways, thereby contributing to placental vascular dysfunction and impaired placental perfusion [26,36].

ROS generated through NADPH oxidase activation may further reduce NO bioavailability, promoting vasoconstriction, inflammation, and endothelial dysfunction. In addition, SARS-CoV-2-induced dysregulation of the renin–angiotensin–aldosterone system (RAAS) may enhance oxidative stress and vascular injury, further contributing to impaired placental perfusion and placental dysfunction [26].

Maternal COVID-19 significantly disrupts iron homeostasis, characterized by elevated ferritin concentrations

and dysregulated hepcidin expression, which may exacerbate oxidative stress. During pregnancy, this disruption is particularly critical, as the placenta requires tightly regulated iron transport for fetal development. Excessive maternal iron release, often driven by inflammatory signaling, increases the pool of non-protein-bound iron (NPBI) in the placental microenvironment. This labile iron acts as a potent catalyst for the Fenton reaction, directly fueling the production of hydroxyl radicals. In the context of placental vascular malperfusion, this iron-mediated oxidative damage impairs nutrient exchange and contributes to the pathophysiology of adverse fetal outcomes, such as fetal growth restriction and placental insufficiency [34,36].

Maternal Inflammation and Fetal Consequences

Maternal SARS-CoV-2 infection is characterized by activation of both innate and adaptive immune responses, resulting in increased production of proinflammatory cytokines. In severe cases, excessive immune activation may lead to a cytokine storm, characterized by markedly elevated levels of inflammatory mediators, including IL-6, interleukin-7 (IL-7), IL-2, interleukin-10 (IL-10), and TNF-α. Among these cytokines, IL-6 has emerged as a key mediator associated with disease severity and adverse clinical outcomes in patients with COVID-19. Elevated concentrations of proinflammatory cytokines contribute to systemic inflammation, endothelial dysfunction, and oxidative stress, which may adversely affect placental function and fetal development [37].

Placental vascular injury and impaired perfusion may reduce oxygen delivery to the fetus, potentially resulting in fetal hypoxia. Persistent inflammation and oxidative stress may further interfere with normal placental development and nutrient exchange, thereby potentially increasing the risk of fetal growth restriction and other adverse perinatal outcomes [34,35,38].

Large systematic reviews and meta-analyses have demonstrated that pregnant women with COVID-19 are at increased risk of preterm birth, neonatal complications, and adverse perinatal outcomes compared with uninfected pregnant women [38,39].

Collectively, these findings indicate that oxidative stress, endothelial dysfunction, placental vascular injury, and maternal inflammation act synergistically in the development of placental dysfunction and adverse fetal outcomes associated with COVID-19 during pregnancy [26,34,36].

Neuronal Dysfunction and Fetal Brain Injury

Elevated concentrations of proinflammatory cytokines, including IL-6, TNF-α, and other inflammatory mediators, can activate microglial cells and promote neuroinflammation within the central nervous system. Increased systemic cytokine levels may also compromise blood-brain barrier integrity, facilitating the passage of inflammatory mediators into neural tissues [40,41]. Following their entry into the central nervous system, cytokines activate microglia and astrocytes, which subsequently release additional proinflammatory cytokines, reactive oxygen species, complement proteins, excitatory neurotransmitters, and other neurotoxic mediators [42,43]. This self-perpetuating inflammatory response amplifies oxidative damage, promotes excitotoxicity, and contributes to neuronal dysfunction and injury [44]. Activated microglia, therefore, play a central role in linking systemic inflammation to neurotoxicity and neurological sequelae associated with SARS-CoV-2 infection [41]. In addition, activated microglia and infiltrating immune cells generate excessive amounts of reactive oxygen species, further amplifying oxidative stress within neural tissues. Excessive production of reactive oxygen species may directly damage neuronal lipids, proteins, and nucleic acids, resulting in impaired neuronal function, mitochondrial dysfunction, and cellular injury [45]. Oxidative stress has been recognized as an important contributor to neurological complications associated with SARS-CoV-2 infection [19,45]. Through the interplay between inflammatory signaling, microglial activation, and oxidative damage, neuroinflammation may represent an important mechanism underlying SARS-CoV-2-associated neurological injury.

