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# THE MUMBAI OBSTETRIC & GYNECOLOGICAL SOCIETY

# MOGS MEDIA

## VOL 7 | COVID - 19

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## President's Message

Dear Colleagues,

It gives me great pleasure to bring to you the seventh edition of **'MOGS MEDIA'**. This is a series of focussed newsletters where we bring to you an important subject discussed in detail with all the latest updates. This issue is focussed on the most important problem at present, **COVID-19** pandemic. This pandemic has totally changed our lives and the way we practise has also been affected. Many changes have been brought in including tele consultation, changes in ANC visit schedules, infection prevention protocols etc. The information about effects of COVID-19 on pregnancy, mother and neonate are constantly being upgraded. The editor Dr Pratik Tambe and all the contributors have made a lot of effort to bring you the latest information on the subject and we are thankful to them.

The Fertility Enhancement and Management Conference, FEM 3.0 , by MOGS in association with IVF Worldwide, held virtually on 21st and 22nd November 2020 was a record breaking success with more than 5000 delegates from 127 countries participating. More than 20 International Faculty from all over the world as well as leading Indian ART specialists shared their knowledge. For the first time ever we had posters and free papers not only from all over India, but also from Europe. I am sure you have benefited from the many focussed webinars we have been doing. I hope the **'Pearls of Wisdom'** videos which you are receiving regularly are adding to your knowledge. Our digital PG training programme-The NA Purandare practical training event which has hundreds of young doctors tuning in, is helping young doctors get ready for exams and clinical practise. We will soon be hosting a Crash course for extensive training for postgraduate students.

**MOGS V Care & Share** programme which was started by us to support our frontline workers and the women whose health we look after, is going very well. In December to spread the Christmas cheer we distributed nutritional food, masks, Xmas candy, caps etc to doctors, patients, nurses in municipal and government hospitals all over Mumbai. We need your help and support for this ongoing programme . You can donate by online payment on our website or by bank transfer.

We have many different academic and fun activities planned this year. We have announced an **MOGS Personality of the Year** contest in which many of you must participate. Our Annual Conference is scheduled for April 2021.

Do visit our website for updates. www.mogsonline.org

Thank you once again for all your support over the years and we look forward to a wonderful year at MOGS.

Stay safe, stay healthy.

Best wishes,

**Dr Rishma Dhillon Pai**

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**MOGS V Care & Share**

**MOGS extends a helping hand to our frontline healthcare workers and patients.**
**Support our efforts - contribute generously - if not now, when?**

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## Editors' message

Dear MOGS members,

The MOGS Media series of newsletters have been one of the highlights of the MOGS year so far. The newsletter is themed on areas of practical interest with individual topics having relevance in day-to-day practice for practising obstetricians and gynaecologists. The previous six issues on **Preterm Birth, Anaemia and Nutrition in Pregnancy, Optimising IUI Results, Endometriosis, PCOS and Premature Ovarian Insufficiency** were well received and widely appreciated by readers throughout the country.

It is with great pride that we bring you the seventh issue on the global pandemic **"COVID-19"**, which has completely changed how we practice and caused severe restrictions to be placed on the freedoms which we take for granted. A galaxy of eminent senior stalwarts has authored the articles on various aspects of the pandemic and how it has affected our practice.

We thank the MOGS President Dr Rishma Dhillon Pai and the office bearers for giving us the opportunity to be part of such an innovative, important and immensely practical initiative. We hope you enjoy reading the articles and find them useful. We would welcome any comments or suggestions regarding the same and encourage you to reach out to us with feedback.

Wishing you, your families and staff good health and safety in these difficult times!

**Dr Pratik Tambe**
**Dr Reena Wani**
**Dr Ameya Purandare**
**Dr Komal Chavan**
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# Pathophysiology of Severe Acute Respiratory Syndrome Coronavirus-2 (COVID-19)

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## Background

Corona virus disease 2019 (COVID-19) is defined as an illness caused by a novel corona virus now called severe acute respiratory syndrome corona virus [2] (SARS-CoV-2), which was first identified amid an outbreak of respiratory illness cases in Wuhan City, Hubei Province, China.[1] On January 30, 2020, the WHO declared the COVID-19 outbreak a global health emergency.[2,3] On March 11, 2020, the WHO declared COVID-19 a global pandemic.[4] The SARS CoV-2 belongs to the family Coronaviridae and is responsible for severe acute respiratory illness with multi system involvement.

The virus is transmitted via respiratory droplets and aerosols from person to person. Once inside the body, the virus binds to host receptors and enters host cells through endocytosis or membrane fusion. The corona viruses are made up of four structural proteins, namely, the spike (S), membrane (M), envelope (E) and nucleocapsid (N) proteins.[5,6] The spike (S) protein is the most important one for host attachment and penetration. It is composed of two functional subunits, S1 which is responsible for binding to the host cell receptor and S2 which plays a role in the fusion of viral and host cellular membranes.[5]

ACE-2 has been identified as a functional receptor for SARS-CoV and is highly expressed on the pulmonary epithelial cells. The type 2 transmembrane serine protease (TMPRSS2), present in the host cell, promotes viral uptake by cleaving ACE2 and activating the SARS-CoV-2 S protein, which mediates corona virus entry into host cells.[7] Co-expression of ACE2 and TMPRSS2 on the cell surface is required for the completion of this entry process.

Once inside the host cell, the virus undergoes replication and formation of a negative strand RNA by the pre-existing single-strand positive RNA through RNA polymerase activity (transcription). This newly formed RNA helps in synthesis of new proteins in the cell cytoplasm through translation.[8-10]

Post membrane fusion, the virus enters the pulmonary alveolar epithelial cells and the viral contents are released inside. The viral N protein and M proteins facilitate integration into the cellular endoplasmic reticulum. These newly formed nucleocapsids are transported via exocytosis to the extracellular space. The new viral particles are now ready to invade the adjacent epithelial cells as well as for providing fresh infective material for community transmission via respiratory droplets.[5]

**Pathogenesis**

Key mechanisms that may have a role in the pathogenesis of multi-organ injury secondary to infection with SARS-CoV-2 include

- Direct viral toxicity
- Dysregulation of the renin–angiotensin–aldosterone system (RAAS)
- Endothelial cell damage and thromboinflammation
- Dysregulation of the immune response (Fig. 1)[11]

**Direct Viral Toxicity**

SARS CoV-2 has tropism for the respiratory tract, given the high expression of ACE2 in multiple epithelial cell types of the airway, including alveolar epithelial type II cells in the lung parenchyma.[12,13] Live SARS-CoV-2 virus and viral mRNA isolated from the upper airway can successfully be detected by RT-PCR.

RNA-sequencing studies have confirmed expression of ACE2 and TMPRSS2 in lung alveolar epithelial type II cells, nasal goblet secretory cells, cholangiocytes, colonocytes, esophageal keratinocytes, gastrointestinal epithelial cells, pancreatic-cells beta, and renal proximal tubules and podocytes.[14-17] These findings suggest that multiple-organ injury may occur at least in part due to direct viral tissue damage explaining the mechanism of extrapulmonary spread of SARS-CoV-2.

**Dysregulation of the renin–angiotensin–aldosterone system (RAAS)**

RAAS is composed of a cascade of regulatory peptides that participate in key physiological processes of the body, including fluid and electrolyte balance, blood-pressure regulation, vascular permeability, and tissue growth.[18]

ACE2, a membrane-bound aminopeptidase, is a potent counter-regulator of the RAAS pathway and cleaves angiotensin I into inactive angiotensin 1-9 and cleaves angiotensin II into angiotensin 1-7, which has vasodilator, anti-proliferative, and antifibrotic properties.[19-21] Downregulation of ACE2 has been related to viral entry, which leads to decreased cleavage of angiotensin I and angiotensin II resulting in dysregulation of the RAAS.

**Endothelial cell damage and thromboinflammation**

Infection-mediated endothelial injury (characterised by elevated levels of von Willebrand factor) and endothelialitis (marked by the presence of activated neutrophils

and macrophages), found in multiple vascular beds (including the lungs, kidney, heart, small intestine, and liver) in patients with COVID-19, can trigger excessive thrombin production, inhibit fibrinolysis, and activate complement pathways, initiating thromboinflammation and ultimately leading to microthrombi deposition and microvascular dysfunction.[22-26] Platelet–neutrophil cross-communication and activation of macrophages in this setting can facilitate a variety of proinflammatory effects, such as cytokine release, the formation of neutrophil extracellular traps (NETs) and fibrin and/or microthrombus formation.[27-30]

**Dysregulation of the immune response**

Dysregulated immune response and cytokine-release syndrome with subsequent multiorgan dysfuncion, due to over activation of innate immunity in the setting of T cell lymphodepletion, characterise the presentations of severe COVID-19.[31] Prior preclinical and human studies with pathogenic human corona viruses have proposed rapid viral replication, antagonism of interferon signaling, and activation of neutrophils and monocyte-macrophages as mediators of hyperinflammation.[32,33]

