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REVIEW ARTICLE

Gynecology

COVID-19 in pregnant women and children: Insights on clinical manifestations, complexities, and pathogenesis

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Abstract

Pregnancy changes the body's immune system to counteract the spectrum of infections, including COVID-19, which can pose complications. Pregnant women are less likely to contract COVID-19 infections than the general public. However, pregnant women are at slightly increased risk of becoming severely unwell if they do catch COVID-19, and congenital conditions in pregnant women may worsen the state of infection and lead to critical stages and even mortality. The possibility of vertical transmission has been reported in only a few cases of COVID-19; however, it was not noted in cases of SARS and MERS. Vaccination coverage in pregnant women remains a challenge. Children are the next suspected and vulnerable population to acquire infection after the first and second waves. Children are disproportionately infected compared with older populations, but the severity of infection is less compared to adults. This review highlights the complexities of COVID-19 in pregnant women and the underlying reasons why children tend to be comparatively less severely affected. Ethnicity, nutrition, lifestyle, and therapeutics influence the severity of infection in children. Low expression of angiotensin-converting enzyme 2 receptors, indigenous virus competence, and maternal immunity is the first-line defense for children against COVID-19. Habituating herbal medicines from childhood may help support a robust and defensive immune system to counteract novel antigens and encourage healthy generations.

KEYWORDS
ACE2, children, comorbidity, COVID-19, immunity, pregnancy, vaccines, virus competence

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1 | INTRODUCTION

Understanding the span of coronavirus disease (COVID-19) that onset towards the end of 2019 has become an urgent undertaking.[1–4] The virus causing the disease (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) indiscriminately affected individuals with varying severity, causing the ongoing global pandemic. Research has revealed that the pathogenesis and transmission of COVID-19 are similar to those of severe acute respiratory syndrome (SARS). Extensive acceptance of COVID-19 vaccines is the crucial step in fighting the pandemic; however, achieving a high percentage of vaccinated populations is challenging. Vaccination campaigns are needed to create awareness to prevent public misconceptions. Social distancing, wearing masks, quarantine measures, and curfews are the suggested ways to break the chain of transmission.

COVID-19 is analogous to existing viruses such as SARS, Middle East respiratory syndrome (MERS), and other respiratory viruses. No proven reports on vertical transmission (i.e. mother to neonate) were available for SARS and MERS, and most infected pregnant women experienced mild symptoms. In the first wave of COVID-19 clinical findings became more complicated and frequent in pregnant women and were oriented with a spectrum of complications such as severe pneumonia, cardiovascular disease, multiorgan failure, thrombosis, and ventilation requirement.[5] The higher percentage of maternal morbidity and mortality reflected the increasing numbers of neonates testing positive for SARS-CoV-2. The potential capability of SARS-CoV-2 for intrauterine maternal–fetal transmission is concerning.[6] The most crucial, complex, and challenging concern is the effects of viral infection in pregnant women, fetuses, and neonates. The severity of the disease is closely associated with still birth; the pandemic may also indirectly influence the birth weight of neonates due to the poor nutrition and health of mothers exposed to the associated socio-economic crisis.

The immune complex differs between a child and an adult, with different stages during childhood, namely newborn, infant, toddler, and preschooler; there should be a notable difference in the expression of children's immune systems to viral infection, environmental exposure, and novel antigens such as SARS and COVID-19. Recent research pointed out the possibility of analogous viruses in the mucosa of respiratory pathways in young children which impede the growth of SARS-CoV-2 through virus-to-virus interactions and competition.[7] The infection is mediated by the angiotensin-converting enzyme 2 (ACE2) receptor, which is lodged abundantly in the lower respiratory passages (lungs and intestine) and is not localized to any immune cells.[5] Several studies have shown that COVID-19 shares the same common receptor as SARS,[7] which provided indicators for drug development by blocking the virus's receptor binding sites for ACE2.

The aim of the present review is to highlight the complexities associated with COVID-19 in pregnant women and the precautionary measures needed in neonatal care, and to raise awareness of the susceptibility of children to counteract infection in the forthcoming waves by recognizing mild onset of clinical symptoms.

