

REVIEW



## COVID-19 during Pregnancy and Postpartum: I) Pathobiology of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) at Maternal-Fetal Interface

Sreus A. G. Naidu, MS, PharmD<sup>a</sup> , Roger A. Clemens, DrPH, FIFT, CFS, FASN, FACN, CNS, FIAFST<sup>b</sup> , Peter Pressman, MD, MS, FACN<sup>c</sup> , Mehreen Zaigham, BSc, MD, PhD<sup>d</sup> , Kamran Kadkhoda, PhD, SM(ASCP), D(ABMM), D(ABMLI)<sup>e</sup> , Kelvin J. A. Davies, PhD, DSc, MAE, FRSC, FRCP, FLS, FRI<sup>f,g,h</sup> , and A. Satyanarayan Naidu, PhD, FACN, FLS, FISSVD<sup>a</sup> 

<sup>a</sup>N-terminus Research Laboratory, Yorba Linda, CA, USA; <sup>b</sup>University of Southern California, School of Pharmacy, Los Angeles, CA, USA; <sup>c</sup>The Daedalus Foundation, Mount Vernon, VA, USA; <sup>d</sup>Department of Obstetrics & Gynecology, Skåne University Hospital, Malmö, Sweden; <sup>e</sup>Immunopathology Laboratory, Robert J. Tomisch Pathology & Laboratory Medicine Institute, Cleveland Clinic, Cleveland, OH, USA; <sup>f</sup>Division of Biogerontology, Leonard Davis School of Gerontology, The University of Southern California, Los Angeles, CA, USA; <sup>g</sup>Division of Molecular & Computational Biology, Dornsife College of Letters, Arts, and Sciences, The University of Southern California, Los Angeles, CA, USA; <sup>h</sup>Department Biochemistry & Molecular Medicine, Keck School of Medicine of USC, The University of Southern California, Los Angeles, CA, USA

### ABSTRACT

Coronavirus Disease 2019 (COVID-19) triggered by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection has been declared a pandemic by the World Health Organization (WHO) on March 11, 2020. Oxidative stress and its related metabolic syndromes are potential risk factors in the susceptibility to, and severity of COVID-19. In concert with the earliest reports of COVID-19, obstetricians started to diagnose and treat SARS-CoV-2 infections during pregnancy ("COVID-19-Pregnancy"). High metabolic demand to sustain normal fetal development increases the burden of oxidative stress in pregnancy. Intracellular redox changes intertwined with acute phase responses at the maternal-fetal interface could amplify during pregnancy. Interestingly, mother-to-fetus transmission of SARS-CoV-2 has not been detected in most of the COVID-19-Pregnancy cases. This relative absence of vertical transmission may be related to the presence of lactoferrin in the placenta, amniotic fluid, and lacteal secretions. However, the cytokine-storm induced during COVID-19-Pregnancy may cause severe inflammatory damage to the fetus, and if uncontrolled, may later result in autism spectrum-like disorders and brain development abnormalities in neonates. Considering this serious health threat to child growth and development, the prevention of COVID-19 during pregnancy should be considered a high priority. This review summarizes the intricate virulence factors of COVID-19 and elucidate its pathobiological spectrum during pregnancy and postpartum periods with a focus on the putative and complex roles of endogenous and exogenous lactoferrin in conferring immunological advantage to the host.

### KEYWORDS

lactoferrin; coronavirus infections; pregnancy; infant; female

## Introduction

In December 2019, the first reports of an unknown respiratory infection, in some cases fatal, emerged from Wuhan, China. The etiological agent was identified as a novel coronavirus (CoV), related to pathogens that previously caused outbreaks of *Severe Acute Respiratory Syndrome* (SARS) from 2002-2004 and *Middle East Respiratory Syndrome* (MERS) in 2012 (Zhou et al. 2020). This illness named as *coronavirus disease 2019* (COVID-19) triggered by the *Severe Acute Respiratory Syndrome Coronavirus 2* (SARS-CoV-2) (CSG 2020), has been declared a pandemic by the World Health Organization (WHO) on March 11, 2020. COVID-19 is spreading globally at an accelerated rate, with a basic reproductive number ( $R_0$ ) of 2.0 to 2.5, indicating that two to three individuals could be infected from an index patient. By September 1, 2020, COVID-19 infected more than 25,765,168 persons worldwide and killed at least 857,243 (World Health Organization, 2020). Whether this pandemic “fizzles out” or expands into an enduring public health calamity remains to be witnessed.

Obstetricians started to diagnose and treat SARS-CoV-2 infections during pregnancy (“COVID-19-Pregnancy”) and it was proposed that pregnant women were particularly susceptible to SARS-CoV-2 infection and COVID-19 could increase health risks for both mothers and infants during pregnancy (Zaigham and Andersson 2020). It was also suggested that the clinical outcomes of SARS-CoV-2 infections in pregnant women may differ from those in general population; therefore, pregnancy has been considered a potential risk factor for COVID-19 susceptibility as well as for illness and death (Dashraath et al. 2020).

Pregnant women are particularly susceptible to respiratory infections and severe pneumonia due to altered body habitus, physiology, and immune-suppressive state (Jamieson et al. 2006). High metabolic demand to sustain normal fetal development increases the burden of oxidative stress in pregnancy (Thompson and Al-Hasan 2012; Naidu 2013). For example, pregnant women with *Varicella* virus pneumonia have higher case fatality rate (CFR, 35%) than non-pregnant women (11%) (Haake et al. 1990). During the 1918–19 Spanish influenza pandemic, the CFR was 27% for pregnant women (higher in the last trimester), and reached 50% if pneumonia developed (Harris 1919). During the 2002–03 SARS pandemic, nearly 50% of pregnant women were admitted to intensive care, about 33% required mechanical ventilation with CFR reached 25%. Overall, about 57% of the pregnant women in the 1<sup>st</sup> trimester had miscarriage and, 40% women in the 2<sup>nd</sup> to 3<sup>rd</sup> trimester suffered fetal growth restriction (FGR) (Wong et al. 2004). In 2009, the H1N1 influenza pandemic witnessed a higher risk of complications among pregnant women with four times more hospitalizations than the general population (Jamieson et al. 2009). During the MERS outbreak, 91% of pregnant women experienced adverse outcomes. Among neonates, 55% required intensive care with 27% CFR and 18% newborns were delivered premature from mothers with severe maternal respiratory failure (Alfaraj et al. 2019). Also, several studies have demonstrated an increase in the risk for maternal mortality and morbidity with influenza infection as compared to non-pregnant women (Rasmussen et al. 2012; Silasi et al. 2015).

Current knowledge with regards to pathobiological spectrum and risk analysis of SARS-CoV-2 infections in pregnancy (hereafter “**COVID-19-Pregnancy**”) is still preliminary due to limited access to ongoing clinical investigations. Since therapeutics and drug treatments are known to adversely affect the fetal development and pregnancy outcomes, it is of critical importance to understand the role of innate host defense factors that may barricade pathogen transmission from mother to fetus or newborn. Retrospective analyses of the maternal-fetal interface during COVID-19-Pregnancy are needed for better understanding of the novel SARS-CoV-2 and for development of effective protocols to study potential adjunctive prophylactic and clinical management strategies.

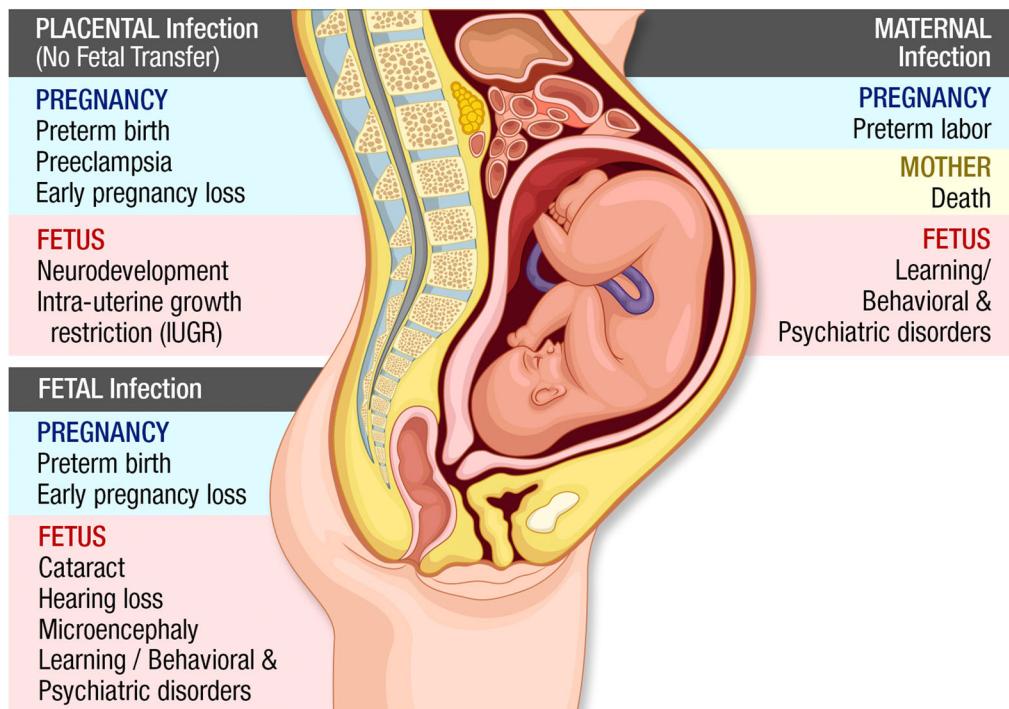
### **Covid-19 during pregnancy (covid-19-pregnancy)**