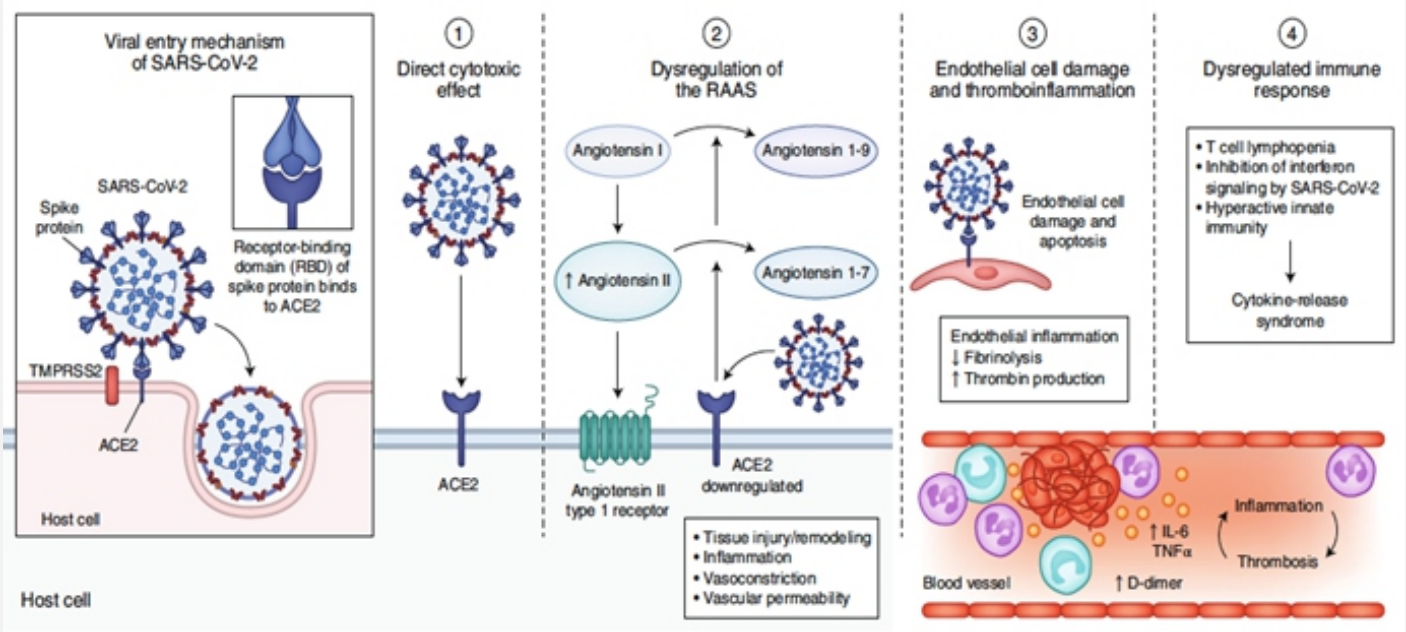


**Fig 1 Key mechanisms that may have a role in the pathogenesis of multi-organ injury secondary to infection with SARS-CoV-2** [Adapted from: Gupta, A, Madhavan, MV, Sehgal, K et al. Extrapulmonary manifestations of COVID-19. Nat Med 26, 1017–1032 (2020) https://doi.org/10.1038/s41591-020-0968-3][11]

**Infection of the host airway**

The SARS-CoV-2 which is received via respiratory aerosols binds to ACE-2 receptors in the nasal epithelial cells in the upper respiratory tract and undergoes local replication and propagation, along with the infection of ciliated cells in the conducting airways.[34] This stage lasts a couple of days and the immune response generated during this phase is a limited one.

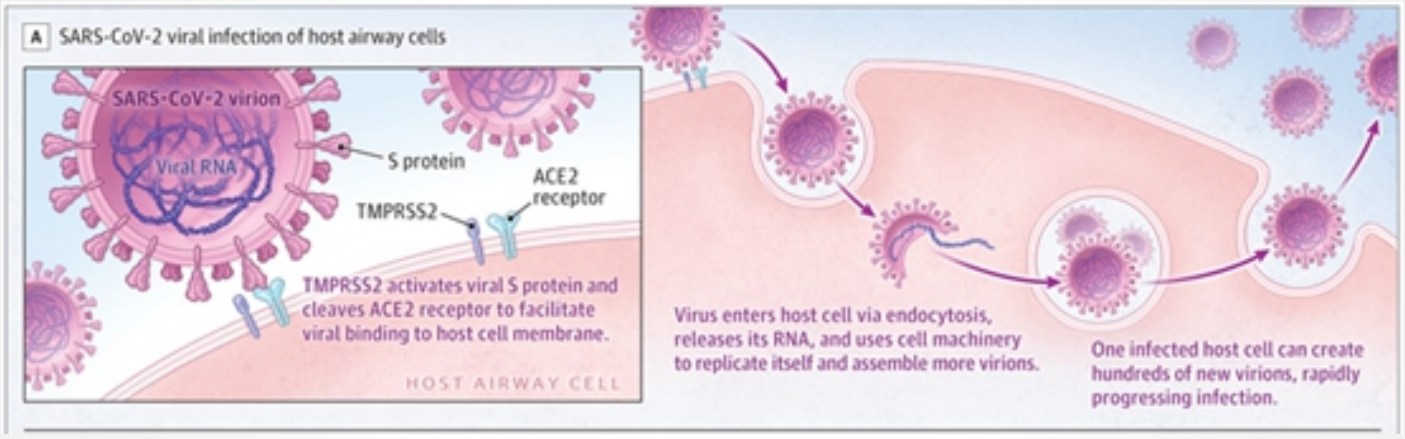


**Fig 2 Infection of host airway cells** [Adapted from: Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC Pathophysiology, transmission, diagnosis, and treatment of Corona virus Disease 2019 (COVID- 19): a review. JAMA. 2020;324:782–793][37]

When viral replication accelerates, epithelial-endothelial barrier integrity is compromised. SARS-CoV-2 also infects pulmonary capillary endothelial cells, accentuating the inflammatory response and triggering an influx of monocytes and neutrophils.[35] Interstitial mononuclear inflammatory infiltrates and edema develop and appear as ground-glass opacities on computed tomographic imaging. Pulmonary edema filling the alveolar spaces with hyaline membrane formation follows, compatible with early-phase acute respiratory distress syndrome (ARDS).

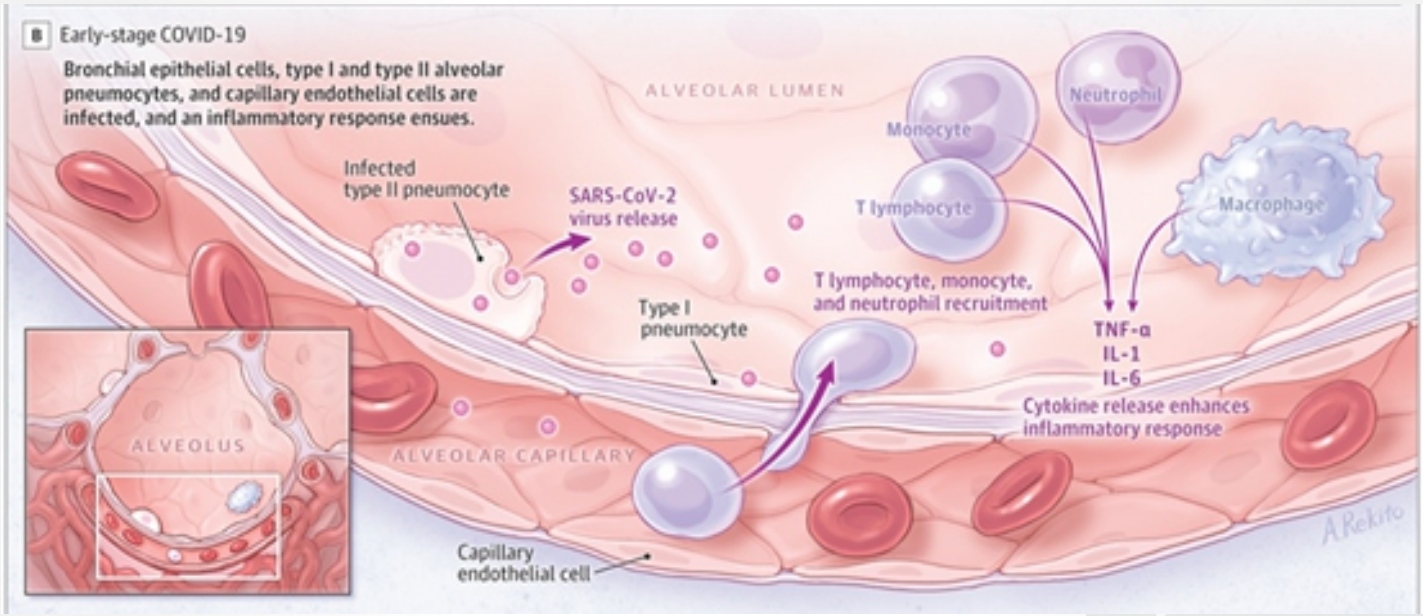


**Fig 3 Early stages of pulmonary infection** [Adapted from: Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC Pathophysiology, transmission, diagnosis, and treatment of Corona virus Disease 2019 (COVID- 19): a review. JAMA. 2020;324:782–793][37]