Hypoxia may represent an important mechanism contributing to neuronal injury during severe maternal SARS-CoV-2 infection. Reduced oxygen availability may increase reactive oxygen species production, resulting in enhanced lipid peroxidation, membrane instability, and neuronal damage [46,47]. Lipid peroxidation is one of the major consequences of oxidative stress and may disrupt neuronal membrane structure and function. Furthermore, oxidative degradation of membrane lipids generates reactive metabolites that propagate cellular injury and inflammatory responses [18,48]. Mitochondrial dysfunction plays an important role in oxidative stress-related cellular injury. SARS-CoV-2-associated oxidative stress may impair mitochondrial bioenergetics, increase reactive oxygen species generation, and activate signaling pathways involved in inflammation and cell death [24]. Since neurons are highly dependent on mitochondrial energy production, mitochondrial dysfunction could contribute to neuronal vulnerability and degeneration [49]. Recent evidence suggests that ferroptosis, an iron-dependent form of regulated cell death characterized by excessive lipid peroxidation, may contribute to SARS-CoV-2-associated tissue injury [50]. However, its potential role in fetal neuronal injury remains insufficiently understood and warrants further investigation. In addition, oxidative stress may further exacerbate neuronal injury through mechanisms involving impaired neurotransmitter homeostasis and calcium dysregulation, ultimately contributing to neuronal dysfunction [47,51].

While the mechanisms described above explain systemic neurological dysfunction in adults—including

headache, dizziness, anosmia, ageusia, impaired concentration, encephalopathy, and altered mental status [41,44,52]—the relevance of these pathways in the fetus requires specific consideration. Maternal neurological manifestations arise from interacting mechanisms such as systemic inflammation, endothelial dysfunction, and immune-mediated cross-reactivity [52]. Evidence of persistent injury, such as elevated serum neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP), confirms ongoing axonal and astrocytic damage in symptomatic patients [53]. However, in the context of pregnancy, these maternal-derived markers and neurological symptoms (anosmia, brain fog) serve as indices of maternal status rather than direct fetal brain pathology. The fetal-specific risk is governed by the maternal-fetal inflammatory crosstalk: proinflammatory cytokines and oxidative metabolites can traverse the placenta, directly impacting the developing fetal brain despite the absence of maternal neurological symptoms [54,55]. Unlike the mature brain, the fetal brain is uniquely susceptible to this environment due to its developmental programming. Thus, while neuroinflammation and oxidative stress characterize the general SARS-CoV-2 neurobiology, fetal neuronal injury is specifically mediated by placental dysregulation of the maternal-fetal interface, necessitating further study in cord blood and fetal neural tissues to clarify these long-term developmental consequences.

Long-Term Neurodevelopmental Consequences

The potential long-term neurodevelopmental consequences of prenatal exposure to maternal SARS-CoV-2 infection remain an area of active investigation. Although vertical transmission appears to be uncommon, maternal inflammation, oxidative stress, placental dysfunction, immune activation, and fetal hypoxia have been proposed as mechanisms that may influence fetal brain development and subsequent neurological outcomes [36,56,57].

Several biological mechanisms have been proposed to link maternal SARS-CoV-2 infection with altered fetal neurodevelopment. Maternal immune activation and elevated concentrations of proinflammatory cytokines, including IL-6 and interleukin-17A (IL-17A), may disrupt critical developmental processes, whereas epigenetic alterations, oxidative stress, mitochondrial dysfunction, and placental dysfunction may further influence fetal brain development and neurodevelopmental trajectories [57,58,59,60].

Current evidence suggests that prenatal exposure to maternal SARS-CoV-2 infection may be associated with subtle alterations in early neurodevelopment. However, findings remain heterogeneous, with some studies reporting increased developmental vulnerability, particularly among male offspring, whereas others have observed minimal or no significant differences compared with unexposed children [61,62].

Recent systematic reviews and meta-analyses indicate that available evidence remains insufficient to establish a definitive association between prenatal SARS-CoV-2 exposure and long-term neurodevelopmental impairment. While some studies suggest possible developmental effects, others report largely normal developmental outcomes during infancy and early childhood [63,64]. Therefore, continued longitudinal follow-up of exposed children is required to determine the long-term clinical significance of prenatal exposure to maternal SARS-CoV-2 infection [65].

However, it is crucial to interpret these findings by acknowledging that maternal SARS-CoV-2 infection is not a uniform exposure. Substantial heterogeneity exists, depending on gestational age at the time of infection, disease severity, maternal oxygenation status, and vaccination history [38,39]. Furthermore, variables such as viral variants, comorbid conditions—including obesity and pre-existing metabolic disorders—as well as pharmacological treatments and the risk of preterm birth, serve as critical independent factors. These factors can independently modulate oxidative stress levels, placental pathology, and neonatal susceptibility to injury [26]. Future research must rigorously control for these confounding variables to better disentangle the specific impact of SARS-CoV-2-induced oxidative stress from other maternal or obstetric complications.

Oxidative Stress in Newborns

Why Neonates are Vulnerable

Newborns, particularly preterm infants, are highly susceptible to oxidative stress because of the immaturity of their antioxidant defense systems. Fetal levels of antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase, increase progressively during gestation. Consequently, premature infants have a limited capacity to neutralize excessive ROS and are particularly vulnerable to oxidative injury [66,67].