Due to pregnancy-related physio-anatomical changes, women are susceptible to microbial infections. Furthermore, the maternal-LF and other amniotic defense factors are primed at protecting the fetus and leave the mother vulnerable to viral infections. The cytokines produced by T-helper ( $T_H$ ) lymphocytes regulate both immune and inflammatory responses. The  $T_{H1}$ -type cytokines are pro-inflammatory mediators, which include gamma-interferon (IFN- $\gamma$ ), interleukin (IL)-1 $\alpha$ , IL-1 $\beta$ , IL-6, and IL-12. Conversely,  $T_{H2}$ -type cytokines are anti-inflammatory factors comprised of IL-4, IL-10, IL-13, and transforming growth factor-beta (TGF-  $\beta$ ) (Berger 2000). During pregnancy, the downregulation of pro-inflammatory  $T_{H1}$  cells alter the physiological milieu to an anti-inflammatory  $T_{H2}$  dominant phase to protect the fetus. This shift in the inflammatory cell cascade contributes to overall infectious morbidity by increasing maternal susceptibility to viral pathogens such as SARS-CoV-2.

The difference in cytokine profiles between SARS and COVID-19 infections in non-pregnant patients provide the basis for assessing and extrapolating disease progression and severity in affected pregnant women. Patients with SARS show preferential activation of  $T_{H1}$  immunity resulting in marked elevation of proinflammatory cytokines (IFN- $\gamma$ , IL-1 $\beta$ , IL-6, and IL-12) for at least two weeks after the disease onset, leading to extensive lung damage (Wong et al. 2004). In contrast, patients with COVID-19 show activation of both  $T_{H1}$  and  $T_{H2}$  immunity over similar time frame of disease course, culminating in the presence of IFN- $\gamma$  and IL-1 $\beta$  in addition to IL-4 and IL-10 (Huang et al. 2020). Additionally, elevated levels of IL-6 (the predominant  $T_{H1}$  responder), is associated with an increased risk of mortality in COVID-19 patients (Ruan et al. 2020). However, in COVID-19, an early adaptive immune response is predictive for a less severe disease outcome (Thevarajan et al. 2020). Changes in the hormonal status during pregnancy could influence immune responses against viral pathogens (Littauer et al. 2017). Taken together, the transition to  $T_{H2}$  expression with anti-inflammatory cytokines (IL-4 and IL-10) and other immune adaptations may serve as the predominant immune response to SARS-CoV-2, which may result in lesser severity of COVID-19 compared to non-pregnant individuals (Chen et al. 2020).

Viral infections during pregnancy may result in detrimental clinical outcomes. Viral pathogens at the maternal-fetal interface could affect placental function and may cause pregnancy complications such as miscarriage, intrauterine growth restriction (IUGR), or

## Viral Infections during Pregnancy: Clinical Outcomes



**Figure 1.** Viral infection at the maternal-fetal interface affects both maternal health and fetal development. Any disruption to the placental function results in pregnancy complications such as miscarriage, IUGR, PTB or even early pregnancy loss. Viruses rarely cross the placental barrier; however, when the pathogen does reach the fetus, it may lead to severe birth defects and brain disorders. *Adapted from Racicot and Mor 2017* (Racicot and Mor 2017).

preterm birth (PTB). The placenta functions as a physiological and immunological barrier to prevent viral transfer from mother-to-fetus. However, an immunological response to infection may negatively impact fetal circulation or predispose the mother to an abnormal response. Viral infection of the decidua and/or placenta may result in the production of soluble immune factors that may reach fetus and affect its development. Viruses rarely cross the placental barrier; however, when a pathogen does reach the fetus, it may cause severe birth defects such as microcephaly or even death (Figure 1) (Racicot and Mor 2017). A recent study examined the placentas from sixteen patients with SARS-CoV-2 and compared histopathological findings to control. Placentas from COVID-19 mothers were significantly more likely to show abnormal or injured maternal vessels, and intervillous thrombi (Shanes et al. 2020).

### Covid-19 during postpartum (covid-19-postpartum)

Several viruses affect the course of pregnancy and may vertically transmit the infection. For example, pregnant women with influenza (*H1N1 virus*) are at increased risk of morbidity and mortality (Mak et al. 2008). Also, mother-to-child transmission (MCTC) of *Human Immunodeficiency Virus* (HIV) infection during pregnancy is still a major

concern. In 2008, an estimated 430,000 HIV-infected infants were born worldwide (Mofenson 2010). With regards to COVID-19, analyses of amniotic fluid, cord blood, and neonatal throat swab samples at birth have all returned negative for SARS-CoV-2. Therefore, any possible intrauterine transmission of COVID-19 during late stages (3<sup>rd</sup> trimester) of pregnancy was ruled out (Chen et al. 2020). This clinical observation was similar to the SARS outbreak in 2002, where no evidence was found for MCTC of CoV (Shek et al. 2003; Wong et al. 2004). Initial results showed that breastmilk from mothers with COVID-19 are free from SARS-CoV-2. A recent study analyzed daily, consecutive breast milk samples from two SARS-CoV-2 infected mothers (Groß et al. 2020). SARS-CoV-2 was detected from one of the mothers during four consecutive days, which coincided with a positive diagnostic test of that newborn. The mother in question has been wearing a surgical mask since the onset of symptoms, followed safety precautions when handling and feeding the infant (including proper hand and breast disinfection, sterilization of milk pumps, tubes, and other recommended safety procedures). It is still unclear whether the infant was infected by breastfeeding or other modes of transmission. Therefore, the possibility of maternal-fetal transmission cannot be completely ruled out and a close monitoring of the newborn from mothers with COVID-19-*Pregnancy* is warranted. The pathobiology of COVID-19-*Pregnancy* and COVID-19-*Postpartum* is outlined (see INSET).

### ***Pathobiology of COVID-19-pregnancy and COVID-19-postpartum***

Few retrospective studies with small sample sizes of SARS-CoV-2 positive COVID-19-*Pregnancy* cases have been reported since December 8, 2019 (Hong et al. 2020; Liu et al. 2020; Zhu et al. 2020); therefore, caution should be exercised while interpreting these clinical findings. Furthermore, a majority of the admitted patients in these cases are in the 3rd trimester; therefore, the possibility of intrauterine vertical transmission of SARS-CoV-2 during the 1<sup>st</sup> or 2<sup>nd</sup> trimester is not fully known (Chen et al. 2020; Zhang et al. 2020). A study of SARS-CoV-2 positive cases from 108 pregnant women between December 8, 2019, and April 1, 2020 (mostly originated from China, also included incidents from Sweden, USA, Korea, and Honduras), summarized the clinical features of COVID-19-*Pregnancy* (Zaigham and Andersson 2020).

***Signs and symptoms:*** Pregnant women with COVID-19 are commonly admitted with fever (68%), with less frequent symptoms such as persistent dry cough (34%) with malaise (13%) and dyspnea (12%), while diarrhea was observed in 6% cases (Zaigham and Andersson 2020).

***Maternal characteristics:*** Mean maternal age ranged from 29-32 years and women with COVID-19-*Pregnancy* are mostly in their 3<sup>rd</sup> trimester. Twenty-two pregnant women (20%) in early gestational weeks were discharged, undelivered, without major complications. Mean gestational age varied and birth before 37 completed weeks of gestation was not uncommon (42%). These patients also had other co-morbidities or complications with their pregnancies such as preeclampsia, gestational diabetes, hypothyroidism, placenta previa, previous uterine surgeries etc (Dashraath et al. 2020; Zaigham and Andersson 2020).