2 | CORONAVIRUSES AND COVID-19

Coronaviruses are a group of nonsegmented, positive-stranded RNA viruses with a genome size of approximately 30 kilobases surrounded by a distinct protein envelope with specific receptors to mediate the infection. Almost all strains of coronaviruses cause diseases in their respective host species (high host specificity) and can infect humans through cross-species transmission. The mechanism of SARS-CoV-2 is similar to the SARS coronavirus, with critical clinical infections and impairment of organs including lungs, heart, liver, and kidney, and a high risk of pneumonia in patients.[8] Human populations are at high risk of COVID-19 infection, particularly pregnant women and children owing to the unique state of immune suppression. Furthermore, perinatal infection may lead to fetal distress, premature labor, respiratory complications, thrombocytopenia accompanied by abnormal liver function, and even fatality.[9] The possibility of vertical transmission of SARS-CoV-2 is currently being investigated.[9]

3 | PREGNANCY AND COVID-19

In a standard population it is estimated that 81% of those with COVID-19 have mild symptoms, 14% have severe complications, and 5% experience a critical stage of the disease.[10] Pregnant women suffer a similar rate of clinical complications; however, pregnant women with mild infection experience the same outcomes as uninfected pregnant women, while pregnant women with severe and critical disease have much higher risks of perinatal infection, morbidity, and mortality.[11] The higher rate of positive cases is due to the increased percentage of screening; however, most pregnant women undergo testing only if they are only symptomatic, while most asymptomatic cases are often excluded from testing procedures. The degree of disease complexity in pregnant women increases with comorbid conditions such as diabetes, cardiovascular disease, hypertension, transplantation, pregestational diabetes mellitus, age, chronic lung disease, healthcare occupation, and trauma. Risk factors are found to vary across race, maternal age, and body mass index (BMI).[12] Older age and increased BMI were critical factors associated with severe disease in pregnant women in France and Latin America.[13] Plausible reasons for racial variation in the severity of COVID-19 depend upon genetics and lifestyle.[13] Indeed, the presence of asthma has been over-represented in pregnant women with severe disease.[14]

Pregnancy-related complexities associated with COVID-19 were commonly reported during the second wave (more so than in the first wave), with comorbidities and secondary infections threatening the affected population. According to a recent study, COVID-19-positive pregnant women have a higher risk of miscarriage, pre-eclampsia, preterm labor, and cesarean delivery.[15] The risk is exponentially higher in the third trimester due to increased BMI, which proportionally increases pneumonia, hypoxia, and coagulation complications.[15] Multiorgan failure is due to the inflammatory action of cytokines leading to a cytokine storm that activates thrombin.[16]

A high concentration of D-dimer (>1 μg/ml) is a biomarker for high thrombin levels associated with greater risk of mortality due to sepsis-induced coagulopathy.[17] However, anticoagulant treatment involving heparin has improved prognosis in patients with severe infection.[17] These complications directly induce fetal distress, leading to mechanical support ventilation and ICU monitoring.[18]

The long-term effects of COVID-19 on maternal, neonatal, and child health have been considered largely in terms of noncommunicable diseases. Neonates born prematurely have exponential risks of developing metabolic syndrome, type 2 diabetes, hypertension, and stroke compared to those born at full term.[19] A review by Parazzini et al.[20] during the first wave reported that the the rate of vertical or peripartum transmission of SARS-CoV-2 and spontaneous preterm birth was low, and that the rate of vertical or peripartum transmission of SARS-CoV-2 was low for cesarean delivery. Increased stillbirth rates and postnatal complications suggest a direct impact of COVID-19 on the fetus and neonate. Viral infection in the placenta or amnion often results in stillbirths, while neonatal complications may suggest dysbiosis. Furthermore, lack of breastfeeding may alter the beneficial microbiome, thereby contributing to both short- and long-term noncommunicable diseases.[21]

Medications available to treat pregnant women with COVID-19 include antenatal corticosteroids, which increase lung maturation by stimulating type 2 alveolar cells in the developing fetus. ACE2 receptors are specific binding sites for the entry of COVID-19 into the cell,[22] hence caution should be exercised in administration of antenatal corticosteroids to pregnant women prone to preterm labor.[23]

International bodies representing OBGYNs, such as the Royal College of Obstetricians and Gynaecologists (RCOG)[24] and American College of Obstetricians and Gynecologists (ACOG)[25] have recommended vaccines for pregnant women and suggested that vaccination was the only way to protect from the risks of COVID-19. In certain cases, joint decision-making together with healthcare experts is suggested in order to understand more clearly the benefits and risks based on individual medical history.[24] FIGO (the International Federation of Gynecology and Obstetrics) supports offering COVID-19 vaccination to pregnant and breastfeeding women.[26] Figure 1 represents the complexities associated with COVID-19-affected pregnant women, and precautionary methods to be used during delivery and neonatal management.