Oxidative stress is a physiological consequence of the transition from the relatively hypoxic intrauterine environment to extrauterine life. The sudden increase in oxygen exposure after birth may enhance ROS production and contribute to oxidative imbalance, particularly in premature infants whose antioxidant defenses remain underdeveloped [67,68].

In addition to hyperoxia, other perinatal conditions including hypoxia, ischemia, reperfusion injury, inflammation, and elevated levels of non-protein-bound iron may further increase oxidative stress during the neonatal period [67].

Maternal SARS-CoV-2 infection may further contribute to an oxidative intrauterine environment through placental dysfunction, inflammation, and alterations in iron metabolism, potentially affecting fetal redox homeostasis [36].

Respiratory distress syndrome frequently requires supplemental oxygen administration and, in severe cases, mechanical ventilation. Although these interventions are often life-saving, prolonged exposure to high oxygen concentrations may further increase oxidative stress and contribute to cellular injury in vulnerable neonatal tissues [67].

Neonatal Complications Associated With Oxidative Stress

Oxidative stress has been implicated in the pathogenesis of several major neonatal disorders. Because preterm infants have limited antioxidant defenses, excessive production of ROS may result in cellular injury affecting multiple organs, including the lungs, retina, brain, and gastrointestinal tract [67]. ROS can damage lipids, proteins, DNA, and cellular organelles, thereby contributing to tissue injury and impaired organ development [69].

Bronchopulmonary dysplasia (BPD) is one of the most extensively studied neonatal diseases associated with oxidative stress. Hyperoxia-induced oxidative injury and inflammation may interfere with normal lung development and contribute to chronic pulmonary dysfunction [67,70].

Necrotizing enterocolitis (NEC) has also been associated with oxidative stress, which may contribute to intestinal injury and disease progression through interactions with inflammatory and ischemic pathways [67].

Retinopathy of prematurity (ROP) is strongly associated with oxygen-induced oxidative injury. Disturbances in retinal vascular development resulting from fluctuations in oxygen exposure and oxidative stress may lead to abnormal retinal neovascularization and visual impairment [70].

Hypoxic-ischemic encephalopathy (HIE) is another neonatal condition in which oxidative stress is believed to play a significant pathogenic role. Both hypoxia and subsequent reperfusion may stimulate excessive ROS generation, leading to lipid peroxidation, mitochondrial dysfunction, DNA damage, and neuronal injury. Increased levels of oxidative stress markers have been reported in newborns with HIE and appear to correlate with disease severity. Given the limited antioxidant capacity of the neonatal brain, oxidative stress may substantially contribute to the development and severity of hypoxic-ischemic brain injury [66,71].

Periventricular leukomalacia (PVL) represents a major form of white matter injury in premature infants. The developing brain is particularly vulnerable to oxidative damage because of its high oxygen consumption, abundant lipid content, and limited antioxidant defenses. In addition to hyperoxic injury, hypoxia is a potent activator of oxidative stress pathways, and reactive oxygen species are believed to contribute substantially to neonatal brain injury. Oxidative stress may therefore promote oligodendrocyte damage, impaired myelination, and subsequent neurological sequelae [66,71].

Maternal SARS-CoV-2 infection may create an intrauterine environment characterized by increased inflammation, placental dysfunction, and redox imbalance, which could potentially influence neonatal oxidative status. However, the precise contribution of these mechanisms to specific neonatal complications remains incompletely understood and requires further investigation [36].

Collectively, available evidence indicates that oxidative stress plays an important role in the pathogenesis of several neonatal complications and may significantly influence both short-term and long-term outcomes, particularly in premature infants.

Genetic Susceptibility, Gene Expression, and Epigenetic Alterations Associated With Prenatal SARS-CoV-2 Exposure

Host Genetic Factors Influencing Susceptibility and Response to SARS-CoV-2

Although prenatal SARS-CoV-2 exposure primarily affects the fetal environment through maternal and placental mechanisms, host genetic factors may also contribute to variability in susceptibility and clinical responses to infection. Genome-wide association studies have identified several genes involved in cytokine signaling, immune regulation, and inflammatory responses that may influence the host response to SARS-CoV-2 infection. These include genes associated with cytokine receptor activity, such as *CCR1*, *CCR3*, *CCR9*, *CXCR6*, *IFNAR2*, *IL10RB*, *LIFR*, and *XCR1*, highlighting the potential importance of immune signaling pathways in COVID-19 pathogenesis in pediatric populations [72].