**Mode of delivery:** Cesarean section accounted for 92% of all COVID-19-*Pregnancy* deliveries; however, successful vaginal delivery was reported in 8% cases. Fetal distress was common indication for cesarean sections (Chen et al. 2020; Liu et al. 2020). Lymphocytopenia (59%) with elevated C-reactive protein (70%) was noted in 91% of COVID-19-*Pregnancy* patients those delivered by cesarean section. Three intensive care unit (ICU) admissions with no maternal deaths were recorded. Although most mothers were discharged without major complications, two cases of maternal ICU admission were reported (Breslin et al. 2020). Therefore, severe maternal morbidity indications cannot be ruled out during the COVID-19-*Pregnancy*.

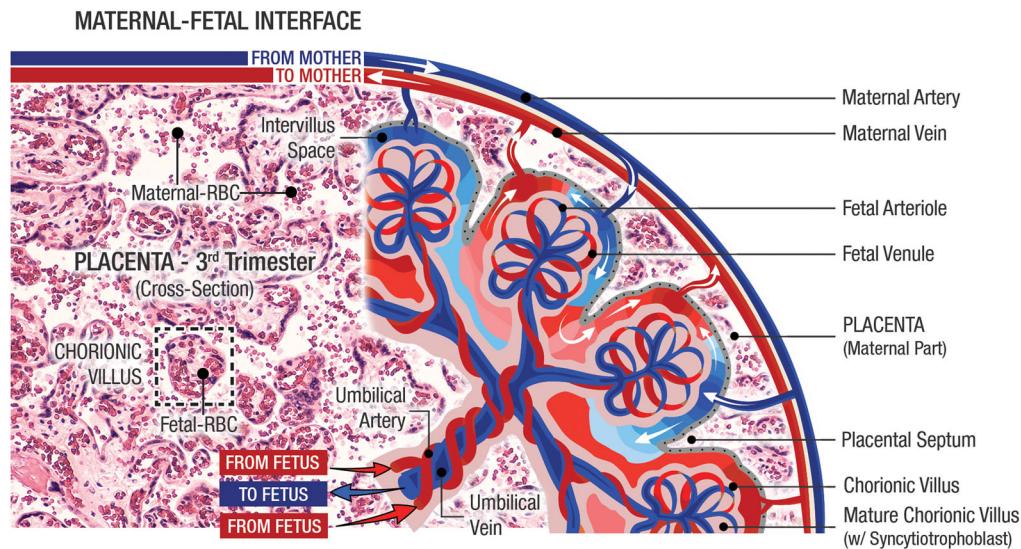
**Postpartum outcomes:** Most COVID-19-*Pregnancy* cases had no adverse events. However, six admissions were reported to the neonatal ICU (Zhu et al. 2020). The prominent clinical symptom among the newborns was shortness of breath accompanied by fever, thrombocytopenia, abnormal liver function, tachycardia, vomiting, and pneumothorax (Zhu et al. 2020). There is one case each of intrauterine fetal death and neonatal death, while two pregnant mothers with *Multiple Organ Dysfunction Syndrome* (MODS) and *Acute Respiratory Distress Syndrome* (ARDS) underwent an emergency cesarean section. One neonate was stillborn, and the mother required intubation with ventilator support and *Extra-Corporeal Membrane Oxygenation* (ECMO) (Liu et al. 2020). Neonatal death was reported of a male infant born at 34 weeks and 5 days gestational age with an Apgar Score of 8 at 5 min. This neonate developed refractory shock, gastric bleeding with multiple organ failure, and disseminated intravascular coagulation. A throat swab at the 9th day of post-delivery was negative for SARS-CoV-2; however, a poor immune response and massive viremia were considered as probable causes of this neonatal death (Zhu et al. 2020).

**Maternal-fetal transmission** of SARS-CoV-2 was not detected in most of the COVID-19-*Pregnancy* cases; however, one neonate was found qRT-PCR positive, 36 h of post-delivery despite isolation from the mother (Wang et al. 2020). Careful surveillance of pregnant women with COVID-19 and clinical measures to prevent viral transmission to the neonate are warranted.

**Maternal-neonatal transmission:** Out of 75 newborns tested, one (1.3%) was positive for SARS-CoV-2 infection with transient lymphocytopenia and abnormal liver function (Wang et al. 2020). Out of 33 neonates born to mothers with COVID-19 (in Wuhan, China), three infants delivered by cesarean section were tested positive for SARS-CoV-2, two days after birth (Zhang et al. 2020). However, another analysis of COVID-19-*Pregnancy* with 38 patients showed no evidence for intrauterine transmission. Nonetheless, lymphocytopenia and thrombocytopenia were evident in seemingly healthy babies born to SARS-CoV-2 infected women (Schwartz 2020).

## Immuno-redox biology at maternal-fetal interface

Pregnancy is a complex state of immunological dichotomy. The maternal-fetal interface of the decidua provides immune tolerance toward the “foreign” allogeneic fetus; while simultaneously maintaining immune competence to wade off invading pathogens (Figure 2). The interface also facilitates the transfer of O<sub>2</sub>, CO<sub>2</sub>, and nutrients to support the synthesis of different hormones, enzymes, and cytokines (Yang et al. 2019).



**Figure 2.** The maternal-fetal interface of the decidua provides immune tolerance toward the “foreign” allogeneic fetus, while simultaneously maintaining immune competence to wade off invading pathogens. It also facilitates the transfer of  $O_2$ ,  $CO_2$ , and nutrients to support the synthesis of different hormones, enzymes, and cytokines. Placental syncytiotrophoblasts express LF, an extra-embryonic maternal allogeneic recognition factor for trophoblastic cell protection. *Cross section of 3<sup>rd</sup> trimester placenta:* Erythrocytes (RBC) inside the chorionic villi are fetal, whereas the RBC between the villi are maternal.

This unique immune dichotomy in pregnancy is achieved through a programmed cytokine switch from  $T_{H1}$  to  $T_{H2}$ . Progesterone, estradiol, prostaglandin D2, and leukemic inhibitory factor during pregnancy promote the  $T_{H2}$  cytokine profile and are responsible for the  $TH_2$  bias associated with normal pregnancy (Sykes et al. 2012). This  $T_{H2}$ -related immune shift is a major predisposing factor for COVID-19 infection in pregnant women. The increased susceptibility causes suppression of cell-mediated immunity, as pregnancy shifts away from proinflammatory  $T_{H1}$  to  $T_{H2}$  immune environment (Jamieson et al. 2006; Mor and Cardenas 2010).

### ***Immune transitions at maternal-fetal interface***

The immunology of pregnancy is a combination of signals and responses from the maternal immune system and the fetal-placental immune system. Signals originated in the placenta modulate maternal immune response in the presence of potential pathogen (Mor and Cardenas 2010). The trophoblast, the cellular unit of the placenta, releases antimicrobial peptides such as human  $\beta$ -defensins, secretory leukocyte protease inhibitor (SLPI) and express toll-like receptors (TLR-3, TLR-7, TLR-8, and TLR-9) (Abrahams et al. 2006; Koga and Mor 2008). Placental syncytiotrophoblasts express “maternal lactoferrin” (LF), an extra-embryonic response to inflammation, and maternal allogeneic recognition to protect trophoblastic cells (Thaler et al. 1999). Placental-LF, IFN- $\beta$ , and

SLPI production by trophoblast cells, in response to a viral infection at the maternal-fetal interface, may represent a potential mechanism by which the placenta appears to markedly inhibit transmission of viral infection to the fetus during pregnancy. Together with the trophoblast factors in placenta, LF may be critical in providing the first line of defense against viral infections (Thaler et al. 1999; Srinivas et al. 2006). Although viral infections are common during pregnancy, transplacental passage and fetal infection appear to be the exception rather than the rule (Mor and Cardenas 2010).

### ***Redox transitions at maternal-fetal interface***

Partially reduced reactive oxygen species (ROS) such as the free radical, superoxide, and the non-radical mild oxidant, hydrogen peroxide are actively involved in placental biology. ROS are generated at the maternal-fetal interface at the level of decidual, trophoblast and mesenchymal components (Bevilacqua et al. 2012). In normal conditions, ROS produced in low concentrations participate in different cellular functions such as signaling, regulation of redox-sensitive transcription factors and protein kinases for cell survival, proliferation, adaptive homeostasis, and apoptosis (Davies 2016). Physiological ROS generation is also associated with host defense mechanisms such as phagocytosis and microbicidal activities (Naidu 2013). Pregnancy is a physiological state accompanied by a high energy demand of many physiological functions with an increased oxygen demand and elevated oxidative stress (John et al. 2012). Placental oxidative stress with resultant damage to the syncytiotrophoblast, secondary to early onset of the maternal circulation cause miscarriages (Hempstock et al. 2003). Infection-induced inflammation and other risk factors may cause redox imbalance, increase the release of free radicals and other oxidants, and rapidly consume antioxidant defenses. In turn, oxidative stress can initiate intracellular signaling cascades that increase the production of pro-inflammatory mediators. Oxidative stress causes placental dysfunction and leads to abnormal fetal development. Prevention of placental oxidative stress is important to ensure positive birth outcomes (Xu et al. 2018). Oxidative stress and the ensuing severe inflammatory response ("cytokine storm") are implicated in the pathogenesis of COVID-19 (Delgado-Roche and Mesta 2020). Therefore, monitoring of redox during COVID-19-Pregnancy may provide a rapid prognostic advantage.