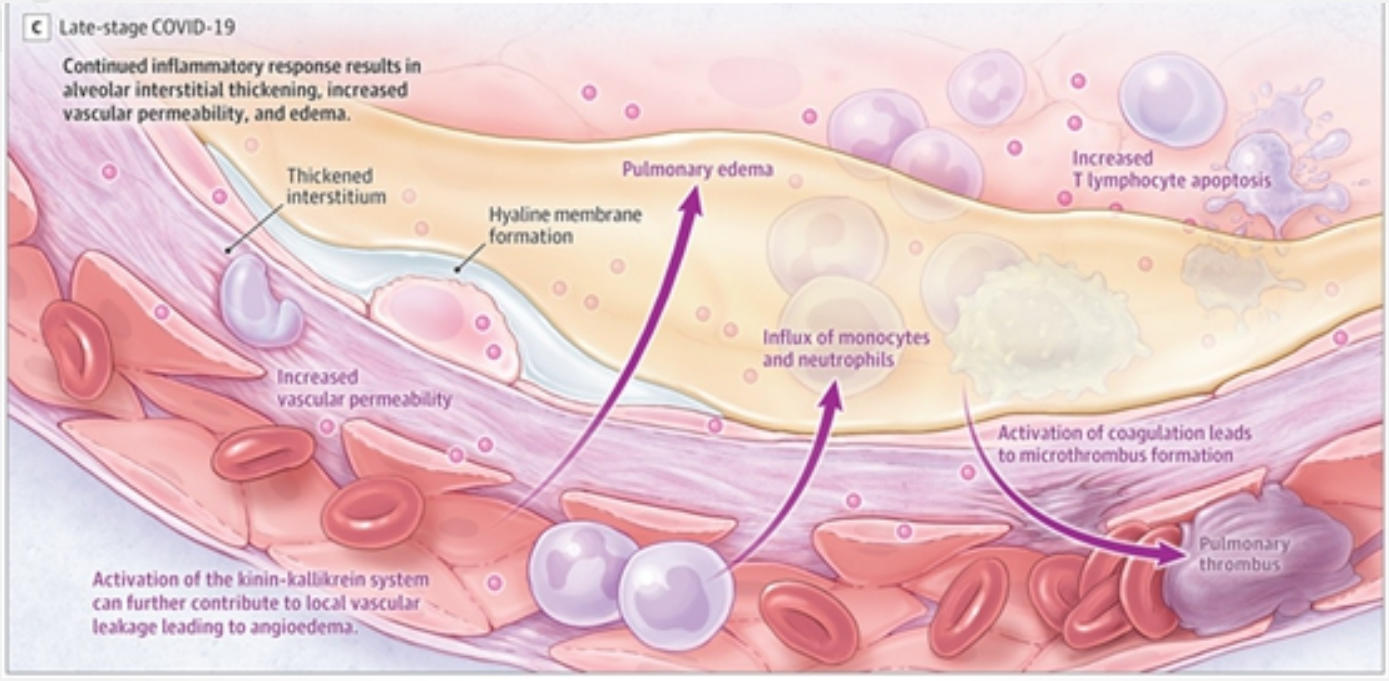


**Fig 4 Late stages of pulmonary infection** [Adapted from: Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC Pathophysiology, transmission, diagnosis, and treatment of Coronavirus Disease 2019 (COVID- 19): a review. JAMA. 2020;324:782–793][37]

In severe COVID-19, fulminant activation of coagulation and consumption of clotting factors occur.[35] Inflamed lung tissues and pulmonary endothelial cells may result in microthrombi formation and contribute to the high incidence of thrombotic complications, such as deep venous thrombosis, pulmonary embolism, and thrombotic arterial complications (eg. limb ischemia, ischemic stroke, myocardial infarction) in critically ill patients.[36]

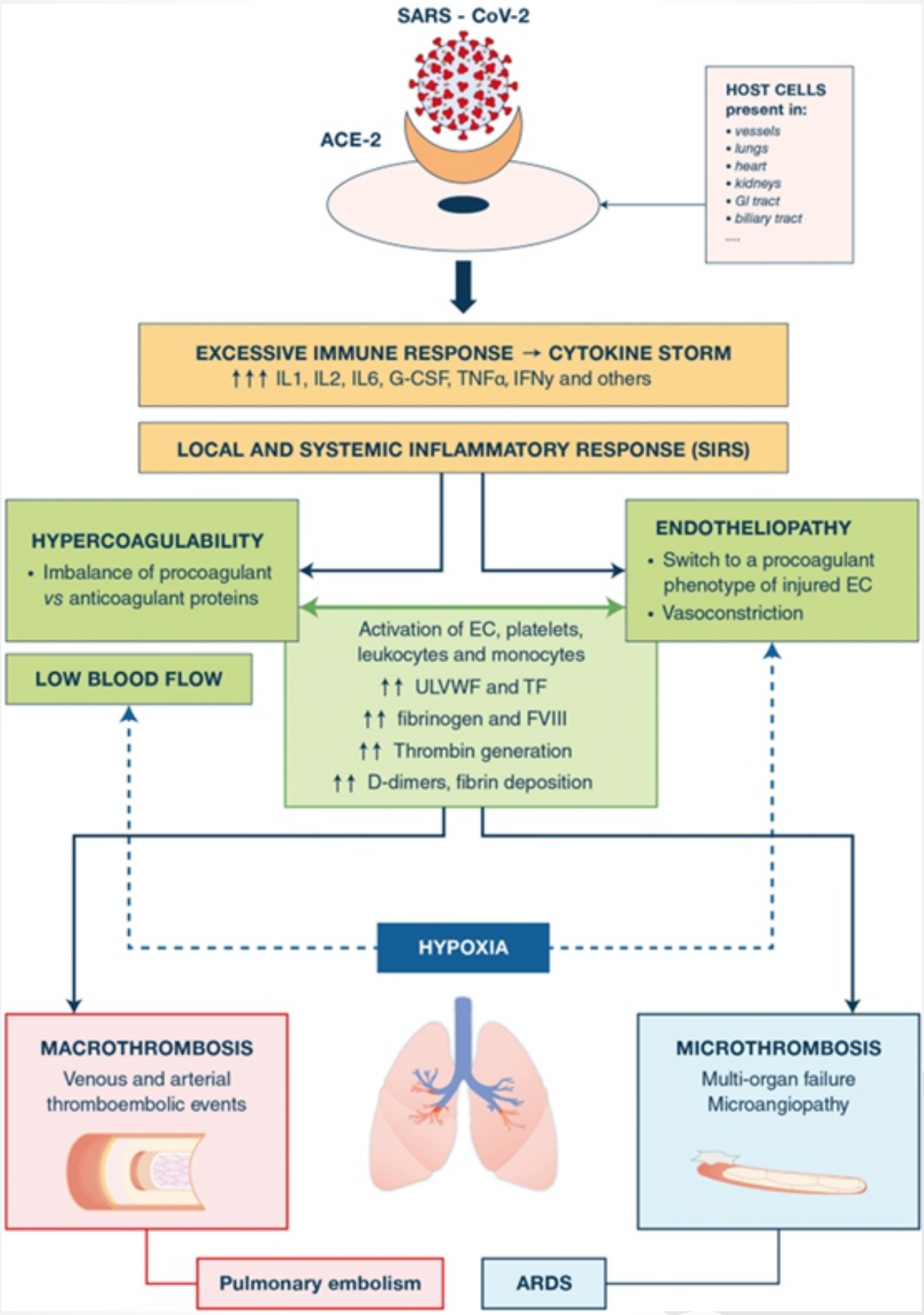


**Fig 5 Severe Covid 19 with widespread thromboinflammation** [Adapted from: Joly, BS, Siguret, V & Veyradier, A. Understanding pathophysiology of hemostasis disorders in critically ill patients with COVID-19. Intensive Care Med 46, 1603–1606 (2020). https://doi.org/10.1007/s00134-020-06088-1][38]

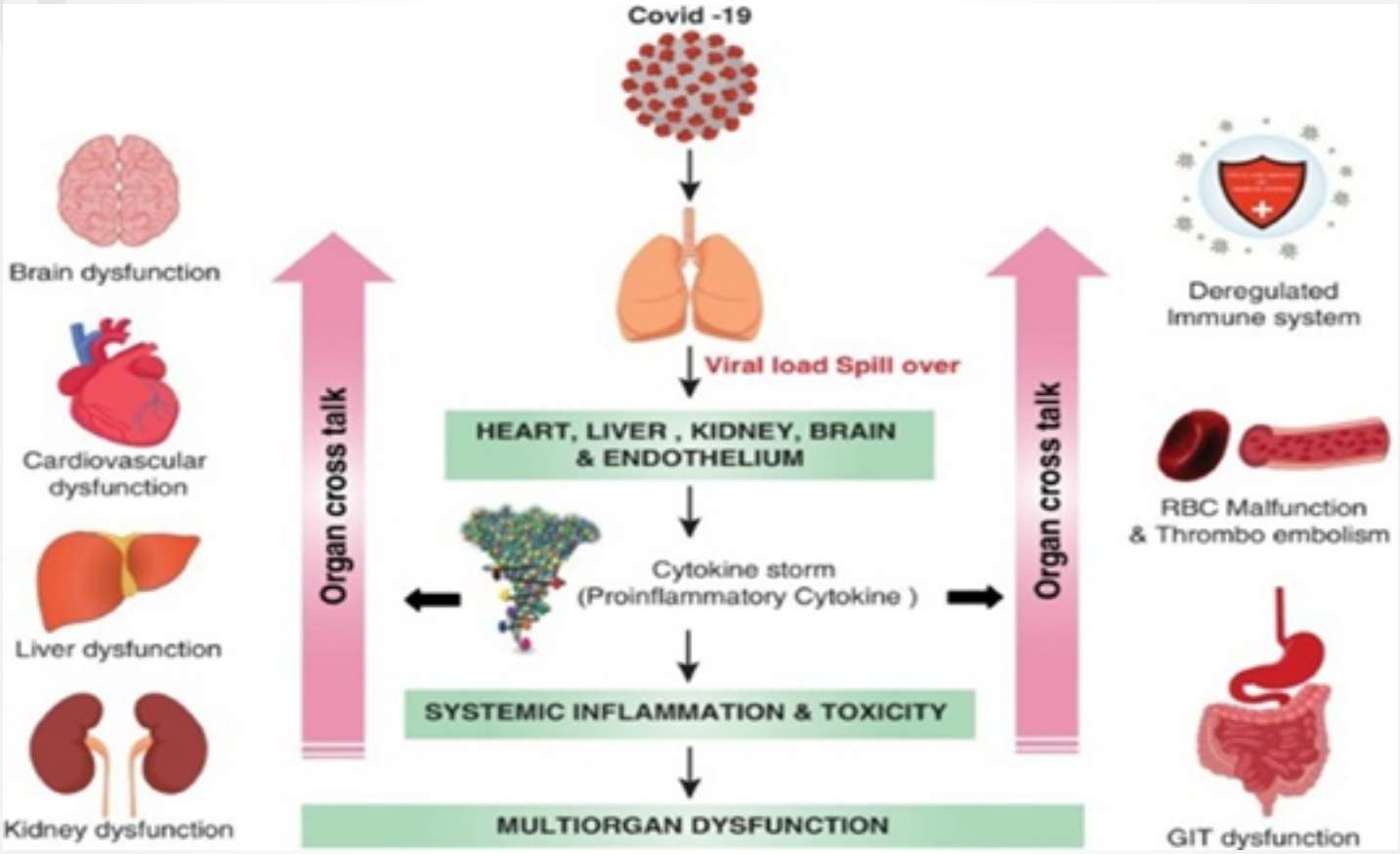


**Fig 6 Severe Covid 19 with multiorgan dysfunction** [Adapted from: S Loganathan, M Kuppusamy, et al. Angiotensin-converting enzyme 2 (ACE2): COVID-19 gate way to multiple organ failure syndromes, Respiratory Physiology & Neurobiology, Volume 283, 2021, 103548, ISSN 1569-9048, https://doi.org/10.1016/j.resp.2020.103548][39]

Recovery from COVID-19 produces antibodies, but the response is heterogeneous, especially lower in asymptomatic infected patients, and measurable responses may diminish significantly in as little as 2–3 months. The protective immunity duration is unclear. T cell responses also likely important.