In addition, several loci associated with pediatric susceptibility to COVID-19, including *ACTN1*, *PDS5B*, *SEMA6D*, *SPRY4*, and *TENM3*, have also been linked to asthma susceptibility, suggesting possible interactions between immune regulation, respiratory function, and host response to viral infection [73].

Genetic variability within components of the renin–angiotensin system may also influence clinical outcomes. A systematic review reported associations between the angiotensin-converting enzyme 1 (ACE1) D/D genotype (rs4646994), the ACE2 G/G genotype (rs2285666), and an increased risk of severe COVID-19 in children younger than two years of age. Given the central role of ACE2 as the cellular receptor for SARS-CoV-2, these findings suggest that host genetic background may contribute to differences in disease susceptibility and severity [74].

Altered Gene Expression and Inflammatory Signaling

Maternal SARS-CoV-2 infection may induce inflammatory responses that extend beyond the placenta and influence fetal gene expression. Proteomic analyses have demonstrated that neonates exposed to SARS-CoV-2 in utero, despite the absence of confirmed infection, may exhibit evidence of immune activation and altered inflammatory signaling. Changes involving the IFNL1/IFNLR1

pathway, together with increased expression of TREM2 and IDUA and reduced expression of AGR3, suggest that maternal inflammation may influence neonatal immune regulation and respiratory adaptation [75,76].

Prenatal exposure to maternal SARS-CoV-2 infection has also been associated with differential gene expression in umbilical cord blood cells. These observations suggest that maternal inflammation may trigger a fetal inflammatory response that modulates immune pathways and developmental processes, even in the absence of vertical viral transmission [59].

Epigenetic Modifications and Potential Long-Term Consequences

Growing evidence suggests that maternal SARS-CoV-2 infection may be associated with epigenetic alterations that could affect offspring development and health. Saulle and colleagues reported upregulation of several placental microRNAs, including miR-21, miR-29, miR-150, and miR-155, which are involved in immune regulation, inflammation, angiogenesis, and placental development. Dysregulation of these pathways has previously been associated with pregnancy complications such as preeclampsia, intrauterine growth restriction, and fetal hypoxia [77].

Differential DNA methylation patterns have also been identified in cord blood cells from neonates prenatally exposed to maternal SARS-CoV-2 infection. Hypomethylated genes included *BMP7*, *RHOBTB1*, *WWOX*, and *HLA-DOB*, whereas hypermethylated genes included *XYLB*, *CLDN6*, *UBTF*, *LPCAT2*, *STRN4*, and *HLA-DPB1*. Several of these genes are involved in developmental, immunological, cardiovascular, renal, and neurological pathways, suggesting that prenatal exposure may be associated with molecular changes affecting multiple biological systems [60].

The same study identified altered methylation of regulatory genes such as *KLF5*, *MITF*, *EPAS1*, and *EZH2*, which are implicated in cellular differentiation, tissue development, and organ function. Together, these findings support the possibility that maternal COVID-19 may influence fetal programming through epigenetic mechanisms. However, the long-term clinical significance of these molecular alterations remains uncertain and requires further investigation [60].

Collectively, current evidence suggests that prenatal exposure to maternal SARS-CoV-2 infection may be associated with alterations in immune signaling, gene expression, and epigenetic regulation. Although these findings provide biologically plausible mechanisms through which maternal infection could influence fetal and neonatal development, their long-term functional and clinical consequences remain to be fully elucidated (Fig. 1).

Potential Strategies to Mitigate Oxidative Stress

Given the potential role of oxidative stress in the pathophysiology of COVID-19 and its possible involvement in placental dysfunction, neurodevelopmental alterations, and adverse neonatal outcomes, several nutritional and antioxidant interventions have been proposed as strategies to reduce oxidative damage. However, current evidence remains limited, particularly in the context of maternal SARS-CoV-2 infection, and the potential benefits of these interventions should therefore be interpreted with caution. The interventions discussed herein are categorized as experimental or theoretical approaches; they are not intended to serve as clinical guidelines or standard-of-care recommendations.

Maternal Nutritional and Antioxidant Support

Adequate maternal nutrition is essential for maintaining redox homeostasis during pregnancy. Nutritional status influences immune function through multiple mechanisms, including modulation of cellular signaling pathways, gene expression, and gut microbial composition. Because several micronutrients participate in both antioxidant defense and immune regulation, maintaining an adequate nutritional status during pregnancy may support maternal resilience to infectious and inflammatory challenges. Vitamins C and D, together with zinc, have received particular attention because of their established roles in immune function and antioxidant protection [78].