4 | COVID-19 IN CHILDREN

Various countries have developed protocols to align public health, laboratory, and clinical systems according to the strength and availability of their resources. According to the Centers for Disease Control and Prevention (CDC) in the USA, children are less likely to develop coronavirus symptoms than adults.[27] Among the reported cases of children infected with COVID-19 in the USA (where

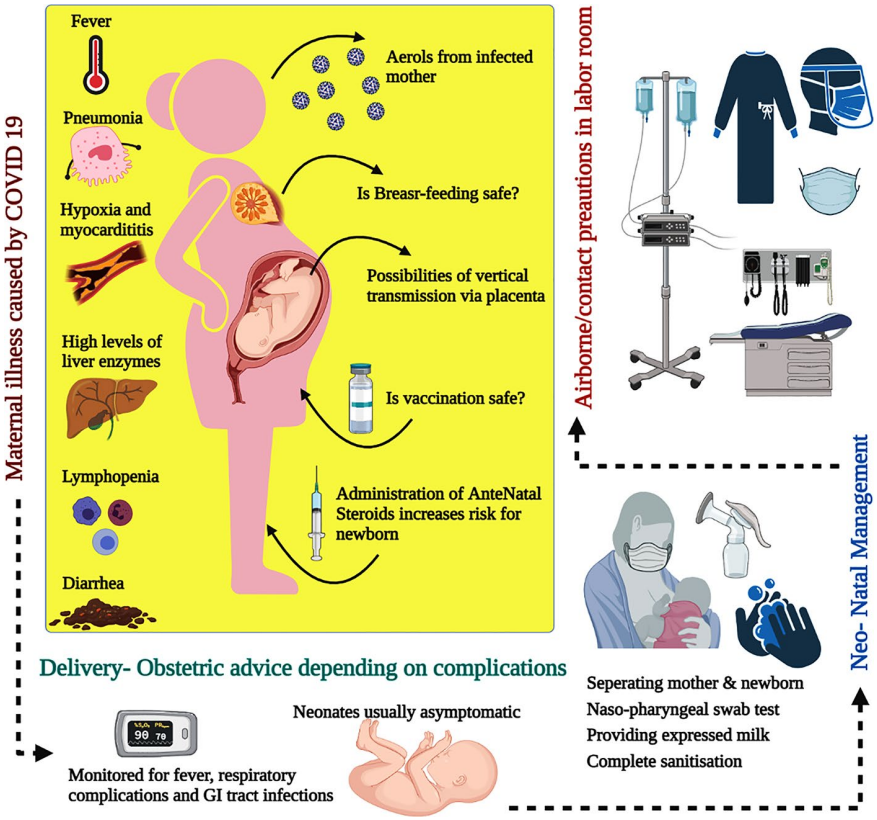

FIGURE 1 Clinical features of pregnant women infected with COVID-19 and the significance of neonatal management and precautionary modules to be followed in the labor room

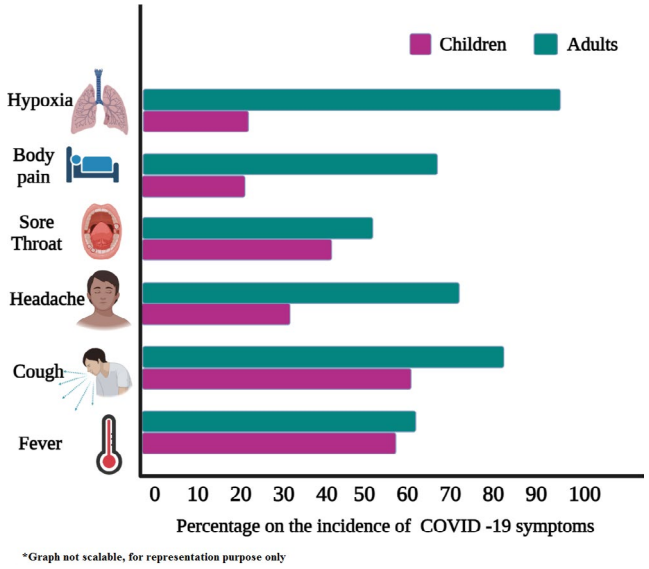

FIGURE 2 Morbidity and description of preliminary symptoms in children and adults testing positive for COVID-19. CDC USA, 2021