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# Maternal and Fetal Issues in COVID-19

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## Introduction

A pneumonia of unknown cause emerged in Hubei province of Wuhan, China and rapidly spread across the globe. On February 11, 2020 WHO named this new coronavirus disease: COVID-19 caused by SAR-CoV-2.1 This viral infection has spread rapidly and has become the International Public Health Emergency. WHO declared COVID-19 a pandemic on 11th March 2020.[2]

Most people infected with the COVID-19 virus will experience mild to moderate respiratory symptoms and recover completely without requiring special treatment. It is seen that older people and those with underlying medical conditions like diabetes, cardiovascular disease, chronic respiratory disease and cancer are more likely to develop serious illness.

With COVID-19 rapidly spreading, it is reasonable to assume that pregnant women are also likely to get infected. The physiological and immunological changes during pregnancy result in systemic effects that predispose women towards complications from respiratory infections leading to increasing maternal and fetal morbidity. Worldwide, concerns have been raised about the risk of intrauterine transmission of the virus from the mother to the fetus.

## Transmission of SARS-COV-2[3]

- The primary mode of transmission for SARS-CoV-2 is droplets and aerosols, mainly through inhalation of respiratory droplets produced by coughing or sneezing by infected persons.
- Spread also occurs via hand to mouth/nose route from infected droplets deposited on different surfaces and fomites.
- The virus transmission can potentially occur in individuals at a distance of 1 meter from the infected person.

## Pregnancy and susceptibility to SARS-COV-2 infection

In this current COVID-19 pandemic, pregnant women constitute a vulnerable population. During pregnancy, women undergo physiological changes that make them prone to severe respiratory infections and subsequent respiratory failure. These changes in the respiratory system include reduced functional residual volume, elevation of the diaphragm, relaxation of ligaments in the ribs, increased pulmonary hypertension resulting in hyperventilation, and even hypoxic respiratory failure.[4] There is an alteration in the cell mediated immunity that increases the risk of an immunocompromised state.

Viral infection in pregnancy further increases the metabolic rate and oxygen consumption, increase the pulmonary vascular resistance, and may even cause heart failure.

**Pregnancy outcomes in COVID-19**

The symptoms of COVID-19 in pregnant women are thought to be due to the direct effect of the virus on the mother. Pregnant women infected with COVID-19 infection present with

- Asymptomatic
- Sore throat, cough and runny nose
- Fever and chills
- Body ache and fatigue
- Anosmia
- Pink eye
- Shortness of breath

The disease course in pregnant women can vary from either asymptomatic or with mild to moderate symptoms (fever and cough) to severe disease, similar to that seen in non-pregnant women. In a systematic review on symptoms in COVID-19 patients, 95% cases in pregnant women were asymptomatic, and 59% remained asymptomatic through follow-up.[5] In a study conducted by Nayak et al in a tertiary care centre in Mumbai, it was seen that 97% of patients were either asymptomatic or had mild symptoms like fever or cough not requiring any oxygen therapy.[6]

Once a pregnant woman develops the infection, it is important to monitor the woman to prevent and manage adverse maternal and fetal outcomes. As more and more data is available, it is becoming clear that complications are not uncommon in pregnant women infected with SARS-CoV-2. The various complications seen are pneumonia, thromboembolic complications, sepsis and sometimes severe acute respiratory distress syndrome (ARDS) necessitating hospitalisation and intensive care unit (ICU) admission.[7] As per the World Health Organisation data, 8% of pregnant or postpartum women with COVID-19 have severe disease and approximately 1% are critically ill.[8] A recent meta-analysis reported that less than 20% of pregnant women need admission to the intensive care unit (ICU).[9]

In general, it is seen that pregnant women positive for COVID-19 with co-morbidities are more likely to develop complications than those without. Obstetric complications included preterm birth, stillbirth, caesarean section and fetal distress.10 Pneumonia is one of the most common complications in pregnant women infected with COVID-19. In severe cases of pneumonia, the need for ventilatory support was the main causes of admission to hospital. A meta-analysis of data from nine publications which included 87 pregnant women with SARS-CoV-2 infection concluded that most pregnant women had mild to moderate COVID-19 pneumonia, similar in clinical characteristics to that seen in an adult population.[11]

Data related specifically to maternal mortality from COVID-19 remain sparse. In a review published by Nakamura-Pereira et al, there were 160 cases of maternal deaths reported from 6 countries. Most of the deaths occurred in women with comorbidities.[12]

**Neonatal outcomes of COVID-19 mostly included**[13]

- preterm birth
- premature rupture of membranes
- fetal distress
- stillbirth
- intrauterine growth retardation

In a multicentre study from Spain by Gabriel et al, the incidence of prematurity was 14.5%, respiratory distress in 10.5% and need for mechanical ventilation was 1.2%. There were no cases of stillbirths or neonatal deaths in this study.[14]

The current data do not suggest a high risk of abortion, amniotic fluid abnormality and congenital defects in neonates in mothers infected with COVID-19.[13]

**Intrauterine vertical transmission**

For obstetricians, when a new virus appears, a major concern is the risk of feto-maternal transmission. The risk of vertical transmission can theoretically exist in COVID-19 since angiotensin-converting enzyme 2 (ACE-2) receptors are significantly expressed in the placenta with which SARS-CoV-2 can bind and enter.

Vertical transmission may occur via trans-placental route, or through ingestion or aspiration of cervicovaginal secretions. The exact extent of vertical transmission remains unclear. An analysis of literature showed that n the majority of the cases, infected women gave birth to healthy babies with an Apgar score above 7 and negative reverse transcription polymerase chain reaction (RT-PCR) test results.[13,14]

**Testing in pregnant women**

SARS-CoV-2 is highly contagious and can spread from both symptomatic and pre-symptomatic patients. The ICMR guidelines of April 2020 recommend testing of all pregnant women above 34 weeks of gestation and likely to be delivered in the next 5 days, or those hailing from hotspots/ containment areas with likely contact to positive case, even if asymptomatic.[15]

It is essential to offer testing of all pregnant women and enforce strict infection control measures to manage suspected or confirmed patients to provide safety to both mothers and babies as well as healthcare workers. RCOG recommends that every pregnant woman is at high risk and should take preventive measures including wearing masks, washing hands, and strictly maintaining social distancing when interacting with others.[16]

It is important to note that RT-PCR may give false negative results and therefore some pregnant women with COVID-19 pneumonia may be missed unless a CT scan is performed.[17]

## Conclusions

- At present, there is limited knowledge about COVID-19 disease in pregnancy. Based on available data, the clinical characteristics of pregnant women with COVID-19 seem to resemble those of non-pregnant women.
- Pregnant women positive for COVID-19 with co-morbidities are at increased risk of maternal, fetal and neonatal complications.
- Although uncommon, vertical transmission of the disease is possible.
- Currently, evidence is lacking to suggest that expedited delivery changes any maternal or neonatal outcomes. Further, there is no evidence to suggest a contraindication to vaginal delivery.
- The association of IUGR, stillbirth and fetal distress in infected women suggests a role for monitoring fetal growth in mothers affected by COVID-19.
- Involvement of the neonatologist is crucial due to potential risk of neonatal/vertical transmission of COVID-19.

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# Institutional Care Protocols and Practice Points

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## Background

The corona virus (COVID-19) pandemic is a global health crisis of our time and the greatest challenge we have faced since world war II. Countries are racing to slow the spread of the virus by testing and treating patients, quarantining citizens, maintaining social distance, limiting travel and cancelling social gatherings.

Although there is no current data that shows that COVID-19 affects pregnant women different from other patients, it is known that pregnant women are at a larger risk of falling from respiratory viruses than women who are not pregnant. Hence an abundance of caution is advised for pregnant women at this time.[1]

Now that we have entered 2021, our knowledge about COVID has evolved since the time of lockdown, fears decreased but we should be cautious and aware about the changing pattern of virus and updates in protocols.

## Epidemiology

Corona viruses belong to a large family of viruses, some causing illness in people and others that circulate among animals, including camels, cats, bats etc. The aetiologic agent is SARSCoV-2 which is a novel corona virus. Transmission of corona viruses can occur via respiratory secretions. There is evidence of nosocomial transmission. The incubation period ranges from 2-14 days. Most common symptoms include fever, fatigue, dry cough and breathing difficulty. Upper respiratory tract symptoms like sore throat, rhinorrhoea and gastrointestinal symptoms like diarrhoea and nausea / vomiting are seen in some cases.

## Case definitions

### Suspect case[2]

A patient with acute respiratory illness fever and at least one sign/symptom of respiratory disease eg. cough, shortness of breath), AND a history of travel to or residence in a country / area or territory reporting local transmission of COVID-19 disease during the 14 days prior to symptom;

OR

A patient/health care worker with any acute respiratory illness AND having been in contact with a confirmed COVID-19 case in the last 14 days prior to onset of symptoms;

OR

A patient with severe acute respiratory infection (fever and at least one sign/symptom of respiratory disease eg. cough, shortness of breath) AND requiring hospitalisation AND with no other etiology that fully explains the clinical presentation;

OR

A case for whom testing for COVID-19 is inconclusive.