### **Covid-19 paradox**

CoVs have a remarkable potential to change host tropism. The divergent mechanisms by which CoVs enter host cells, and subsequently spread intercellularly, may explain the remarkable transmission of these viral pathogens into new hosts, including humans (Hulswit et al. 2016). The tremendous pandemic potential of CoVs was proven in the past two decades by three global outbreaks of deadly pneumonia: the SARS-CoV, the MERS-CoV and the ongoing SAR-CoV-2 pandemic. One of the primary determinants of CoV tropism is the spike (S) protein for viral entry. Trimers of the S-protein facilitate the initial steps of viral pathogenesis: i) viral docking to a cell surface receptor (CSR) and ii) fusion of the viral and cellular membrane. Interestingly, S-protein also contains the principal antigenic domains and is the target of neutralizing antibodies.

The prevalence of community acquired CoVs, immunizations with CoV/influenza vaccines with shared antigenic epitopes, and the consequential anamnesis may lead to “original antigenic sin (OAS)” (Kadkhoda [2020](#); Roncati and Palmieri [2020](#)). Considering the inherent genetic flexibility of CoV S-proteins, it is possible that new outbreaks with novel viral mutants or their genetic variants may emerge in the future.

### ***Original antigenic sin (OAS)***

The immunological imprint established by the original virus infection governs the antibody response thereafter, which is conventionally known as the doctrine of the “Original Antigenic Sin”. Some viruses (e.g. CoVs, HIV, HBV) are initially controlled by cytotoxic T-lymphocytes, but may subsequently escape through mutation of the relevant T-cell epitope. Some of these mutations preserve the normal binding to MHC class-I molecules, but present an altered surface to the T-cell antigen receptor (Klenerman and Zinkernagel [1998](#)). Therefore, human individuals primed with a virus (i.e. SARS-CoV) may respond to a subsequent infection by related virus bearing-epitope variant (i.e. SARS-CoV-2) with a CTL response directed against the initial epitope rather than against the new variant epitope. This phenomenon of ‘original antigenic sin (OAS)’ was initially described with influenza and is an asymmetric pattern of protective antibody cross-reactivity determined by exposure to previously existing strains. OAS leads to impaired clearance of variant viruses infecting the same individual and may enhance the immune escape of mutant viruses evolving in an individual host.

The genome of the SARS-CoV-2 shows 89% nucleotide identity with bat-SARS-like-CoVZXC21 and 82% with that of human SARS-CoV (Chan et al. [2020](#)), as well as homology with all the encoded proteins of SARS-CoV (Xu et al. [2020](#)). During the SARS outbreak, the onset of ARDS (“cytokine storm”) coincides with antiviral IgG sero-conversion in 80% of patients (Peiris et al. [2003](#)). Patients that rapidly develop S-protein neutralizing antibodies also show higher mortality rate (Zhang et al. [2006](#)). An incompetent immune response against the virus mutant (i.e. SARS-CoV-2) due to OAS, may produce high levels of cross-reactive antibodies, elevate inflammatory response, and facilitate the cellular entry of viral pathogen. Intracellular localization of virus could trigger a massive release of cytokines (“cytokine storm”), as observed in many fatal cases of COVID-19 (Mehta et al. [2020](#)). The strongest objective evidence that common CoVs implicate OAS in COVID-19 was recently presented (Grifoni et al. [2020](#)), in which over 50% of donors from 2015-2018 had SARS-CoV-2-positive CD4+ T cells responsive to SARS-CoV-2 peptide mega-pools.

### ***Intrinsically disordered regions (IDRs)***

Viruses, with their compact genomes, small proteomes, and high adaptability for rapid changes in their biological and physical milieu, utilize several advantages of intrinsic disorder. Viral proteins are generally rich in intrinsic disorder with intrinsically disordered regions (IDRs). IDRs are commonly used by viruses to invade and hijack various host systems, to infect and propagate in hostile habitats and to manage an energy-efficient usage of genetic material (Xue et al. [2010](#)).

Recent shell disorder analysis predicted a high resilience of the SARS-CoV-2 outside the body and in body fluids (Goh et al. 2020). Based on the “percentage intrinsic disorder (PID)” of nucleocapsid (N) and membrane (M) proteins, CoVs are clustered into three groups: i) the SARS-CoV (M PID = 8%, N PID = 50%) was listed under Category B, in which viruses have intermediate levels of both respiratory and fecal-oral transmission potentials; ii) the MERS-CoV (M PID = 9%, N PID = 44%) is in Category C, with lower respiratory transmission potential and higher fecal-oral transmission capabilities; iii) the SARS-CoV-2 (M PID = 6%, N PID = 48%) was listed in Category B, based on specific disorder distribution. SARS-CoV-2 is unique with its hardest protective outer shell, (M PID = 6%) among the CoVs; suggests a high resilience of the virus in saliva, other body fluids, and outside the body. Therefore, an infected host is likely to shed significant numbers of SARS-CoV-2 and the virion may remain active for extended time, depending on the surface and environment, and present a potentially high infectious rate.

**Intrinsically Disordered Proteins (IDPs)** are characterized by their biased amino acid composition and low sequence complexity with low content of bulky hydrophobic amino acids. Such protein sequences are unable to fold spontaneously into stable, well-defined globular 3-D structures. However, these sequences are dynamically disordered and fluctuate rapidly over a continuum of conformational space ranging from extended statistical coils to collapsed globules (Dyson and Wright 2005). Some proteins are entirely disordered, while others contain disordered sequences, referred to as IDRs, in combination with structured globular domains. IDPs function as hubs in protein interaction networks (Dunker et al. 2005). Furthermore, IDPs play a pivotal role in the ordered assembly of macro-molecular machines (i.e. ribosomes), in the organization of chromatin, in the assembly/disassembly of microfilaments and microtubules, in the transport through nuclear pore, in the binding and diffusion of small molecules, in the activity of protein and RNA chaperones as well as flexible “entropic” linkers to separate functional protein domains (Wright and Dyson 2015; Uversky 2019).

### ***Unique virulence traits***

Surface glycoproteins of enveloped viruses require thiol/disulfide balance to mediate virus/cell binding and membrane fusion. Chemical manipulations or charge rearrangements with reducing agents or free sulphydryl reagents affect virus/cell interaction (Lavillette et al. 2006). The presence of a positively charged, polybasic cleavage site in hemagglutinin (HA) is a signature of virulent influenza viruses (Steinhauer 1999). Acquisition of polybasic cleavage sites in HA, by insertion or recombination, converts low-pathogenic avian influenza viruses into highly virulent forms. Insertion of a furin cleavage site in SARS-CoV at the S1-S2 intersection enhances cell-cell fusion without affecting viral entry (Follis et al. 2006). CoVs have evolved multiple proteolytic strategies to activate S-protein. Several host proteases, such as furin, trypsin, trans-membrane protease/serine (TMPRSS), and cathepsins could process the S-protein. Furin cleaves S-protein at a polybasic cleavage site (minimal motif R-X-X-R) during its biosynthesis in the trans-Golgi compartments or during virus entry in endosomes (Sun et al. 2020). Trypsin and TMPRSS cleave at the monobasic site of S-protein, which takes place at the

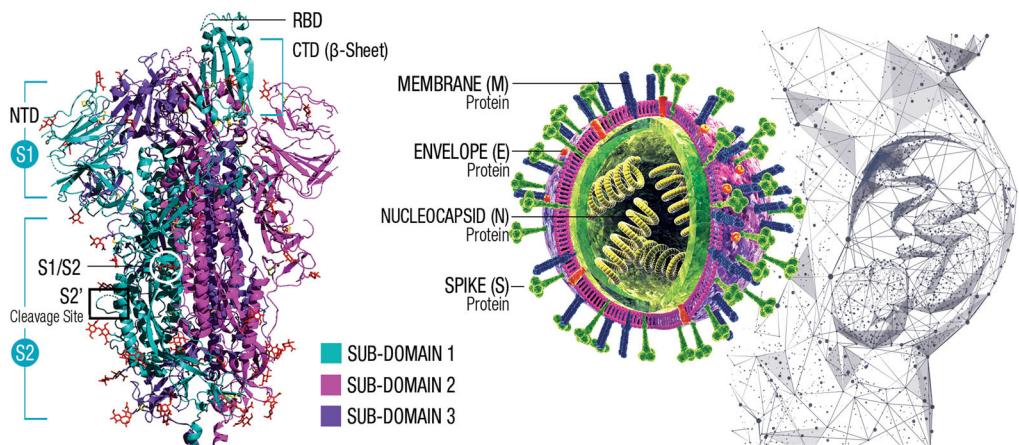
cell surface. Cathepsins, the ubiquitous lysosomal enzymes with broad substrate specificity, cleave S-protein during the viral entry (Millet and Whittaker 2015).