children make up 22% of the population), only 1.7% became unwell. Figure 2 shows the initial symptoms recorded in COVID-positive adults and children in the USA between February and April 2020.[27] This information was coherent with previous research reports from the Chinese CDC, which found that most infected children had mild symptoms or were asymptomatic. However, in the new CDC study from the USA, some children developed severe illness: out of 147 children, 5 (3.4%) were admitted to intensive care and 3 (2.0%) died.[28] Infants in Italy reported a higher rate of hospitalization (i.e. out of 95 COVID-19-infected infants, 62% required medical care facilities). The estimated rate of infection between the ages of 1 and 17 years was 14%.[29] The scenario in India was entirely different, with 21.7% of the confirmed cases of COVID-19 aged between 30–39 years, 20.8% aged from 20–29 years, 17.4% aged 40–49 years, and only 2.5% aged 0–9 years. Therefore, the primary reason for the spread of the disease relied on the productive age group (30–39 years) who travelled internationally. Despite the quarantine and checks, the surge in incidence was due to asymptomatic carriers who tested negative at airport screening because symptoms appear virtually immediately after infection. It is significant to understand that children can be asymptomatic but may potentially transmit the virus to others during the preclinical or symptomatic stages.[29]

Reports from Italy showed similar results, with 318 (0.5%) confirmed cases in children aged 0–9 years and 386 (0.7%) in those aged 10–19 years. None of the infected children were admitted to intensive care units and there were no deaths.[30] South Korea had an early surge in cases; the death rate of COVID-19 patients was 10.4% in those aged 80–89 years, 5.4% in 70–79-year-olds, 1.5% in 60–69-year-olds, and 0.4% in 50–59-year-olds. Even lower rates were seen in younger people, dropping to zero in those aged 0–29 years.[31] A similar pattern was observed in Wuhan,[32] where no children were affected between November 2019 and mid-January 2020, while the elderly population was highly vulnerable.

5 | THE THRESHOLD ACE2 RECEPTORS

In general, infants and young children are at high risk and may be admitted to hospital owing to infection in the upper respiratory pathways due to respiratory syncytial virus and influenza virus. The underlying reason is the immature respiratory tract and immune system in this age group.[31] In contrast, COVID-19 had very few pediatric patients worldwide, which has confused clinicians, epidemiologists, and scientists.

ACE2 is a type I membrane protein widely expressed in the lungs (type II alveolar epithelial cells and type II pneumocytes), heart, intestine, and kidneys, where it is essentially involved in the maturation of angiotensin II.[33] ACE2 has been proven to be the functional receptor of severe acute respiratory syndrome-associated coronavirus (SARS-CoV) and, recently, of SARS-CoV-2.[34] Xu et al.[35] modelled the spike protein to identify the receptor for SARS-CoV-2 and confirmed that ACE2 could be the receptor for this virus. Previously, ACE2 was identified as the receptor for SARS-Cov and NL63.[36] Interestingly, the reports of simulation studies revealed that the binding strength between SARS-CoV-2 and ACE2 is weaker than SARS-Cov and ACE2. Thus, SARS-CoV had a much higher specificity and threshold than SARS-CoV-2 for acute virus infection.

Although SARS-CoV-2 and SARS-CoV have a highly homologous genome and share the same host receptor, there is variation in the mechanism of pathogenesis. Zhou et al.[37] conducted virus infectivity studies and reported ACE2 as an essential component necessary for the entry of SARS-CoV-2 to infect HeLa cells.[37] These data indicated ACE2 to be the likely receptor for HeLa cells. However, Cristiani et al.[38] clarified that immature low-level expression of the ACE2 receptor raised the lymphocyte count, and trained/acquired immunity through vaccinations were the underpinned reason for less susceptibility to infection in children. In summary, the above research findings suggested that a low concentration of ACE2 receptors in lung pneumocytes in children rendered a protective effect against severe clinical manifestations of SARS-CoV-2.