**Laboratory confirmed case**[2]

A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

**Experience at our institution**

As per the directives of the ICMR Guidelines for COVID-19 testing in pregnant women, our hospital, a non-COVID designated centre, started testing all pregnant patients at entry point in Labour ward casualty/triage area by collecting nasopharyngeal swabs for COVID-19. The swabs were collected with a swab stick and sent in transport medium for COVID-19 testing by real time PCR. Samples were processed according to the standards prescribed by GOI. Based on the results, patients with positive results were triaged and managed as per the standard protocols for further care.

Patients were admitted and managed as per their symptoms according to standard protocols. Labour management was as per standard guidelines and Caesarean section was done only for obstetric indications.[3]

Symptomatic and suspected patients were delivered in a separate isolation room; operative procedures in suspected cases were performed in a separate designated operation theatre as per standard guidelines.[4]

Precautions as per standard protocols were implemented in Labour Ward and Operation Theatre viz. wearing Personal Protective Equipment (PPE), N95 masks and face shield.[5]

The trend of COVID positive cases we observed at Dr RN Cooper Hospital in 2020 showed a decline in the last quarter but rise at the end of year.[6]

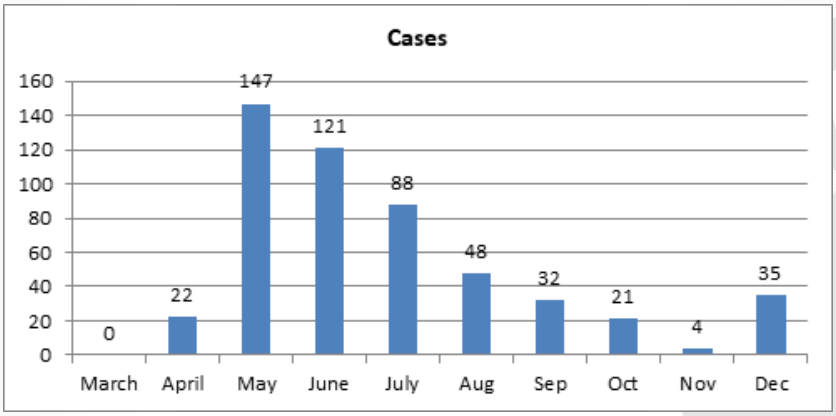



**Fig 1 Cases managed at Dr RN Cooper Hospital**

**Management of COVID positive pregnant patients**

Health Care Personnel (HCP) to be in full Personal Protection Equipment (PPE), and patients can be categorized into three groups irrespective of gestational age based on which type further care and management are required.[7,8]

| | |
|---|---|
| **Group A** | Asymptomatic/Patients with mild symptoms<br>**RR <24/m & SpO2 >94% in room air** |
| **Group B** | Symptomatic patient with mild to moderate pneumonia with no signs of severe disease<br>**RR 24-30/m (or) SpO2 90-94% at Room Air** |
| **Group C** | Symptomatic patient with severe pneumonia with<br>**RR > 30/min (or) SpO2 < 90% at Room Air (or) less than 94% with oxygen, ARDS, septic shock** |

**Table 1 Patient triage**

**Table 2 Clinical categories[7,8]**

| Clinical category | Description | Parameters |
|---|---|---|
| Asymptomatic | No symptoms | SpO2: ≥94% in room air RR ≤ 24/m<br>**No evidence of hypoxemia or breathlessness** |
| Mild | Patients with uncomplicated upper respiratory tract infection | SpO2: ≥94% in room air RR ≤ 24/m<br>**No evidence of hypoxemia or breathlessness** |
| Moderate | Pneumonia with **no signs of severe disease** | Sp02 94-90% in room air<br>RR 24-30/m |
| Severe | Severe pneumonia | SpO2 < 90% room air<br>RR >30/m |
| **Critical** | **Acute Respiratory Distress Syndrome (ARDS)** | Onset: new or worsening respiratory symptoms within one week of known clinical insult.<br>Chest imaging (Chest X ray and portable bed side lung ultrasound): bilateral opacities, not fully explained by effusions, lobar or lung collapse, or nodules.<br>Origin of pulmonary infiltrates: respiratory failure not fully explained by cardiac failure |

| | | |
|---|---|---|
| | | or fluid overload. Need objective assessment (eg. echocardiography) to exclude hydrostatic cause of infiltrates/ oedema if no risk factor present. |
| **Critical** | Septic shock | Adults: persisting hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥65 mmHg and serum lactate level > 2 mmol/L |

**Table 3 Investigations**[7,8]

| Timing | Mild | Moderate | Severe/Critical |
|---|---|---|---|
| At admission | CBC<br>RBS<br>ECG<br>$HbA_1C$ (if diabetic)<br>d-Dimer<br>**(If starting on Tab Favipiravir)**<br>RFT<br>s Electrolytes<br>s Uric Acid | Complete Blood Count (with N/L ratio)<br>LFT, RFT, RBS<br>s Electrolytes<br>12 lead ECG<br>Chest X Ray PA view<br>CRP, d-Dimer<br>s Ferritin, s LDH<br>Procalcitonin<br>Trop– I and T<br>PT/INR<br>ABG<br>CT Thorax (if available)<br>**Blood culture (if total count is high)**<br>**IL–6**<br>**s Cortisol**<br>**2D Echocardiography**<br>**COVID Antibody IgM/IgG Tests** | Complete Blood Count (with N/L ratio)<br>LFT, RFT, RBS<br>s Electrolytes<br>12 lead ECG<br>Chest X Ray PA view<br>CRP, d-Dimer<br>s Ferritin, s LDH<br>Procalcitonin<br>Trop– I and T<br>PT/INR<br>ABG<br>CT Thorax (if available)<br>**Blood culture (if total count is high)**<br>**IL–6**<br>**s Cortisol**<br>**s $Mg^{2+}$, s $Ca^{2+}$**<br>**2D Echocardiography**<br>**NT-proBNP**<br>**HsCRP**<br>**s Lactate**<br>**COVID Antibody IgM/IgG** |

| | | | |
|---|---|---|---|
| Repeat daily | _ | Complete Blood Count, LFT, RFT, ABG | Complete Blood Count, LFT, RFT, ABG |
| Repeat every 72 hrs | **If initial d-Dimer is high** | CRP, d-Dimer<br>s Ferritin, s LDH<br>Chest Xray | CRP, d-Dimer<br>s Ferritin, s LDH<br>Chest Xray |
| At the time of discharge | _ | CRP, d-Dimer<br>s Ferritin, s LDH<br>Chest Xray | CRP, d-Dimer<br>s Ferritin, s LDH Chest Xray RT-PCR nasal and throat<br>swab |

**Other investigations should be done based on patient's co-morbid status**

**Table 4 Identification of high-risk patients[8,9,10]**

| Co-morbidity | Clinically | Laboratory value |
|---|---|---|
| Obesity | Hypoxia - SpO2 < 94% | **Lymphopenia ss (<20) with Neutrophil/Lymphocyte ratio > 17** |
| Ischaemic heart disease | Tachycardia > 100/min | CRP > 100 mg/L |
| Diabetes | Respiratory distress RR > 30/min | s Ferritin > 300 microg/L |
| Hypertension | Hypotension<br>systolic BP < 90mm Hg | **LDH > 450** |
| Lung disease (COPD/ Asthma/ Post TB sequelae) | Altered sensorium | d-Dimer > 1000ng/m L* (Generally raised in pregnancy) |
| Chronic kidney disease/ Chronic liver disease | | |
| Immunosuppression / HIV / Malignancy | | |
| | | |