Dietary patterns rich in fruits, vegetables, whole grains, fish, and unsaturated fatty acids, particularly the Mediterranean diet, have been associated with reduced oxidative stress and improved maternal and neonatal health outcomes. Consistent with these observations, a prospective birth cohort study reported that greater adherence to healthy dietary patterns during pregnancy, including the Mediterranean diet, Dietary Approaches to Stop Hypertension (DASH) diet, and Alternative Healthy Eating Index (AHEI) dietary patterns, was associated with lower levels of oxidative stress biomarkers in both mothers and offspring [79].

Such dietary approaches may help support antioxidant defenses during pregnancy and could potentially mitigate oxidative stress associated with maternal inflammatory conditions, although direct evidence in pregnancies complicated by SARS-CoV-2 infection remains limited.

Several micronutrients involved in antioxidant defense have also attracted attention. Selenium is an essential component of glutathione peroxidases and other antioxidant enzymes, while zinc contributes to antioxidant protection, immune regulation, and DNA repair. Adequate intake of these micronutrients may support maternal antioxidant capacity and immune function during pregnancy. Nevertheless, their specific role in preventing adverse maternal, fe-

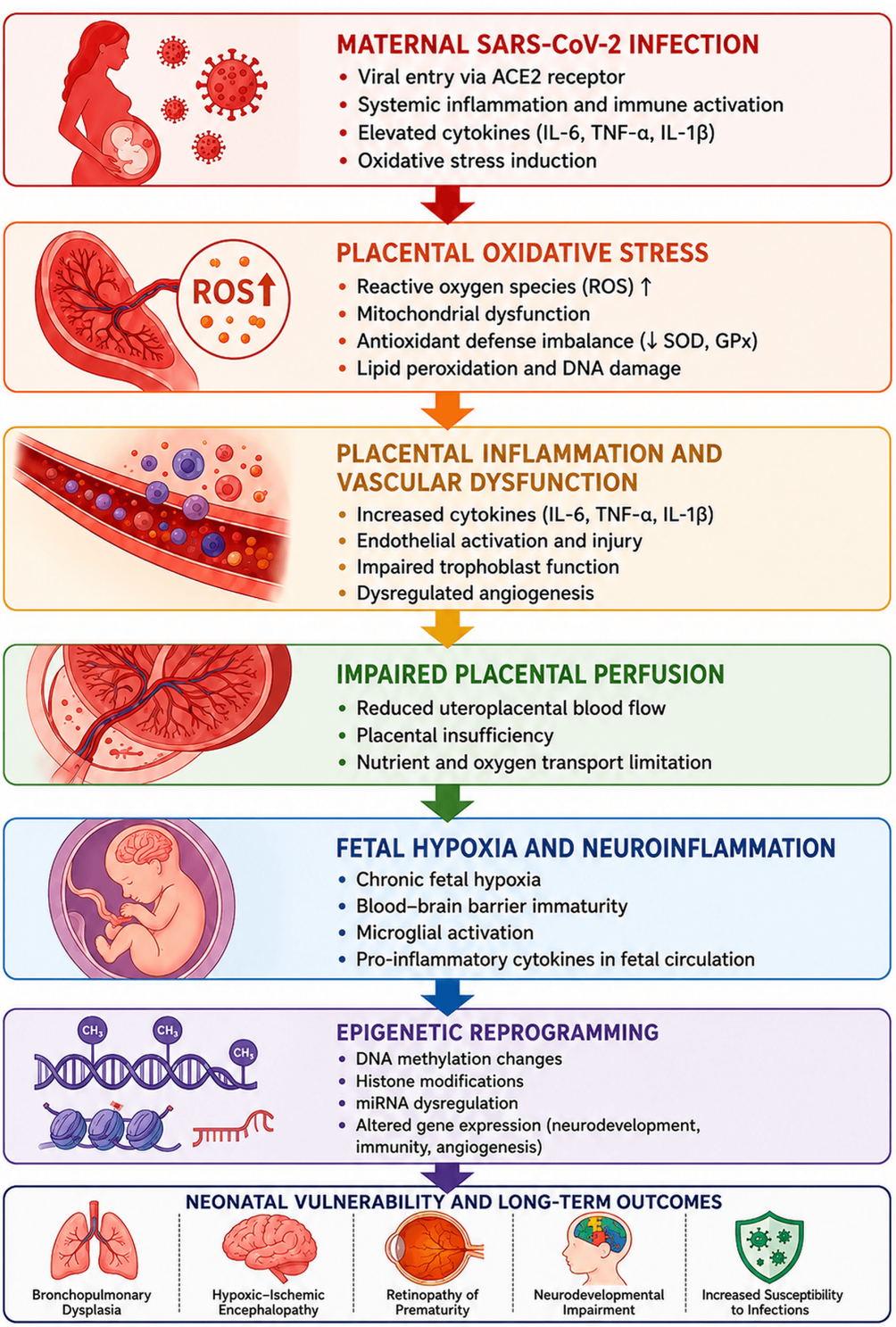

Fig. 1. Conceptual framework of maternal SARS-CoV-2 infection, placental dysfunction, and potential fetal neurodevelopmental sequelae. This figure illustrates the proposed pathogenetic continuum from maternal SARS-CoV-2 infection to long-term neonatal outcomes. The pathway highlights key stages, including maternal systemic inflammation, placental oxidative stress, vascular dysfunction, and subsequent fetal environmental changes. Solid arrows denote the proposed mechanistic flow supported by clinical observations and experimental models. Note that while the initial stages—such as maternal systemic inflammation and placental dysfunction—are well-documented in human pregnancy, the subsequent processes involving specific fetal epigenetic reprogramming and chronic long-term outcomes represent mechanistic hypotheses requiring further longitudinal validation to confirm direct causality. The figure was created using Adobe Photoshop 2026 (Adobe Inc., San Jose, CA, USA). SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IL-6, interleukin-6; TNF-α, tumor necrosis factor alpha; IL-1β, interleukin-1β; SOD, superoxide dismutase; GPx, glutathione peroxidase.