SARS-CoV-2 has acquired a polybasic cleavage motif (RRAR) at the S1/S2 intersection of S-protein, which is processed during biosynthesis (Walls et al. 2019). The presence of a furin cleavage site sets SARS-CoV-2 S apart from SARS-CoV S that possesses a monobasic S1/S2 cleavage site processed upon entry of target cells (Millet and Whittaker 2015; Coutard et al. 2020). The ubiquitous expression of furin-like proteases could expand SARS-CoV-2 cell and tissue tropism, relative to SARS-CoV, as well as increase its transmissibility and/or alter its pathogenicity. The presence of hepta-nucleotide slippery sequence in ORF1 (which results in ribosomal frame shifting) and the occurrence of transcription regulatory sequences between ORFs (which results in discontinuous transcription), both are unique features of COVID-19 infection cycle (Jain et al. 2020). For SARS-CoV-2, it was shown that TMPRSS2 primes S-protein, the cathepsins B and L are only required in the absence of this protease (Hoffmann et al. 2020). Furthermore, a leading proline residue has been inserted to the cleavage sequence (PRRA). The structural turn created by the proline residue may add O-linked glycans to Serine<sup>673</sup>, Threonine<sup>678</sup>, and Serine<sup>686</sup> residues flanking the cleavage site and unique to SARS-CoV-2 (Andersen et al. 2020). The amino acid sequence in RBD of S-protein of SARS-CoV-2 which is critical for its docking to cellular receptor is different in SARS-CoV. The predicted O-linked glycans could create a “mucin-like domain” to shield antigenic epitopes or key residues on the SARS-CoV-2 S-protein. Several viruses use mucin-like domains as glycan shields to evade immune defense (Bagdonaitė and Wandall 2018). An extensive glycan shield could obstruct the CoV S-protein surface. Thus, CoVs use molecular trickery, based on epitope masking with glycans and activate conformational changes, to evade immune defense of the infected host (Walls et al. 2016; 2016).

## **Adhesins (attachment factors) of CoV**

Viruses are mobile genetic particles with either an RNA or DNA genome surrounded by a protective, virus-coded protein shield, the “capsid”. They are obligate intracellular parasites and their propagation depends on specialized host cells that provide complex metabolic and biosynthetic machinery (Flint et al. 2015). CoVs are enveloped, spherical or pleiomorphic viruses, with typical sizes ranging from 80 to 120 nm. They possess a 5' capped, single-strand positive sense RNA genome, with a length between 26.2 and 31.7 kb, the longest amongst all RNA viruses. The genome is composed of 6 to 10 open reading frames (ORFs). The first ORF comprises two-thirds of the genome and encodes the replicase proteins, whereas the last third contains the structural protein genes in a fixed order: S-E-M-N (Belouzard et al. 2012). The genome is packaged into a helical “nucleocapsid” (N) surrounded by a host-derived lipid bilayer. The virion envelope contains at least three viral proteins, the “spike” (S) protein, the “membrane” (M) protein, and the “envelope” (E) protein (Figure 3). The M and E proteins are involved in virus assembly, whereas the S-protein facilitates the viral entry. SARS-CoV-2 genome displays a high degree of plasticity in terms of gene content and recombination. Also, the relatively large genome increases the probabilities for adaptive mutations, which is relatively easy for the S-protein to exploit multiple cellular receptors for virus attachment and

### SARS-CoV-2 'Spike' (S) Protein



**Figure 3.** (Left) SARS-CoV-2 spike protein side view (5-HT2AR/Wikimedia). Homotrimer. RBD binds human ACE2 receptors through which SARS-CoV-2 attaches to and infects human lung cells. Sub-domain monomers are shown as monomer-1 (teal), monomer-2 (magenta) and monomer-3 (purple). (Right) The virion envelope contains at least three viral proteins, the “spike” (S) protein, the “membrane” (M) protein and the “envelope” (E) protein. The M and E proteins are involved in virus assembly, whereas the S-protein facilitates the viral entry. The viral genome is packaged into a helical “nucleocapsid” (N) surrounded by a host-derived lipid bilayer.

entry (Sun et al. 2020). The versatile mechanisms of viral attachment, host cell invasion, and subsequent inter-cellular spread, may explain, the remarkable adaptability and transmission of SARS-CoV-2 across different hosts, including humans.

### **Spike (S)-protein**

S-protein is the major determinant of cell tropism and inter-species transmission of SARS-CoV-2 (Ou et al. 2020). S-protein docks the CoV to host cell surface receptor (CSR) and subsequently catalyzes the virus entry by membrane fusion. The S-protein is a type I trimeric transmembrane glycoprotein with *S1-domain*, an N terminal cleavable signal peptide (a large heavily N-glycosylated ectodomain with 60–90 sugars per trimer); *S2-domain*, a transmembrane region; and *S3-domain*, a cytoplasmic tail containing a cluster of S-acylated cysteine residues (Hulswit et al. 2016; Li 2016). Specific proteases cleave the S1 ectodomain (with “receptor-binding domain”, RBD) and the S2 domain (that catalyzes membrane fusion) (Walls et al. 2016). The S1 domain is further divided into an N terminal domain (NTD) and a C terminal domain (CTD). The NTD exhibits a structural fold as human galectins; therefore, any sugar present at the host cell surface serves as a virus attachment factor. The CTD binds to ‘angiotensin-converting enzyme 2’ (ACE2), the host CSR (Figure 3). The CTD contains two sub-domains, i) a core structure with a 5-stranded antiparallel  $\beta$ -sheet, and ii) the actual RBD, which determines the receptor-binding specificity. Structural analysis of the RBD-ACE2 complex revealed that most S-residues that interact with ACE2 are identical between SARS and COVID-19 viruses (Sun et al. 2020). However, certain motifs are unique, including an

important salt bridge in ACE2 that bind to S-proteins of SARS and COVID-19 viruses. These variations might explain the high affinity S-protein interactions of SARS-CoV-2 with ACE2 (Wrapp et al. 2020). More than one RBD raises the question on whether RBDs operate independently, and if so, whether one RBD provides complete infection competence, while the other remains as an inactive domain (Qing et al. 2020). S-protein is a critical virulent factor of COVID-19, responsible for tissue tropism, host range, and one of the main targets for neutralization antibodies and vaccine design.

### **Membrane (M)-protein**

M-protein is important during the early stages of certain CoV infections. The combined activity of S- and M-proteins is a prerequisite for an effective infection of certain tissue sites. Human CoV NL63, a common respiratory virus, uses heparan sulfate proteoglycans (HSPGs) for viral attachment. Its entry into the host CSR is mediated by M-protein (Naskalska et al. 2019).

### **Cell surface receptors (CSRs) for CoV interactons**

Receptor recognition is the first step of viral infection, a key determinant of host cell/tissue tropism. CoVs have evolved complex host CSR recognition patterns. After binding to CSR, the S-protein catalyzes fusion between virus/cell membranes and inserts the viral genome into the cytosol. In addition to ACE2, the S-protein may bind to four other protein CSRs; and recognize various sialosides and different GAGs as cellular targets *via* lectin-type interactions. Some of these SARS-CoV-2 binding to host cells are predicted from CSR interactions of other CoVs. This wide spectrum of CSR binding attribute makes SARS-CoV-2 a versatile, multi-opportunistic pathogen.

### **Protein-based CSRs**

In addition to interactions with CoVs, the protein-based putative CSRs on human epithelia have specific physiological functions.

- **Angiotensin Converting Enzyme 2 (ACE2)** is a zinc-dependent carboxypeptidase that cleaves one residue from the C terminus of angiotensin peptide and regulates blood pressure (Donoghue et al. 2000; Kuba et al. 2005). ACE2 protects against severe acute lung failure; however, COVID-19-induced down-regulation of ACE2 promotes lung injury (Zou et al. 2020). Binding of SARS-CoV S-protein with human ACE2 (hACE2) correlates with increased viral transmission and disease severity in humans (Li et al. 2005).
- **Glucose Regulated Protein 78 (GRP78)** is found in the lumen of the endoplasmic reticulum (ER) and regulates programmed cell death (“apoptosis”) or differentiation by inhibiting the enzyme-cascade during protein synthesis. GRP78 is released into the cell membrane during oxidative stress and serves as a COVID-19 receptor to facilitate viral entry into the host cell (Ibrahim et al. 2019; 2020).