## General measures and guidelines

1. Categorize as per A, B, C based on symptoms, SpO2 and respiratory rate
2. Supportive care:

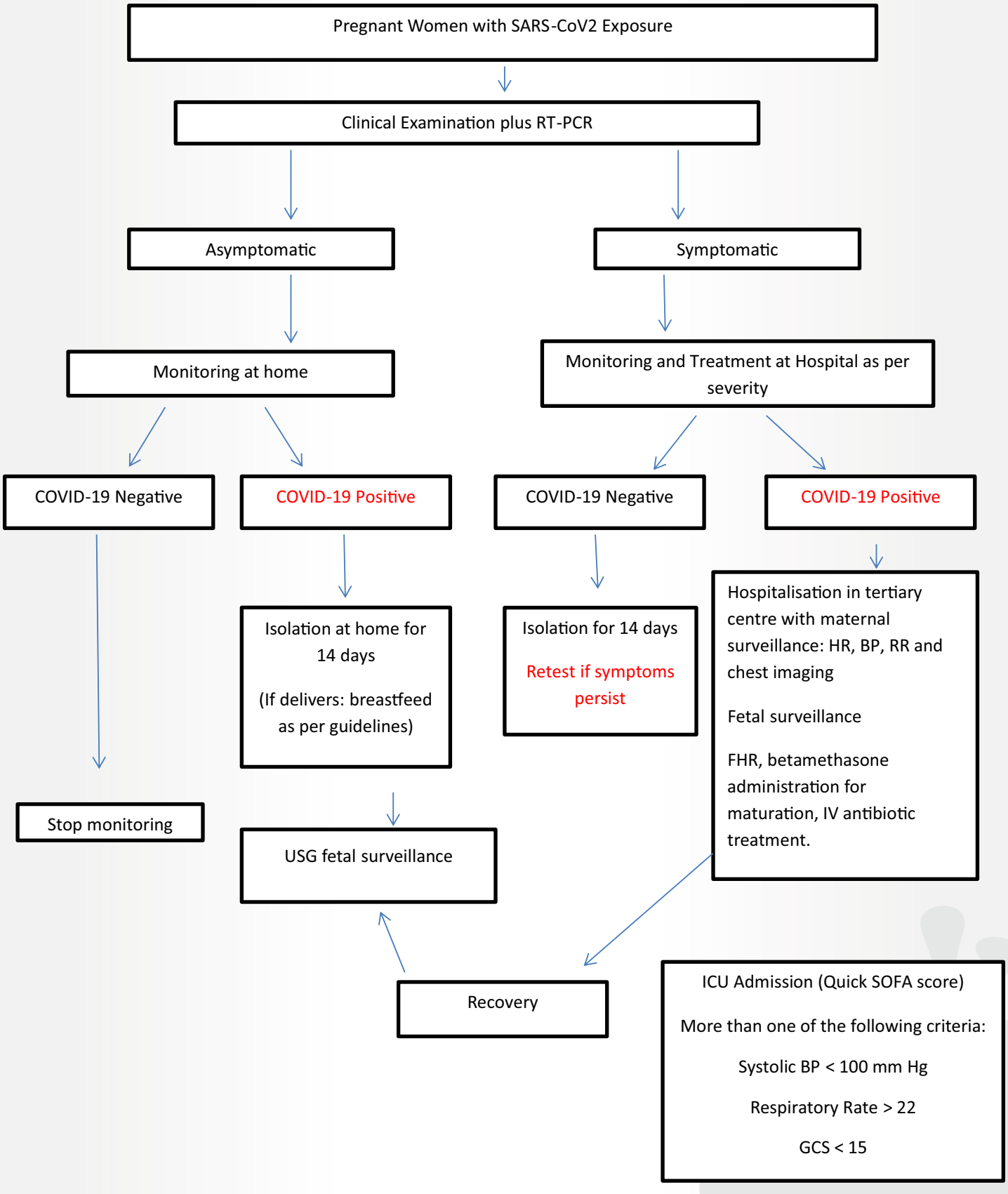
- Finger pulse oximeter for continuous monitoring of heart rate and oxygen saturation
- Start oxygen with mask at saturation of 94% or lower
- HFNC to be used if there is failed oxygen therapy and non-invasive ventilation (NIV) to be used appropriately with two limb circuit expiratory filters
- Counselling of COVID-19 patients (by counsellor/psychologist/psychiatrist)
- Normal feeding, no dietary restrictions, good oral hydration
- Maintenance IV fluids (If indicated)
- Maintain blood glucose levels <180 mg/dl
- Avoid using NSAIDs other than paracetamol unless absolutely necessary
- Avoid using nebulized drugs to avoid aerosolization of virus. Prefer MDI with spacer
- Antibiotic selection in case of superadded bacterial pneumonia should be according to institution antibiogram

**Table 5 Group A (mild cases)** [8,9,10]

| Treatment | Precautions |
|---|---|
| **Antiviral therapy**<br>Tab Hydroxychloroquin (Hcq) 400 mg BD for 1 day followed by 200mg 1-0-1 X 4 days for patients in COVID Care Center/ home isolation<br><br>OR<br><br>Tab Favipiravir 1800mg 1-0-1 on day 1 f/b 800 mg 1-0-1 for 6 days (total 7 days) for patients in DCHC<br>(Role in pregnancy is controversial)<br><br>OR<br><br>If Tab HCQ/Tab Favipiravir is contraindicated, then combination of Cap Doxycyclin 100 mg 1-0-1 for 5 days + Tab Ivermectin 12mg 1-0-0 for 3 days (both are contraindicated in pregnancy)<br>Cap Oseltamavir 75 mg 1-0-1 for 5 days | • Categorisation should be reassessed regularly<br><br>• Contraindication for Hcq<br>• QT interval > 480ms<br>• Pre-existing cardiomyopathy and cardiac rhythm disorders<br>• History of unexplained syncope<br>• Retinopathy<br>• Hypersensitivity to HCQ or 4- aminoquinoline compounds<br>• G6PD deficiency<br>• Epilepsy<br>• Hypokalemia ($K^+$ < 3 mEq/L)<br><br>• **Contraindications for Tab Favipiravir** Hyperuricaemia, severe hepatic and renal impairment, pregnant women and lactating mothers |

| | |
|---|---|
| **Anticoagulation**<br>Inj Enoxaparin 40mg SC 1-0-0 X 7 days (if d-Dimer is more than 1000 ng/ml (or) Xray/CT thorax showing ground glass opacities)<br><br>**Supportive therapy**<br>Tab Zinc 50 mg 0-1-0 X 7 days<br>Tab Vitamin C 500 mg 1-1-1 X 7 days<br>Cap Vit D 60K per week for 4 weeks<br>Tab N-acetylcysteine 600 mg 1-1-1 (if patient has cough) | • Pregnancy is not a contraindication for HCQ<br><br>• Cap Oseltamavir is advised due to possibility of H1N1 co -infection along with COVID -19 disease with present weather condition. Its usage will be reviewed at a later date. |

**Fig 2 Flowchart for management of COVID-19 positive pregnant women[17]**



**Severe Failure Criteria: (consider Caesarean delivery)**
**Septic shock, Acute Organ Failure, Fetal distress**

**Delivery**

**Before 24 weeks:** If severe maternal illness, consider MTP

**After 24 wks:** On site/IRNP, vaginal delivery, early clamping and cleaning of newborn, newborn monitoring in IRNP and newborn RT-PCR test, breastfeeding with precautions

**Management of LSCS in COVID positive patients**

The majority of people (pregnant and general population) may be asymptomatic or present with respiratory symptoms of COVID-19 infection. Most pregnant women are asymptomatic or have mild to moderate like symptoms of cough, sore throat, and fever. Few have difficulty in breathing or shortness of breath. Severe form of respiratory disease is usually associated with pregnant woman having co-morbid conditions such as diabetes, hypertension, obesity, respiratory disease or advanced age.[11]

There is no rationale to induce labour or deliver a woman early because of COVID-19 infection. Decisions regarding route of delivery should be as per standard obstetric practice or as per the maternal condition.[3] There is no evidence that epidural or spinal analgesia or anaesthesia is contraindicated even in the cases of confirmed infection. Epidural analgesia should, therefore, be recommended in labour to women with suspected/confirmed COVID19 to minimise the need for general anaesthesia if urgent delivery is needed.[6]

Anaesthesiologists have a high exposure risk to COVID when conducting Caesarean section for pregnant women with pneumonia. To minimise the occupational risk of anaesthesiologists, special arrangement of using the combined spinal-epidural anaesthesia (CSEA) for COVID-19 patients are used unless contraindicated. According to the Practice Guidelines for Obstetric Anaesthesia by the American Society of Anaesthesiologists Task Force on Obstetric Anaesthesia and the Society for Obstetric Anaesthesia and Perinatology, CSEA has the advantages of combining anaesthesia during operations with postpartum patient controlled epidural analgesia. Compared to epidural anaesthesia, CSEA can provide a more effective and rapid onset of analgesia for labour.[12]

Owing to lack of facilities, spinal anaesthesia (unless contraindicated) is preferred over general anaesthesia, which is associated with maximum aerosol generation. However, in the situation where there is respiratory compromise, general anaesthesia and subsequent ventilation will be needed.[13] Newborn care should be practised as per

routine. At present, testing is recommended if the mother has COVID-19 infection or if the baby is symptomatic. Breastfeeding is encouraged with good hygiene practices.[6]

**Role of thromboprophylaxis**

Pregnancy is a hypercoagulable state characterised by increased prothrombotic factors, such as factors VII, VIII, X, XII, von Willebrand factor and fibrinogen, as well as decreased protein S and altered fibrinolysis, especially in the peripartum period.[14] Postpartum, the prothrombotic changes of coagulation and fibrinolysis take up to 12 weeks to return to the pre-pregnancy state. Normal levels of several coagulation biomarkers differ in pregnancy. Fibrinogen levels can double, the aPTT becomes slightly shortened, d-dimer levels increase throughout pregnancy and, in 99% of women, levels in the third trimester are above the established normal for non-pregnant patients.[14] Inj LMWH 0.6 mg (subcutaneous) is routinely used for thromboprophylaxis in pregnancy.

The RCOG guideline for thromboprophylaxis is as follows[15]

**1. Antepartum (self-isolating at home)**

- Those already receiving thromboprophylaxis should continue
- If VTE risk score at booking visit is ≥3, prophylactic LMWH should be recommended (and continued until recovery from illness for 7-14 days).
- For others, assess VTE risk through a remote or in-person clinical review and prescribe thromboprophylaxis on a case-by-case basis.

**2. Antepartum, hospitalised**

- VTE prophylaxis should be prescribed during admission unless contraindicated or birth expected within 12 hours.

**3. Postpartum**

- Conduct VTE risk-assessment following birth.
- For those with confirmed SARS-CoV-2 infection, prescribe prophylactic LMWH, unless contraindicated ×10 days.

**Key practice points**

- Test and Triage
- Notify
- Preparedness at workplace
- Protocols
- Protect yourself and your team
- Periodic review

As obstetricians, the onus of outcome of two patients, mother and fetus rests on us hence we need to be fully in sync with the current protocols. Despite the high number of cases in India, the case fatality ratio in India is around 1.5%, low compared to other countries.[16] With appropriate care, most pregnant women with COVID-19 should have a favourable outcome.

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# Private Sector Maternity Services During the COVID-19 Pandemic

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## Background

There has been an unprecedented change in our way of life and work since the COVID-19 pandemic has begun a few months ago. The relatively unknown nature of the pathogen and its characteristics has added to the upheaval caused by the sheer volume of the infected individuals that the world has witnessed and is expecting to see. Every country has its mechanisms and infrastructure into which the healthcare response has to be integrated. The continuity of ongoing care for time sensitive health matters such as maternity care is essential.