6 | THE CONNECTING LOOP: TRANSMISSION CHAIN AND SYMPTOMS

The common symptoms of COVID-19 include cough, throat pain, fever, diarrhea and, notably, pneumonia found prevalent in patients with chronic infection. Neonates acquired SARS-CoV-2 infection through close contact with virus-infected patients or carriers. The characteristic pattern of infection of this disease in infants and children seemed to be unusual and nonspecific. Common symptoms observed during diagnosis of SARS-CoV-2 infection in neonates include raised body temperature, hypoactivity, tachypnea, and abnormalities on chest radiograph. The route of infection may be traced

by contact history, which includes the contagious mode of infection from patients' family members or caregivers diagnosed with SARS-CoV-2 or close contact with someone who tested positive for COVID-19.

Infection may also occur from secondary routes through close contact with pneumonia of unknown cause or living in containment zones of infection. The transmission route takes its origin from aerosols from an infected person and traverses through the upper respiratory passages (nostrils and throat), although the lower airway is the primary target of SARS CoV-2 infection.[39] Figure 3 shows the pipeline of transmission, pathogenesis, and clinical infestation of COVID-19. Low levels of receptors in children on the lower respiratory tract make them less susceptible to further replication of the virus. In contrast, in adults the prevalence of plenty of ACE2 receptors can lead to multiple complications and multilevel diseased conditions (e.g. multiorgan failure). More studies are needed to clearly understand SARS-CoV-2 transmission in the pediatric population, which could improve the level of diagnosis, management, and prevention in the future.

7 | ARE CHILDREN RESILIENT TO COVID-19?

Children infected with SARS-CoV-2 may be asymptomatic. Low levels of ACE2 that disrupt adhesion of the virus to host cells and limit