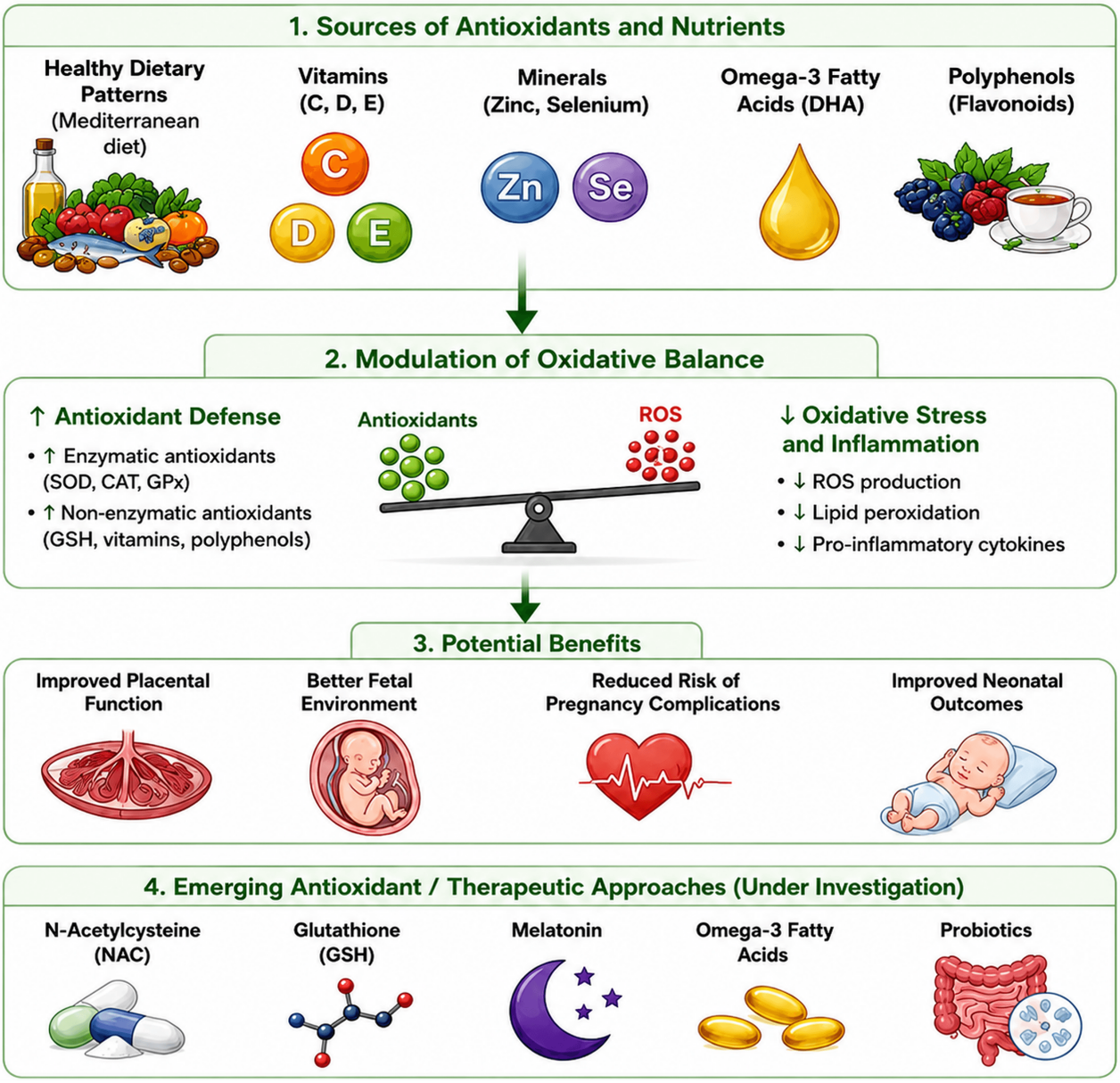

Fig. 2. Potential nutritional and antioxidant strategies for modulating oxidative stress during pregnancy. This diagram summarizes the mechanisms by which nutritional intake and antioxidant supplementation (including vitamins, minerals, omega-3 fatty acids, NAC, and melatonin) may modulate redox balance. By enhancing antioxidant defenses, these strategies aim to reduce reactive oxygen species (ROS) production and systemic inflammation, thereby potentially supporting placental function and improving neonatal outcomes. The figure was created using Adobe Photoshop 2026 (Adobe Inc., San Jose, CA, USA). Note: The interventions illustrated are currently under investigation. Due to limited clinical data regarding safety and efficacy in pregnancies complicated by maternal SARS-CoV-2 infection, these approaches do not constitute established clinical recommendations. NAC, N-acetylcysteine.

tal, or neonatal outcomes associated with COVID-19 has not yet been clearly established [80].

Docosahexaenoic acid (DHA), a long-chain omega-3 polyunsaturated fatty acid, plays an important role in fetal neurodevelopment and exhibits anti-inflammatory properties. These characteristics have generated interest in its potential role in modulating inflammatory and oxidative pathways during pregnancy. However, further studies are required to determine whether DHA supplementation specifically improves outcomes in pregnancies complicated by maternal SARS-CoV-2 infection [80].

Vitamin C and vitamin E are among the most extensively studied dietary antioxidants. Both vitamins participate in the neutralization of reactive oxygen species and protection against oxidative damage. Although their biological properties suggest a potential benefit in conditions characterized by excessive oxidative stress, current evidence remains insufficient to support their routine use for

preventing maternal, fetal, or neonatal complications associated with COVID-19. Furthermore, available evidence suggests that maternal antioxidant intake may influence the antioxidant composition of breast milk and potentially affect the antioxidant status of breastfed infants; however, data remain limited and the optimal type and dose of antioxidant supplementation have not been established [81,82].

Emerging Antioxidant Interventions