## Organization of healthcare facilities

At the outset, it is essential to recognize the infrastructure requirements for COVID or non-COVID healthcare maternity services facilities. They are outlined in the table below.

| | **COVID Maternity Hospital in private sector** | **Non-COVID Maternity Hospital in private sector** |
|---|---|---|
| Typical set up in private sector | Large multispecialty hospitals | Small to medium single speciality (maternity care) hospitals or nursing homes |
| Infrastructure | Separate building with multiple entry and exit facilities, multiple staircases or elevators where some of these can be kept separate | Part of a building where there is a single entry or exit and segregation is not possible |
| | for suspect or confirmed cases<br><br>Separate dedicated Labour Room and Operation Theatre | Separate dedicated Labour Room and Operation Theatre are not possible |
| Medical facilities | Equipped to manage maternity care and medical issues related to the infection.<br><br>Should have facilities similar to a Dedicated COVID Hospital (DCH) | Equipped to manage maternity care and has back-up facilities for emergencies. |
| Personal Protective Equipment | Should have adequate stock of various levels of PPE to cater to the requirements of treating large | Should have stock enough to cover for a few cases for rendering first aid or emergency treatment for suspected or confirmed cases |

COVID facilities would further be designated to represent various levels of healthcare with the fever clinics and COVID Care Centres (CCC) at the bottom and facilities expanding to the Dedicated COVID Health Centres (DCHC) and Dedicate COVID Hospitals (DCH).[1,2] **The DCH is the site where labour and delivery will be managed for suspected or confirmed COVID positive women.**

In the private sector, large multispecialty hospitals can be organized according to the guidance given for the public sector as facilities, infrastructure and finances are feasible. However, this does not hold true for the small to medium sized private healthcare facility which is usually a doctor-owned and operated single specialty (maternity care) facility. Most of such establishments should continue to function as non-COVID hospitals. In India, a significant proportion of maternity care is provided by the private sector and it needs to continue to provide services so that the public healthcare infrastructure does not get overburdened.

**The testing conundrum**

As per the ICMR, the criteria for testing non-pregnant persons are applicable to pregnant women.[3] It is essentially meant for acute respiratory illness with exposure, travel, contact or a HCW or requiring hospitalization. Asymptomatic individuals should be tested between 5 to 14 days of exposure to a known contact. Symptomatic individuals with influenza like illness from hot spots should be tested by RT-PCR (within 7 days) or serology (after 7 days). In addition, there are some special criteria for testing with regards to pregnancy. Pregnant women residing in cluster / containment areas or in large migration gatherings/evacuees centre from hotspot districts presenting in labour or likely to deliver in next 5 days should be tested even if asymptomatic.[4]

There is no recommendation for testing every pregnant woman. At present, universal testing is not feasible, even for a special category such as pregnant women. Besides considerations of cost, the RT-PCR test has a high false negative rate. A detailed critique of universal testing in India is available.[5]

**Checklist tool to identify suspected cases**

In the absence of universal testing, the primary issue remains identification of infected pregnant women. In the absence of a reliable, fast and feasible serology test, a checklist tool is useful.[6] The checklist tool should be used in advance of a patient's physical visit. It should be administered remotely by telemedicine pathways, ideally. For walk-in patients, it can be administered telephonically with the patient waiting outside the facility or at the latest, in the waiting area. If the pregnant woman falls into the group which needs testing, she should be considered as a suspect case until the test report is obtained in the negative. If there is a suspicion, the patient should be directed to a COVID hospital for further care and management. Referral pathways should be established and every private sector non-COVID maternity hospital should be mapped to a private sector COVID hospital providing maternity care as well as having linkages to a public sector COVID hospital for the same.

**COVID-19 SCREENING CHECKLIST TOOL**

- Do you have fever?
- Do you have features of respiratory disease (runny nose, altered smell sensation, blocked nose, cough, sore throat, difficulty in breathing or feeling breathless)?
- Do you have travel abroad in the last 14 days?
- Have you travelled from anywhere outside your locality in the last 14 days? If yes, was this area a hotspot?
- Do you have household or close and direct contact with a person who meets the above two criteria of travel?
- Do you have household or close and direct contact with a person who is confirmed to have COVID-19 infection or who is suspected and undergoing testing?
- Do you reside in a hotspot / containment area / cluster / with migrants / with evacuees from such areas?
- Are you a healthcare provider who has been to work in the last 14 days?
- Have you been hospitalized in the last 14 days?

**Administrative aspects:**

- Only one attendant should accompany the woman and the same person should stay with her for the duration of the admission.
- Visitors should be prohibited entry. This minimizes the traffic to the hospital.
- There should not be any health camps, health education seminars or hospital gatherings or medical representative visits.
- In case of a suspected or confirmed case being admitted to a Non-COVID hospital, notification has to be made to the local health authority.
- By far and large, local health authorities have now agreed that hospitals will not be sealed in the circumstances of a suspected or confirmed COVID case being treated or admitted there as it will result in a marked reduction in facilities from sealing and also from the fear that the premises will be sealed, earning it disrepute.

**Telemedicine during the pandemic**

Telemedicine has been permitted by the Medical Council of India at the present time.[7,8] Below are some pointers towards safe telemedicine practice. Various forms of telemedicine can be practiced including a telephone call, various video or audio media or specialized platforms. It is preferable to provide first consultations by video format to build a rapport. Prescriptions should be provided in a standard format.

**Routine antenatal care during the pandemic**

**Antenatal care visits**

Following the principles of social distancing, it is advisable to minimize the number of antenatal in-person visits. There is a minimum level of antenatal care and investigations which are necessary. For the low risk, asymptomatic and uninfected woman, at present, the recommended strategy for antenatal care is to conduct antenatal care visits by phone or video call supplemented with home blood pressure monitoring.

Some visits may be deferred. Questions, counselling and minor ailments can be addressed remotely.[9,10] An ultrasound is advised at 12-13 weeks and at 18-22 weeks. Pregnancy visits can be timed with these sonographies. The next visit can be at about 30 to 32 weeks. Vaccinations and antenatal profile (blood and other investigations) can be planned during these visits. Growth scans in the last trimester are advised or performed only if indicated. Women are advised to note fetal movements every day. For women who have high risk factors, the pattern of visits and investigations will have to be individualized.

**Providing antenatal care**

Some useful practices to follow in providing antenatal care are outlined below to enhance safety and ensure smooth functioning of the clinic.

- Appointments should be scheduled to avoid waiting time and exposure. The woman should be screened with the checklist tool on the telephone.
- The patient should make the visit alone or at the most, with one attendant.
- The patient and attendant should follow hand hygiene and mask use.
- The doctor should wear appropriate PPE (uniform, scrubs or apron with surgical cap, mask – 3-layer or N95 preferably) while examining every patient.
- The consulting room should be kept free from clutter and have the minimum amount of furniture necessary. The furniture should be hard surfaced to facilitate cleaning.
- The patient examination table can have disposable covers where possible.
- The number of fomites (mobile phones, electronic devices, pens, measuring tapes, stethoscopes and BP apparatus) should be kept to a minimum and frequently sanitized.
- Avoid handling paper, files and reports that the patient brings. It can be seen with the patient holding them or by photographs.
- The consulting room should be cleaned regularly. At the end of the clinic, the examination table should be disinfected. The room may be fumigated at the end of the day.

**Routine labour care during the pandemic**

For the woman who is not infected and with no suspicion (no positive response on the checklist tool), care should proceed as usual practice. A subgroup of women who present in labour with in an asymptomatic state and who have infection will always remain undetectable. Even if universal testing before or in labour is attempted; a large proportion will not be diagnosed.[11] It is believed that the risk of such women transmitting infection, especially with procedures where aerosol is not generated, is very low. Typically, procedures during labour and delivery, such as examinations, rupture of membranes, regional analgesia and anaesthesia, instrumental delivery or caesarean section are do not generate respiratory aerosol. Therefore, for women with no suspicion or diagnosis, standard precautions and added respiratory protection PPE (N95 mask with a three-ply mask on top, surgical cap and face shield) should be adequate.

All women who are admitted to a non-COVID hospital should be additionally monitored for respiratory features. The following features could indicate an undiagnosed COVID-19 infection which requires intensive care. This would be a rare event, which should not be missed.

- respiratory rate > 30 breaths/min
- oxygen saturation < or = 93% at a rest
- arterial partial pressure of oxygen (PaO2)/oxygen concentration (FiO2) < 300 mm Hg
- patients with > 50% lesions progression within 24 to 48 hours in lung imaging

**Labour triage for women with COVID-19 infection**

A protocol should be in place in every maternity unit to receive pregnant women in labour or suspected labour with confirmed or suspected COVID-19 infection. The outline of the arrangements for healthcare facilities has been mentioned in an earlier section. The same principles should be followed. The following aspects should be borne in mind in planning for this triage process. [12]

- The woman should call in advance to alert the maternity unit about her arrival whenever this is possible. This will give some time to the healthcare workers to prepare in triage and don the PPE.
- The woman should use private transport or an ambulance when possible to reach the maternity unit.
- She should be met with appropriately donned PPE at reception itself.
- Reception and triage in the same room as to be used for admission in labour and delivery. This should be a room with negative pressure. But it is not available everywhere.
- Keep the room free from any unnecessary items (decorations, extra chairs, etc) which could act as infected fomites later.
- There should be a restriction on the number of attendants allowed with the woman. There should be a restriction on the entry and exit of non-essential staff into the room. The companion of the woman should be treated as infected and all precautions should be taken.

**Management of labour and delivery in women with COVID-19 infection**

In all circumstances, maternity care providers should continue to provide client-centred, respectful skilled care and support. Birth attendants should be limited to one named contact. There should be adequate counselling of the mother about the infection.

**Separate delivery room and operation theatres** are required for management of suspected or confirmed COVID-19 mothers. Resources required include space, equipment, supplies and trained healthcare providers for delivery, caesarean section and neonatal resuscitation. Depending on the clinical picture and severity of the condition, a multispeciality team may be involved in caring for the pregnant woman in labour. The anaesthetist and neonatologist should be informed of such a woman presenting in labour.