- **Aminopeptidase N (APN)** is a zinc-dependent membrane proteinase that cleaves one residue from the N terminus of many physiological peptides and plays a multifunctional role as in pain regulation, blood pressure regulation, and tumor cell angiogenesis (Luan and Xu 2007).
- **Dipeptidyl Peptidase 4 (DPP4)** is a serine exopeptidase that cleaves two residues from the N terminus of many physiological peptides. DPP4 is known to cleave broad range of substrates including growth factors, chemokines, neuropeptides, and vasoactive peptides. DPP4 functions include immune regulation, signal transduction, and apoptosis (Reinhold et al. 2002).
- **Carcinoembryonic Antigen-related Cell Adhesion Molecule 1 (CEACAM1)** also known as CD66a, is a cell-cell adhesion glycoprotein located on leukocytes, epithelia, and endothelia. Multiple cellular activities of CEACAM1 include the differentiation and arrangement of tissue three-dimensional structure, angiogenesis, apoptosis, tumor suppression, metastasis, and the modulation of innate and adaptive immune responses (Tan et al. 2002).

### **Lectin-type CSRs**

Glyco-conjugates decorate many proteins and fats on cell surfaces and function in many biological processes such as immunity and cell-cell communication (Schwegmann-Wessels and Herrler 2006; Ghazarian et al. 2011). Such sugar-mediated lectin-type interactions facilitate the later stages of virus propagation through cell-cell membrane fusion, without requiring protein receptors. Thus, lectin-type interactions promote CoV infection and support the intercellular spread of CoV infections through syncytial development. Adaptive mutations in the lectin-binding spike domains could increase the intercellular expansion process. These findings raise the possibility that the lectin-like properties of many CoVs may contribute zoonotic transmission and intercellular spread within infected host species. The receptor-interacting site is conserved in all CoV S-proteins known to attach to 9-O-Ac-sialoglycans and shares architectural similarity with the ligand-binding pockets of CoV HEs and influenza virus C/D HEF glycoproteins, thus highlighting common structural principles of recognition (Bakkers et al. 2016; Tortorici et al. 2019).

**Sialosides:** Sialic acids are ubiquitous terminal residues of glycoconjugates that result due to modifications of the core N-acetyl neuraminic acid moiety (Neu et al. 2011; Stencel-Baerenwald et al. 2014). Sialic acids play a role in virus-cell binding, viral spike protein-directed cell-cell fusion, and resultant spread of CoV infections. Sialoside-mediated CoV binding to host cells require transmembrane protein receptors for subsequent virus infection (Qing et al. 2020). Multivalent interactions with sialosides and/or further attachment to putative proteinaceous receptors promote membrane fusion. Domain A of CoV S-protein mediates viral attachment to oligosaccharide receptors. The human CoV-OC43 interacts with 9-O-Ac-Sia (Peng et al. 2011) and the MERS-CoV binds to  $\alpha$ -2,3-linked (and to a lesser extent to  $\alpha$ -2,6-linked) sialic acids, with sulfated sialyl-Lewis X being the preferred binder (Li et al. 2017).

**Glycosaminoglycans (GAGs):** Many viruses take advantage of host dependence on interaction of several extracellular proteins with GAGs and use heparan sulfate

proteoglycan (HSPG) to attach/access to host cells. Moreover, mucosal epithelia in the respiratory tract are protected by a layer of mucin polysaccharides, which are usually sulfated glycans. Consequently, the polydisperse, native biopolymers HSPG and GAGs could reduce the risk of infection by several CoVs (Lang et al. 2011; Milewska et al. 2018). GAGs are present on almost all mammalian cells and these sugar polymers are central to the strategy for SARS-CoV-2 attachment to host target sites. The S1 RBD of SARS-CoV-2 binds to heparin and the interaction induces a significant structural change. Furthermore, the basic amino acid residues on viral surface constitute heparin-binding domains, which are solvent accessible on the SARS-CoV-2 S1 RBD surface and form a continuous patch suitable for heparin-binding (Mycroft-West et al. 2018; Belen-Apak and Sarialioglu 2020).

### ***Antibodies as “trojan horse” receptors***

Serological investigation of SARS-CoV and MER-CoV survivors revealed that their neutralizing antibodies bind to CoV S-protein like a viral receptor (Walls et al. 2019). This antibody/S-protein interaction could trigger a fusogenic conformational change and paradoxically, mediate viral entry into cells *via* surface CD32a through canonical viral-receptor-dependent pathway. In this phenomenon, the antibodies target antigenically similar viruses but only sub-neutralize another, which leads to “antibody-dependent enhancement” (ADE) of the latter virus. Viral entry by ADE has been reported for many pathogens such as *Dengue viruses*, *Zika virus*, *Ebola virus*, and HIV (Wan et al. 2020). Therefore, COVID-19 could possibly use ADE as an entry mechanism for human infection and transmission (Kadkhoda 2020). In this ADE-mediated pathway, the CD32a expressed on the surfaces of monocytes and macrophages could play a prominent role. This may transduce signals through the associated immunoreceptor tyrosine-based activation motif (ITAM) and release of proinflammatory cytokines (i.e. IFN- $\gamma$ , TNF- $\alpha$ , IL-1 and IL-6) (Anania et al. 2019), a prominent feature of COVID-19 cytokine storm. It is important to note that close antigenic relationship may lead to a type of OAS in which cross-protection can result as is the case with influenza whereas when antigenic relatedness is relatively distant, as is the case between SARS-CoV-2 and common CoVs, OAS can be more detrimental than useful and exert its immunopathological harm thorough ADE.

### **Cellular entry and internalization of CoV**

COVID-19 infection may begin in the nasal epithelial cells of the upper respiratory tract, which expresses the highest levels of SARS-CoV-2 receptors (Sungnak et al. 2020). If uncontrolled, the infection spreads to cells in the lower airways of the lung, resulting in respiratory failure and possibly multi-organ failure due to cytokine storm (Liu et al. 2020). SARS-CoV-2 entry into host cells is an important determinant of viral infectivity and pathogenesis. To enter host cells, CoVs first bind to a CSR for viral attachment, subsequently enter endosomes, and eventually fuse viral and lysosomal membranes (Perlman and Netland 2009; Shang et al. 2020).

### **Viral-cell membrane fusion**

The RBD domain of S-protein mediates the entry of both SARS-CoV and SARS-CoV-2 into host cells by binding to hACE2 receptor. Subsequent activation by both human proteases TMPRSS2 and lysosomal cathepsins are critical for SARS-CoV-2 entry (Hoffmann et al. 2020; Ou et al. 2020). For membrane fusion, the S-protein needs to proteolytic activation at the S1/S2 intersection, such that S1 dissociates and S2 undergoes a dramatic structural change (Belouzard et al. 2012). This S1/S2 enzymatic cleavage includes human proteases TMPRSS2 and lysosomal cathepsins (Heald-Sargent and Gallagher 2012). The host protease activation is a significant determinant of SARS-CoV-2 infection and pathogenesis.

Interestingly, the glycan shield on S-protein conceals the antigenic RBD region and empowers SARS-CoV-2 to evade immune surveillance, potentially leading to insufficient immune response and prolonged recovery time (Shang et al. 2020). In clinical observations, COVID-19 patients showed low levels of neutralizing antibodies and suffered prolonged illness compared to SARS patients. These clinical findings indicated that COVID-19 evades the human immune response more effectively than SARS (Zhou et al. 2020). However, unlike SARS-CoV, the cell entry of SARS-CoV-2 is preactivated by proprotein convertase “furin” enzyme, reducing COVID-19 dependence on target cell proteases for entry (Shang et al. 2020). Furin pre-activation allows SARS-CoV-2 to be less dependent on target cells, enhancing its entry into certain cellular targets, particularly cells with relatively low expressions of TMPRSS2 and/or lysosomal cathepsins. Cell surface protease TMPRSS2 and lysosomal cathepsin both activate SARS-CoV-2 pseudovirus entry and that both TMPRSS2 and cathepsins have cumulative effects with furin on SARS-CoV-2 entry. In comparison, SARS-CoV pseudovirus entry is activated only by TMPRSS2 and cathepsins, but not by furin (Shang et al. 2020). These cellular entry mechanisms potentially allow SARS-CoV-2 to maintain efficient cell invasion and rapid spread with tactical evasion of immune surveillance.