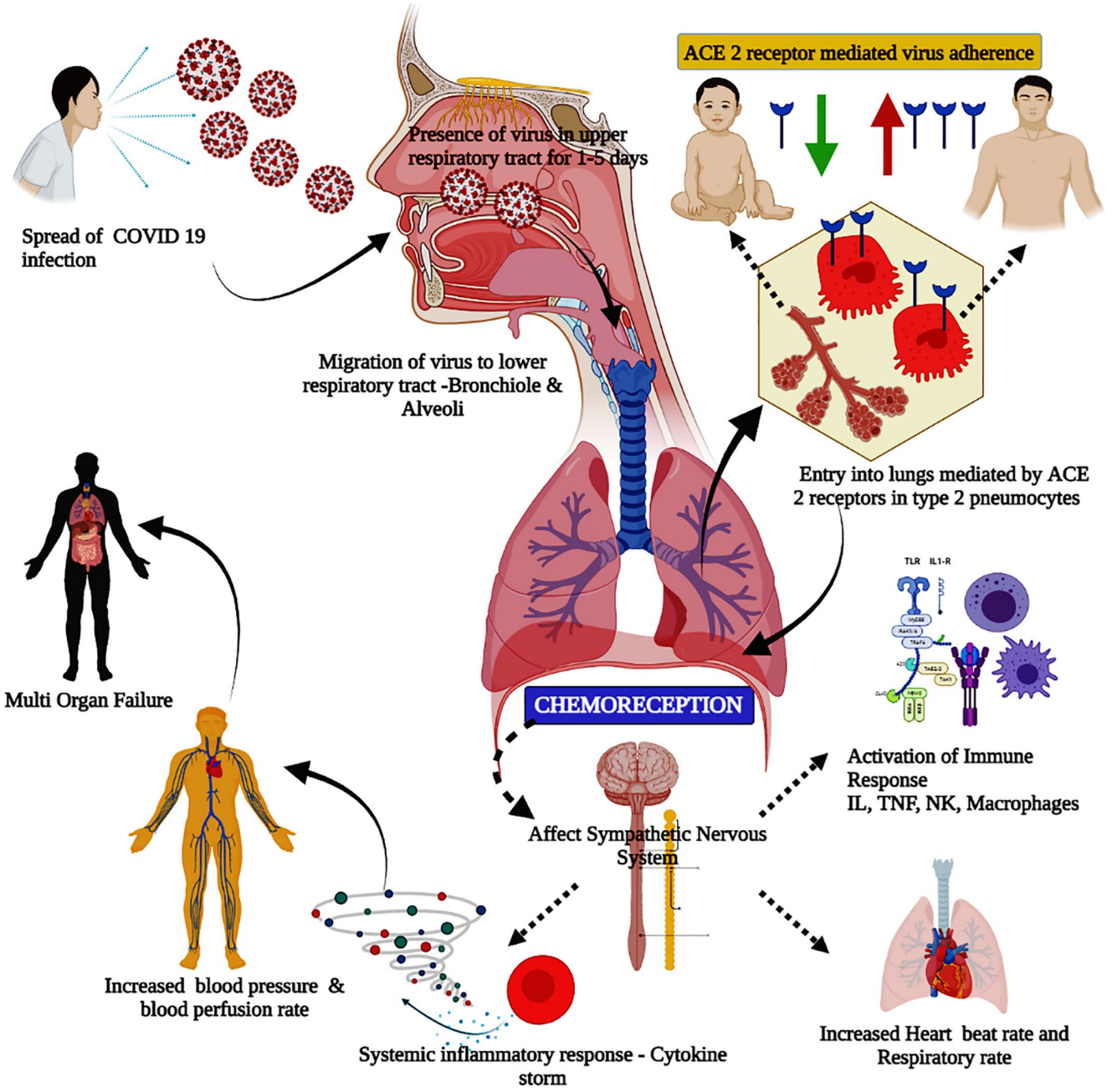

FIGURE 3 The pipeline of transmission and clinical pathogenesis of COVID-19 in children and adults

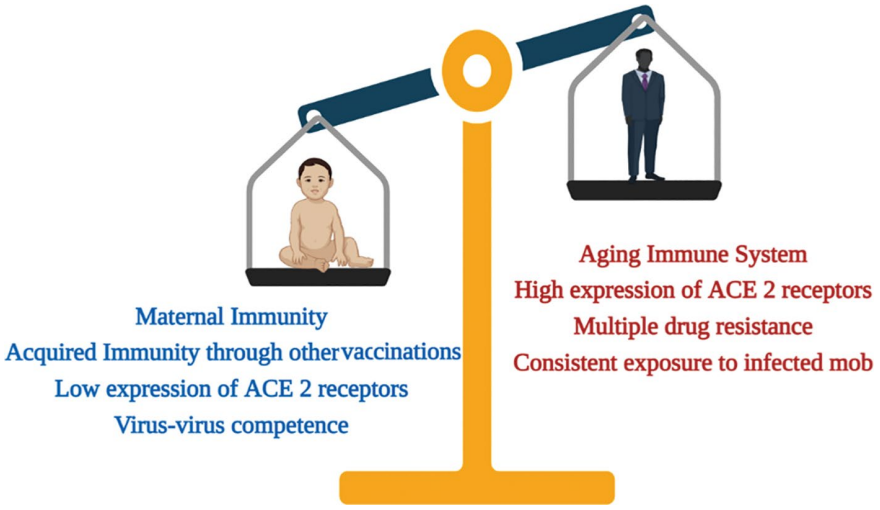

FIGURE 4 Factors associated with SARS-Cov-2 infection in children and adults

the infection process have been linked to children's resilience to COVID-19. Although children carry a high titer of the virus, they suffer less from the disease. Roberts et al.[40] noted the same phenomena from in vivo studies with mice infected with SARS-CoV. Although the virus replicated relatively well, younger animals were resistant to infections, but older animals showed severe clinical complications and mortality. The results conveyed that one-fifth of infected mice aged between 3–4 weeks and all of the mice that were 7–8 weeks old died within a short period.[40] Another similar study showed that young adult mice, at 6 weeks old, cleared SARS-CoV with no significant clinical symptoms, while the same virus in 12-month-old mice exhibited more clinical signs.[41] Thus, it was evident that young mice were infected, but they did not develop the disease. They carried the same virus levels as older mice, but they did not fall sick. Figure 4 depicts the low- and high-risk factors associated with infection among children and adults, respectively.