Several antioxidant agents have attracted interest as potential adjunctive approaches for mitigating oxidative stress in COVID-19. A prospective randomized controlled trial in hospitalized patients with non-critical COVID-19 demonstrated that supplementation with antioxidant vitamins (A, C, and E) together with zinc and selenium was associated with lower levels of inflammatory markers, including IL-6, TNF-α, and monocyte chemoattractant protein-1 (MCP-1), compared with placebo, suggesting a potential role for antioxidant support in modulating inflammatory responses during SARS-CoV-2 infection. Nevertheless, these findings were obtained in non-pregnant adults and cannot be directly extrapolated to pregnancies complicated by maternal SARS-CoV-2 infection [83].

N-acetylcysteine (NAC) is a precursor of glutathione, one of the major intracellular antioxidants. By replenishing glutathione stores and supporting cellular redox balance, NAC may attenuate oxidative injury and inflammatory responses. In addition to its antioxidant effects, NAC has been proposed to protect endothelial function and may help limit microthrombotic processes observed in severe COVID-19. Although experimental and clinical studies have suggested potential benefits in conditions characterized by excessive oxidative stress, evidence regarding its effectiveness during pregnancy and its impact on fetal or neonatal outcomes remains limited [19].

Glutathione (GSH), often referred to as the principal intracellular or “master” antioxidant, plays a central role in maintaining cellular redox homeostasis and participates in numerous biological processes, including detoxification, protein folding, antiviral defense, and immune regulation. Reduced glutathione availability has been associated with increased oxidative stress and inflammation, while depletion of GSH stores may contribute to dysregulated immune responses. Because glutathione is a key antioxidant defense mechanism in virtually all tissues, restoring glutathione homeostasis has been proposed as a potential therapeutic target in COVID-19 and may help limit excessive inflammatory responses. Nevertheless, robust clinical evidence supporting glutathione supplementation in pregnant women or neonates exposed to maternal SARS-CoV-2 infection is currently lacking [84].