### **Endocytosis and viral internalization**

The critical step in the pathogenesis of COVID-19 illness involves penetration of the viral particles into the cytosol. At present, it is widely believed that CoVs enter the host cells *via* two routes: (i) the endocytic pathway and (ii) non-endosomal pathway (Zumla et al. 2016). Most viruses take advantage of the endocytic membrane trafficking of the host cell can include clathrin-dependent endocytosis, caveolae, and clathrin-and caveolae-independent mechanism involving lipid rafts (Lu et al. 2008; Mercer et al. 2010). SARS-CoV and SARS-CoV-2 appear to require endocytosis in cultured cell lines (Wang et al. 2008; Glebov 2020) Both clathrin-dependent endocytosis and cathepsin-mediated S protein cleavage are two critical steps for the viral entry and infection (Yang and Shen 2020). Entry of CoVs into the host cells is mainly mediated by the endocytic pathway, meanwhile, the autophagy has also been implicated in the viral replication in the cells (Mercer et al. 2010). The involvement of endocytic pathway of the SARS-CoV-2 have not been reported directly. However, it has been identified that SARS-CoV-2 binds to hACE2, the same receptor as SARS-CoV, for viral entry into the host cells (Kuba

et al. 2005; Zhou et al. 2020). Therefore, it is highly possible that this novel pathogen uses the same endocytic pathway for entry into the host cells.

### **Covid-19-pregnancy: frontline and barrier defense**

The maternal-fetal interface represents an immunologically unique site designed to promote tolerance to the allogenic fetus and maintain host defense against a diverse array of possible pathogens. Innate immune responses to viruses at the maternal-fetal interface may have a significant impact on pregnancy outcomes. Cytotoxic adaptive immune responses are diminished, bypassed, or even abrogated, while regulatory adaptive immunity is enhanced during pregnancy. By contrast, innate (natural) immunity remains intact, serving two purposes: i) to continue to provide host defense against infection, and ii) to interact with fetal tissues to promote successful placentation and pregnancy. Recent emergence of COVID-19-Pregnancy poses new questions and challenges in clinical obstetrics.

#### ***Frontline defense at mucosal surface***

The airway epithelium acts as the frontline defense against COVID-19, not only as a physical barrier and through the muco-ciliary apparatus but also through its immunological functions. It initiates multiple innate and adaptive immune responses crucial for anti-COVID-19 activity. The interaction between CoVs and airway epithelial cells results in production of antiviral substances, mainly “lactoferrin” (LF), as well as, type I and III interferons,  $\beta$ -defensins, nitric oxide, and the production of cytokines and chemokines that recruit inflammatory cells and influence adaptive immunity (Vareille et al. 2011). These defense mechanisms comprise a fairly effective virus clearance system. On the other hand, SARS-CoV-2 has developed elaborate strategies to evade antiviral mechanisms and immune responses. The virus may disrupt epithelial integrity through cytotoxic effects, increasing paracellular permeability, and damaging epithelial repair mechanisms. In addition, the virus may rather maladaptively interfere with immune responses by blocking interferon pathways and by subverting protective inflammatory responses toward a detrimental “cytokine storm”. Finally, the induction of excess mucus secretion and muco-stasis leads to lung damage and further impairs host defense as observed in COVID-19.

The airway naturally provides several defense mechanisms to prevent infection by the large numbers of viruses present in ambient air, including SARS-CoV-2. An important component of this defense is the antimicrobial peptides and proteins present in the airway surface fluid, the mucin-rich fluid covering the respiratory epithelium. Lactoferrin (LF) arguably constitutes the major host defense factor that regulates acute inflammation and immune modulation in the respiratory tract (Naidu 2000; Laube et al. 2006).

#### ***Maternal barrier defense***

Many factors could influence the incidence, duration, and severity of viral infection at the maternal-fetal interface. Viruses gain access to the cells within the decidua and

placenta by ascending from the lower reproductive tract or *via* hematogenous transmission (Gedeon and Koren 2006). Following access to the upper reproductive tract, viral tropism for the decidua and/or placenta depends on both viral entry receptor expression by these tissues and the specific maternal immune response against the virus. These factors vary by cell type and gestational age and affected by changes in the *in utero* environment and maternal immunity (Vähäkangas and Myllynen 2009). The virus-host interaction during pregnancy is complex and highly variable. Innate immune cells, including NK cells, DCs, macrophages, and the maternal humoral response play a critical role in the infection, which consequently, determines the severity of COVID-19. Contrary to nonpregnant women, the function of the innate immune system during pregnancy is influenced by the fetal/placenta unit (Iqbal et al. 2012).

Severe cases of COVID-19 involve “cytokine-storm” with elevated plasma levels of IL-2, IL-7, IL-10, G-CSF, IFN- $\gamma$ -inducible protein-10, monocyte chemoattractant protein-1, macrophage inflammatory protein-1 $\alpha$ , and TNF- $\alpha$  (Huang et al. 2020) resulting from ADE (Tetro 2020). Since pregnant women are in T<sub>H</sub>2 state during their 1<sup>st</sup> and 3<sup>rd</sup> trimester, the cytokine-storm induced by SARS-CoV-2 may result in severe inflammatory damage. Elevated cytokine response to viral infections during pregnancy may later cause autism spectrum-like disorders and brain development abnormalities in children (Choi et al. 2016; Mor et al. 2017). Fever is the most common clinical manifestation of COVID-19, which can predispose an increased attention-deficit/hyperactivity disorder in the offspring and affect child development (Werenberg Dreier et al. 2016).

Placenta is the only organ composed of cells from two different individuals – *the mother and the fetus*, designed to mediate interactions between the two. The basic functional units of the placenta are the fetus-derived chorionic villi with fetoplacental vessels. The maternal part of the placenta is the decidua with maternal vessels. Between these two regions is the intervillous space filled with the maternal blood that is enriched with “maternal lactoferrin” (LF) (Thaler et al. 1993; 1999). LF expression during pregnancy is regulated by several transcription factors, and steroid hormones present during pregnancy, such as progesterone, estrogen, and corticosteroids (Teng 2002; 2010). LF levels are altered in pathological pregnancies (preterm, pre-eclampsia, growth restriction and infection) (Otsuki et al. 1999). Immuno-histological studies of normal placentae ( $n=35$ ) showed LF positive cells in intervillous spaces and fetal stem vessels (Thaler et al. 1993). Placental cytotrophoblasts express unique epitopes of LF and such expression is increased in the presence of activated macrophages. This expression could be an extra-embryonic response to inflammation and maternal allogeneic recognition as an effort to protect trophoblastic cells (Thaler et al. 1999). LF appears to play a role in placental inflammation and immune pathology of infections during pregnancy. Maternal LF in amniotic fluid and cervical mucus could provide host defense against viral infections in pregnant women. Inflammatory cytokines, in particular, IL-6 elevate during amniotic infection and cause premature labor during pregnancy. LF levels rapidly rise in amniotic fluid during chorioamnionitis (CAM) ( $8.8 \pm 0.7 \mu\text{g/mL}$ ) and effectively suppress the inflammatory IL-6 production during intrauterine infection (Otsuki et al. 1999). Similarly, LF could play a significant role in determining the susceptibility of a fetus to COVID-19.

In addition to the maternal-LF, the placenta also secretes antiviral molecules such as type III IFNs (IFN- $\lambda$ ) and vesicle-enclosed primate-specific placental microRNAs (miRNAs) (C19MC, chromosome 19 microRNA cluster) that restrict viral infections in autocrine and paracrine fashion. Despite this formidable barrier, some viral pathogens are capable of overcoming the host defense; these include *Zika virus*, *Varicella Zoster Virus* (VZV), *Human Immunodeficiency Virus* (HIV), *Rubella virus*, *Cytomegalovirus* (HCMV), and *Herpes Simplex Virus* (HSV). In contrast, and most notably in the context of the COVID-19-Pregnancy, vertical transmission of SARS-CoV-2 does not appear to occur with any clinically significant frequency. Considering the role of LF in placental barrier function, we investigated the maternal-fetal interface to understand the potential interplay of innate defense factors for prevention and control of COVID-19-Pregnancy.

## Conclusions

The SARS-CoV-2 is a novel human pathogen that may interact with host antiviral defense in a unique manner, especially in pregnant women. The interplay between SARS-CoV-2 and host antiviral defense is at the core of COVID-19-Pregnancy. It also determines the clinical outcome and might explain the risk of asymptomatic carriers. The virulence and pathogenicity of COVID-19 seems to fall between those of SARS-CoV and community-acquired human CoVs. SARS-CoV-2 is remarkably like SARS-CoV in several aspects (Fung et al. 2020); therefore, a comparative analysis of these two viruses may advance the understanding the pathobiology of COVID-19 illness. From a COVID-19 vaccine development standpoint, the close antigenic relationship of SARS-CoV-2 with other CoVs may lead to a type of OAS, which can be more detrimental than useful and exert its immunopathological harm through ADE.