8 | THE CRUX: IMMUNE SYSTEM

The connecting link between age and disease severity in humans is that the effectiveness of the immune system is inversely proportional to age as it induces more senescence in immune cells and thus becomes inactive. The adaptive immune response had a critical role in SARS-CoV-2 infection, as stated by Medzhitov and Janeway.[42] The stimulation of pro-inflammatory mediators prompted both Th1 ($CD4^+$ and $CD8^+$ T cells) and B lymphocytes, resulting in an efficient virus-specific antibody response. Adults infected by SARS-CoV-2 experienced decreased lymphocyte count and lymphocytopenia,[43] while affected children mainly remained with the normal range of leucocytes, suggesting minor immune dysfunction.[44] Hence, several intrinsic factors such as more ACE2 receptors, trained immunity, and a constitutional high lymphocyte count in children may be the possible reasons for mild disease observed in the pediatric population. In the acute phase of infection, younger children are uniquely susceptible to multisystem inflammatory syndrome in children (MIS-C), which is caused by insufficient antibodies during development. This developmental immunodeficiency is due to polarization of Th2 in the developing fetus and is sustained for the first 10 years of child development. Evidence suggests that MIS-C is due to the gradual development of IgA complexes produced in a Th2 environment to contradict COVID-19 antigens.[45] Zhao et al.[29] explained that morbidity and mortality associated with respiratory virus infection were felt most keenly among the elderly, where the T cells necessary for viral clearance are scarce. Supportive evidence by Zhang et al.[46] suggested that cytotoxic lymphocytes like cytotoxic T lymphocytes and natural killer (NK) cells were pivotal in checking the viral infection; in parallel, the functional exhaustion of cytotoxic lymphocytes was also anticipated with disease progression.

Mysliwska et al.[47] investigated the physiology of NK cells in the vaccinated population and studied the interface between the specific immune protection against the influenza virus and nonspecific immune protection against other viral infections. Elevated levels of NK cells were found before and after immunization.[47] Significantly, NK cells play a more significant role in protecting against influenza and other respiratory viral infections. Nevertheless, frequent viral infections and vaccines induce the immune system to provoke effective defense mechanisms against pathogens.[48] In contrast, Zheng et al.[49] reported that the total number of NK and $CD8^+$ T cells was decreased markedly in patients with SARS-CoV-2 infection. The function of NK and $CD8^+$ T cells ceases with the increased expression of NKG2A in COVID-19 patients. Viral pathogens often induce strong effector $CD4^+$ T cell responses that stimulate the B cell and $CD8^+$ T cell responses.[50] $CD4^+$ T cells were integrated to provide highly effective immune protection against viral pathogens.[51] Thus, the T cell population dominated in the younger age group responsible for repelling the virus.

Children are widely asymptomatic but may play a role in the spread of SARS-CoV-2 in the community. Primary symptoms are similar in adults and children (e.g. fever, cough, and tachypnea), whereas

dyspnea and renal injury are rarely observed in children. The presence of radiological ground-glass lung opacities in children was reported even before the manifestations of the symptoms. However, digestive tract symptoms, such as diarrhea, were most common in pediatric patients. Clinical indicators such as leukocytosis, elevated serum alanine aminotransferase, aspartate aminotransferase, elevated lactate dehydrogenase, high C-reactive protein, and elevated D-dimer were observed in children. Similar to adults, SARS-CoV-2 nucleic acid (RNA) was identified in respiratory and stool samples of children from 23 to 43 days. Therefore, it is uncertain whether asymptomatic RNA detection represented a potentially transmissible virus. Extensive data on the clinical findings in children needs to validate the potential of virus transmission from children.[52]