Melatonin possesses antioxidant, anti-inflammatory, and free radical-scavenging properties and plays an important role in maintaining placental redox homeostasis during pregnancy. A balanced relationship between reactive oxygen species and antioxidant defenses is essential for normal placental function, whereas excessive oxidative stress has been implicated in adverse pregnancy outcomes, including preeclampsia, preterm birth, and fetal growth restriction. Melatonin contributes to antioxidant protection within the placenta and has attracted interest as a potential modulator of oxidative and inflammatory pathways. Because melatonin readily crosses the placenta and is also produced locally within placental tissues, it may influence the intrauterine environment during gestation. These characteristics have generated interest in melatonin as a potential adjunctive intervention in conditions associated with excessive oxidative stress, including COVID-19. However, evidence regarding its clinical utility in pregnancies affected by maternal SARS-CoV-2 infection remains limited, and further studies are required to establish its efficacy and safety in this setting [85,86].

Omega-3 fatty acids have also been investigated because of their anti-inflammatory and immunomodulatory effects. By modulating inflammatory responses and supporting endothelial function, these compounds may influence oxidative and inflammatory pathways during pregnancy. However, additional studies are required to determine their clinical relevance in pregnancies affected by COVID-19 [80].

Overall, although several nutritional and antioxidant interventions have shown theoretical or experimental promise, current evidence remains insufficient to support their routine use to prevent or treat placental, fetal, or neonatal complications associated with maternal SARS-CoV-2 infection (Fig 2). It is critical to emphasize that these interventions do not constitute established clinical recommendations. Given the significant gaps in pregnancy-specific and neonatal safety data—particularly regarding optimal dosing, timing, and long-term efficacy—clinicians should exercise extreme caution. These strategies are currently experimental and should not be integrated into routine clinical practice until robust, well-designed prospective studies confirm their safety profile and developmental outcomes in this vulnerable population.

Potential Implications for Fetal and Neonatal Health

Oxidative stress has been implicated in placental dysfunction, fetal inflammation, impaired neurodevelopment, and several neonatal complications associated with adverse intrauterine conditions. Therefore, strategies aimed at supporting maternal antioxidant defenses may theoretically contribute to a more favorable intrauterine environment and reduce the burden of oxidative injury affecting the developing fetus. However, the extent to which maternal antioxidant interventions can modify fetal redox status or improve neonatal outcomes following prenatal exposure to maternal SARS-CoV-2 infection remains unclear.

Several antioxidant compounds have also been investigated in neonatal disorders characterized by excessive

oxidative stress, including bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, and hypoxic-ischemic brain injury. Although these approaches have shown biological plausibility and, in some settings, encouraging experimental results, evidence remains insufficient to support their routine application in neonates exposed to maternal SARS-CoV-2 infection. Further studies are needed to clarify whether modulation of oxidative stress pathways during pregnancy or the neonatal period can translate into meaningful clinical benefits.

Future Perspectives

Growing evidence supports the involvement of oxidative stress in the maternal, placental, fetal, and neonatal consequences of SARS-CoV-2 infection. Nevertheless, important knowledge gaps remain regarding the mechanisms linking maternal infection to long-term offspring outcomes and the extent to which oxidative stress directly contributes to these processes.

Future research should focus on identifying reliable biomarkers of oxidative stress, inflammation, and placental dysfunction, as well as determining whether targeted nutritional or antioxidant interventions can safely modify these pathways during pregnancy. Longitudinal studies incorporating prenatal, neonatal, and long-term developmental follow-up will be particularly important for clarifying the clinical significance of oxidative stress-related alterations observed after prenatal exposure to maternal SARS-CoV-2 infection.

A better understanding of these mechanisms may facilitate the development of preventive and therapeutic strategies aimed at improving maternal health, optimizing placental function, and supporting favorable fetal and neonatal outcomes.

Conclusion

Oxidative stress may represent an important mechanistic link between maternal SARS-CoV-2 infection, placental dysfunction, and potential neuronal injury in the fetus and newborn. Our review highlights that the "oxidative burden" experienced during pregnancy acts as a potential driver of fetal programming, capable of altering neurodevelopmental trajectories through epigenetic and inflammatory pathways. Nevertheless, we emphasize the need to rigorously differentiate between the biological plausibility of these mechanisms and direct clinical outcomes, as existing data remain heterogeneous. Future research must shift from observational associations toward mechanistic, longitudinal studies focused on disentangling specific COVID-19 impacts from confounding factors, such as placental injury and prematurity. Identifying reliable oxidative biomarkers will be essential for stratifying neonatal risk, while targeted therapeutic strategies hold the potential to mitigate long-term consequences. Ultimately, integrating these molecular insights into clinical practice is vital for optimizing fetal health in the post-pandemic era.

Availability of Data and Materials

Not applicable.

Author Contributions

MZJ, SM, and BP conceived the review and designed the structural framework, drafted the initial manuscript and performed the literature search and data collection; MZJ and BP provided critical revision of the manuscript for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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