The S-protein is a critical virulent factor of COVID-19, responsible for tissue tropism and a wide range of host infectivity. In addition to ACE2, the S-protein may recognize four other protein CSRs and bind to various sugars as cellular targets *via* lectin-type interactions. These flexible mechanisms of viral attachment, host cell invasion, and subsequent inter-cellular spread, may explain, the remarkable adaptability and transmission across different hosts; thus, transforming SARS-CoV-2 into a versatile, multi-opportunistic pathogen. SARS-CoV-2 has also acquired a unique polybasic furin cleavage site (PRRAR) at the S1/S2 intersection of S-protein; which further expands its tissue tropism, transmissibility and alters the pathogenicity of this novel COVID-19 pathogen. The predicted O-linked glycans at the furin-cleavage site could create a “mucin-like domain” to shield antigenic epitopes on the S-protein. SAR-CoV-2 may use this shield for molecular trickery to evade the immune defense of the infected host.

Although current observations do not support intrauterine vertical transmission of COVID-19-Pregnancy in the fetus, the impact of disease aftermath on fetal development cannot be ruled out. The lack of early gestation data does not exclude the prolonged persistence of placental inflammation. Such inflammatory condition during pregnancy could affect several aspects of fetal brain development and offset a wide range of neuronal dysfunctions and behavioral disorders later in postnatal life of the offspring (Mor et al. 2017). Therefore, the post-recovery phase of COVID-19 needs a close monitoring of the intrauterine development of the fetus. Early detection and intervention of

*COVID-19-Pregnancy* may help avert negative neonatal outcomes and reduce potential obstetric complications such as pregnancy loss, IUGR, and preterm delivery, and may improve pregnancy outcomes.

Drugs should be given to pregnant women only when the maternal benefit outweighs the potential fetal risk. Fetal transfer of drugs primarily depends on the permeability of the placental barrier, which forms the interface between the fetal and maternal circulations (Tomi et al. 2011). Therefore, innate defense factors in the maternal-fetal interface are critical for healthy pregnancy outcomes. Maternal LF is the innate regulator of immune-redox transitions at the maternal-fetal interface with a multifunctional role in antiviral defense, immune-modulation, inflammatory regulation, and redox control of metabolic syndromes. Thus, maternal LF may serve as a potent innate defense factor against COVID-19-*Pregnancy*. Similarly, breast milk LF could play a natural preventive role in MCTC and may also protect the neonate from the COVID-19-*Postpartum*. Understanding the regulation of LF in normal and pathological pregnancies may advance the development of highly targeted maternal and fetal adjuvant protocols for clinical management of COVID-19. Basic research in the field of SARS-CoV-2-host interaction holds the key to many important questions in prevention and control of COVID-19.

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## Declaration of interest

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of the article.

## About the authors

**Dr. Sreus A.G. Naidu**, MS, PharmD, has earned Doctorate in Pharmacy and MS in Regulatory Science from the University of Southern California. Sreus has over 15 years of experience working at N-terminus Research Laboratory based in California, which specializes in the isolation, purification, and activation of bioactive molecules. He is co-inventor on multiple patents with applications in human nutrition and animal healthcare.

**Professor Roger A. Clemens**, DrPH, FIFT, CFS, FASN, FACN, CNS, FIAFST, is Associate Director of the Regulatory Science program and Adjunct Professor of Pharmacology and Pharmaceutical Sciences within the USC School of Pharmacy. Dr. Clemens was the Director of Analytical Research at USC for 5 years, and the Scientific Advisor for Nestlé USA for more than 21 years. He has published more than 50 original manuscripts in nutrition and food science, participated in more than 200 invited domestic and international lectures, and served as an expert panel member for the food industry, scientific organizations, trade associations and regulatory agencies in the United States and Canada.

**Dr. Peter Pressman**, MD, MS, FACN, was trained at Northwestern University and the University of Chicago. He served as a Naval Medical Officer in austere settings in which food insecurity is endemic. Pressman has extensive experience addressing protein calorie malnutrition in conflict zones in central Asia, and the Middle East, and in the developing world in sub-Saharan Africa.

Pressman pursued his interests in medical nutrition at the University of Southern California, as Associate Director of the Internal Medicine Residency Program and Director of Educational Programs of the Pacific Center for Health Policy and Ethics. Subsequently, in collaboration with Professor Roger Clemens, he has co-authored and published papers and book chapters in the realm of medical nutrition and public health, and co-taught the nutrition course in the Global Medicine Program at USC's Keck School of Medicine. He currently holds positions with The Daedalus Foundation and Polyscience Consulting.

**Dr. Mehreen Zaigham**, BSc, MD, PhD, is a post-doctoral fellow and resident at the Department of Obstetrics and Gynecology, Lund University, Sweden. Mehreen has worked on several projects investigating the role of birth asphyxia to short- and long-term neurodevelopmental outcomes in infants including the importance of umbilical cord blood gases. In the current COVID-19 pandemic, her focus has been to understand the effect of SARS-CoV-2 infection in pregnant women and their fetuses.

**Dr. Kamran Kadkhoda**, PhD, SM(ASCP), D(ABMM), D(ABMLI), is the Medical Director of Immunopathology Laboratory, Robert J. Tomisch Pathology & Laboratory Medicine Institute, Cleveland Clinic, Ohio. His research interests are serological diagnosis of infectious diseases, sero-epidemiological investigations, and molecular laboratory diagnosis of blood-borne pathogens.

**Professor Kelvin J. A. Davies**, PhD, DSc, MAE, FRSC, FRCP, FLS, FRI, is the James E. Birren Chair and Dean of Faculty at the University of Southern California's, Leonard Davis School of Gerontology. He is also Distinguished Professor of Molecular and Computational Biology and Biochemistry & Molecular Medicine. Davies was educated at London and Liverpool Universities, the University of Wisconsin, Harvard University, and the University of California at Berkeley. Previously, he was a faculty member at Harvard University, Harvard Medical School, and Albany Medical College. He pioneered the study of protein oxidation and proteolysis during adaptation to oxidative stress and discovered stress-genes including calcineurin regulator RCAN1 whose mis-regulation contributes to Alzheimer and Huntington diseases and Down syndrome. He demonstrated that impaired induction of Proteasome and Lon protease genes contributes to senescence and diminished stress-resistance and has pioneered the concept of impaired 'Adaptive Homeostasis' as a major factor in aging. Davies has been awarded 15 honorary Doctoral degrees and has been elected as a fellow of 14 national and international academies including AAAS, Royal Society of Medicine, Royal Society of Chemistry, Royal College of Physicians, and Academy of Europe. He was knighted in 2012 as a chevalier of France's Ordre National du Mérite and elevated as a Knight Commander in 2018.

**Professor A Satyanarayan Naidu**, PhD, FACN, FLS, FISSVD, is the Director of N-terminus Research Laboratory in California, USA. After receiving PhD in Medical Microbiology (1985) from the Osmania University in India, Dr. Naidu served the Directorate of Public Health Services (DPHS), the Government of A.P., India and the World Health Organization (WHO) Surveillance program. He performed post-doctoral research at the Medical University of Pécs, Hungary and the Biomedical Center-Uppsala, Sweden. Dr. Naidu joined the faculty at the Lund University; Sweden (1988–1992), the University of North Carolina at Chapel Hill, USA (1993–1997). He was appointed as the Director at the Center for Antimicrobial Research, California State University-Pomona, USA (1998–2000). Dr. Naidu's discoveries on Staphylococcal toxic shock syndrome (TSS) and *E. coli* hemolytic uremic syndrome (HUS) have garnered international recognition. He was principal investigator for several NIH grants, published more than 100 peer-reviewed research publications, written over 30 book chapters, and authored 4 reference volumes in the field of medical sciences. He holds 24 core patents, and his technology transfers in biomedical technology reach worldwide. Dr. Naidu is an elected fellow of the Royal Society for Medicine, the Linnean Society of London, the American College of Nutrition, and the International Society for the Study of Vulvovaginal Disease.

## ORCID

- Sreus A. G. Naidu, MS, PharmD  <http://orcid.org/0000-0003-3517-8135>  
 Roger A. Clemens, DrPH, FIFT, CFS, FASN, FACN, CNS, FIAFST  <http://orcid.org/0000-0002-5898-9793>  
 Peter Pressman, MD, MS, FACN  <http://orcid.org/0000-0002-6636-8161>  
 Mehreen Zaigham, BSc, MD, PhD  <http://orcid.org/0000-0003-0129-1578>  
 Kamran Kadkhoda, PhD, SM(ASCP), D(ABMM), D(ABMLI)  <http://orcid.org/0000-0003-1687-651X>  
 Kelvin J. A. Davies, PhD, DSc, MAE, FRSC, FRCR, FLS, FRI  <http://orcid.org/0000-0001-7790-3003>  
 A. Satyanarayan Naidu, PhD, FACN, FLS, FISSVVD  <http://orcid.org/0000-0002-6008-0482>

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