9 | HERBAL MEDICINE: BOOST TO THE IMMUNE SYSTEM

Traditional Chinese medicine and modern Western medicine are being widely used for the treatment of COVID-19. The pedagogy of traditional medicinal practices, like Ayurveda, from childhood will have notable healthy effects that remain throughout the lifespan. Ayurveda has deep roots in Indian traditional medicine, while Ayurvedic treatments using formulations such as *sudarshan churna*, *talisadi churna*, and *dhanwantara gutika* have been used to treat COVID-19.[53] This case report was one of the first to explore the array of medicines in Ayurvedic pharmacopoeia that can be used to treat mild to critical stages of the disease. In South India, the government categorized the infected population based on the severity of illness and advised the use of Ayurvedic medications to mitigate the spread of COVID-19.[54] The COVID-19 pandemic has caused psychological trauma such as anxiety and depression among the people. Stress and anxiety accelerate the immune system and elevate the higher risk of respiratory tract infections.[54] The Indian Government has promoted the traditional system of Ayurveda as an "immune booster," which can benefit mental health and curtail the risk of infection.[55] Therefore, this is an opportunity to investigate the potential of Ayurveda systems and integrative approaches for providing solutions to the COVID-19 pandemic.[56] In this context, the Government of India's Ministry of Ayush has recommended "Ayush Kwath," an Ayurvedic preparation consisting of medicinal plants including *Ocimum sanctum* (Holy basil), *Cinnamomum zeylanicum* (true cinnamon), *Zingiber officinale* (ginger), and *Piper nigrum* (black pepper) for immunoregulation to control viral infections like COVID-19.[57] The medicines or supplements that are available in the form of churna (tablet), Kashayam (decoction), and powders prepared from a variety of medicinal plants (e.g. *Andrographis paniculata*, *Picrorhiza kurroa*, *Ocimum sanctum*, *Withania somnifera*, *Tinospora cordifolia*, *Bacopa monnieri*, *Centella asiatica*, *Piper longum*, *Phyllanthus emblica*, *Vitis vinifera*, *Elettaria cardamomum*, *Curcuma longa*, *Tagetes erecta*, *Azadirachta indica*) can be used to treat respiratory illness and improve immunity.[58–60]

10 | PREPAREDNESS AND UNDERSTANDING FOR THE FUTURE

COVID-19 has been associated with increased risk of preterm birth, intrauterine growth restriction and low birth weight.[53] However, birth and postnatal symptoms are still due to direct viral infection in the placental tissue/amniotic membrane, which directly impacts the fetus and neonate, leading to higher rates of perinatal mortality and critical monitoring in neonatal intensive care units. Despite the existing situation, more clinical evidence is needed to understand vertical transmission of COVID-19. Indeed, vaccination as a preventive measure for pregnant women appears in the protocols of international agencies including the World Health Organization (WHO), CDC, American College of Obstetricians and Gynecologists, Royal College of Obstetricians and Gynaecologists, and Federation of Obstetric and Gynaecological Societies of India.

Future preparedness involves developing rapid strategies to prepare obstetric units and maternity and neonatal wards to counteract the oncoming wave alerted by health experts.[61] Indeed, it is difficult to anticipate the severity of COVID-19 in children and is challenging to discern the incidence of infection. However, children play a prominent role in community-based viral transmission. Children have immature respiratory responses and have acted as a firewall against the COVID-19 pandemic. Studies have evidenced that children play a crucial role in amplifying the infection and potential transmission loops to elderly populations without being severely affected themselves. Many infectious diseases, including COVID-19, affect children via a completely different mechanism compared with adults. Understanding these differences could yield significant knowledge on disease pathogenesis, mitigation strategies, and development of therapeutics.

11 | CONCLUSION

This review looked at the clinical complexities associated with the effect of COVID-19 in pregnant women and children. It highlighted the distinct pattern of manifestations in children compared with adults, to provide a potent foundation for prevention, diagnosis, treatment, and mitigation of COVID-19 in children. Strengthening the immune system and modification of lifestyle can bring about a robust defense in children against novel antigens like SARS-CoV-2 and other related infections in the future. Awareness of vaccination for children and pregnant women should be accelerated; however, achieving this is a challenging task. Misconceptions on the prophylaxis of vaccines should be rectified to encourage and attain the maximum shield against COVID-19 infection through vaccinations. Recommendations from international health agencies like WHO on natural plant-based medicines to strengthen immunity, improve health of respiratory pathways, and relieve psychological stress should be driven to improve the natural immunity of the population.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

GCDR, BB and AM conceptualized the article. KP, HK, and AM wrote the original draft. GCDR, VT, BB, MP, ME, KP, VA, HK, LP, and PM performed the literature search and selected bibliographic sources. GCDR, KP, and BB performed review and editing. All authors read and agreed to the final version of the manuscript.

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