Timing of delivery should not be altered on the basis of COVID-19 infection. The presence of infection is not an indication to induce labour or deliver the woman. The exception to this would be the critically ill pregnant woman where delivery may be indicated to relieve the extra metabolic and pulmonary load. However, the possible benefits of this need to be weighed against the possible risks of worsening the systemic status with a surgical

intervention. Such a decision has to be guided by individual circumstances including the degree of clinical stability, gestational age, available infrastructure and the couple's wishes.

In labour, monitoring should include the periodic evaluation of the respiratory status with a watch for symptoms of difficulty or shortness of breath, respiratory rate, pulse rate and oxygen saturation on pulse oximetry. If there is a deterioration of these features, intensive care measures would be required including ventilation.

As such, the pregnant woman with COVID-19 infection can be allowed to labour and indications for interventions should follow standard obstetric practice. A prolonged labour may be detrimental to the general condition of a woman who has systemic illness. There could be further maternal deterioration. Prolonged oxytocin infusion and volume overload should be avoided. With every examination and contact, healthcare workers should be mindful of adequate protective gear. An intravenous access should be established and fluids should be restricted in labour. It may be prudent to offer continuous electronic fetal monitoring in labour for women with COVID-19 infection wherever such facilities are available. The second stage of labour should be cut short to prevent maternal exhaustion and reducing maternal efforts, in case where there is respiratory involvement by the infection.

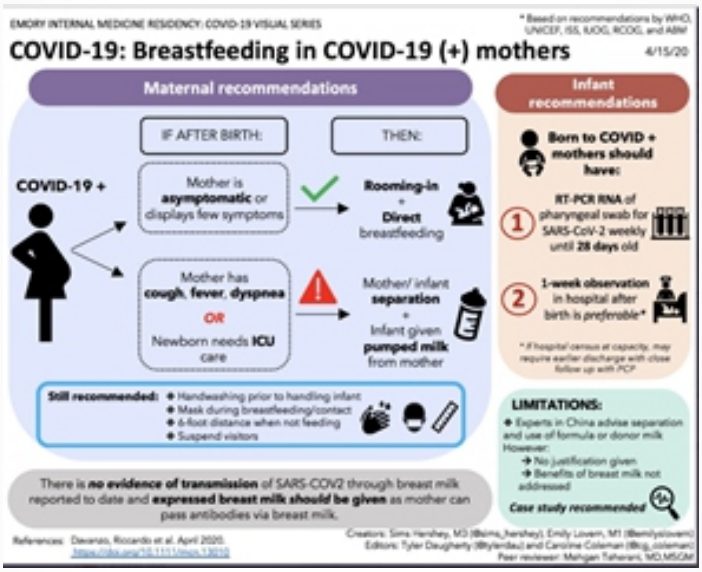
At present, pregnant women have almost universally been delivered by caesarean section when they present in labour with COVID-19 infection. There is no proven scientific rationale for this. It could reflect local preference and practices .[13] Operating with PPE gear can be a formidable task as has been described from some personal experiences.

If a woman with COVID-19 infection has respiratory features, and has PPH, carboprost should be avoided. Methylergometrine can be used with caution. Oxytocin, misoprostol and tranexamic acid can be used as usual.

**Breastfeeding and the COVID-19 infected mother**

As present knowledge stands, there is no evidence that COVID-19 is secreted in breast milk. As breast milk is the best source of nutrition and general immunity for the infant, WHO encourages it. [14] The main risk for infants of breastfeeding is the close contact with the mother, who is also likely to share infective airborne droplets. Precautions should be taken to limit spread to the baby by keeping the baby bay at a distance of at least one metre, hand hygiene and mask use.

The infographic[15] below illustrates the above points and is a useful learning and training tool.

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# COVID-19 Vaccination: A Hope for Humanity

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***Medical science has proven time and again that when the resources are provided, great progress in the treatment, cure, and prevention of disease can occur***
**- Sir Alexander Fleming**

We are at war with COVID 19. A war we must win if we have to return to the life we once lived and cherished. Vaccines are today, the most powerful weapon in our arsenal. These vaccines will give us a head start in our fight, priming the immune system to mount a robust response and vanquish the enemy, whenever challenged. For vaccination to succeed, a strategic identification of the invader's weakness and the immune system's successful attack against it are both crucial. Moreover, the swiftness and capability to deploy this weapon (medical intervention) across the entire humankind will determine how long this battle drags on and how many casualties are incurred.

**COVID-19 vaccine development**

Vaccine development is a well-established process that aims to provide an effective and safe vaccine. Any vaccine planned for use has to go through a defined process. At the outset, preclinical studies of the candidate vaccine are conducted in animals to ensure an adequate protective immune response. Toxicity studies on animals are also conducted to ensure safety.

Successful candidates progress to human trials which are divided into Phase I, II, III. In Phase I trials, a small number of healthy volunteers (usually fewer than 100) generally in the age

group of 18-55 years are enrolled. The primary goal is to establish safety of the vaccine. Vaccine immunogenicity of various dose formulations is also studied. Most Phase I studies have data safety and monitoring committees (DSMCs) that closely monitor trial participants. All Phase I studies have halting rules and the trial is stopped if any severe reaction is encountered.

Vaccines that are deemed safe move on to Phase II trials, where the number of participants is expanded further to several hundred. Safety and immunogenicity data is established under the strict supervision by the DSMCs. Successful vaccines commence Phase III trials, which aim to provide the efficacy data of the vaccine. Participants are randomly assigned and blinded to receipt of the candidate vaccine or control preparation. Study participants are tested for disease when they develop defined signs and symptoms.

Vaccine efficacy in percent is the reduction in specific disease incidence among those who received vaccine versus those who received the control product. Generally, vaccines complete each phase of the trial and obtain authorisation from relevant health authorities to move on to the next stage. In the case of COVID-19 vaccines, candidates have often combined Phase I and II, and Phase II and III studies with seamless transition from one to the next thereby accelerating the development process.

COVID-19 vaccine development benefited greatly from the experience of SARS and MERS vaccine development (both being corona viruses with a similar illness profile as COVID- 19) which provided two critical insights. First, the large surface spike protein was the antigenic target most likely to elicit protective immunity and second, vaccine enhanced disease was a real possibility that could derail all the best efforts. In preclinical animal studies of those vaccines, there were instances, post vaccination, of a non-neutralising immune response and a severe form of eosinophilic lung disease upon subsequent infection challenge. Consequently, stringent criteria for the detection of vaccine enhanced disease were formulated which every vaccine candidate has satisfied prior to the commencement of trials.

**Vaccine types, dosing and efficacy**

The SARS CoV2 virus has a similar antigenic target. Antibodies and cell mediated immune responses to the Receptor Binding Domain (RBD) of the surface spike protein prevent fusion with the human ACE2 receptors, thereby blocking virus entry and eventually neutralising the virus. The response elicited after vaccination resembles that seen after natural infection in both quality and magnitude, and appears to be effective in preventing infection. RBD is then the predominant target for most vaccines in development. These vaccines use different platforms to package and present the target antigen. Current COVID-19 vaccines employ one of five vaccine platforms namely: inactivated vaccines, live attenuated vaccines, vector vaccines, recombinant protein vaccines, and DNA/RNA vaccines. Inactivated and live attenuated vaccines present the entire viral particle to the immune system and elicit a response against a multitude of viral antigens. Live attenuated vaccines potentially mimic natural infection and could be administered intranasally, resulting in local mucosal immunity as well as systemic immunity. Unfortunately,

they carry the risk of vaccine strain infection and cannot be used in pregnancy and immunocompromised individuals. All candidate vaccines based on this platform are in preclinical studies.

Inactivated vaccines are produced in a biosafety level 3 establishment and involve growing of the SARS CoV2 virus in cell culture followed by its chemical inactivation. It is then combined with an adjuvant which boosts the immunogenicity.

Vector vaccines use a different vaccine vector (eg. adenovirus) that is genetically engineered to express the intended antigenic target (eg. RBD). The vector virus used could have the potential to multiply in vivo (replication competent vector vaccine) or be devoid of it (replication incompetent vector vaccine). The problem with vector vaccines is the possibility of prior human exposure to the vector virus which can attenuate immunogenicity.

Recombinant protein vaccines utilise viral proteins that are expressed using a variety of systems including insect and mammalian cells, yeast or plants. These do not require live virus but the yield depends on the efficiency of the production process. NVX-CoV2373 (Novavax) is a recombinant protein nanoparticle vaccine composed of trimeric spike glycoproteins and is in Phase III trials.

RNA vaccines employ a novel approach, wherein RNA resembling that in the viral genome is packaged and presented to the host. The mRNA is translated in the cytoplasm of the host cells to the desired viral protein. This protein serves as the antigen against which the immune response is mounted. The mRNA does not enter the host cell nucleus and does not bind to or modulate the host DNA.

**Table 1: Characteristics of the available COVID-19 vaccines**

| Name | Platform | Dosing regimen | Efficacy | Side effects |
|---|---|---|---|---|
| BNT162b2 (BioNTech and Pfizer) | Lipid nanoparticle mRNA | 2 doses IM, 21 days apart | 95% at or after 7 days of second vaccine dose.<br><br>91.7% among adults ≥ 65 years who had other medical comorbidities or obesity. | Common and more like to be experienced by younger individuals and after the 2nd dose.<br>Fever (16%), severe fatigue (4%), headache (3%).<br>A few cases of severe |

| | | | | |
|---|---|---|---|---|
| | | | | anaphylactoid reaction have been reported. Surveillance for vaccine induced Bell's palsy recommended. |
| mRNA 1273 (Moderna) | Lipid nanoparticle mRNA | 2 doses IM, 28 days apart | 94.1% at or after 14 days of the second dose. 86.4% among individuals > 65 years of age. | Common and more like to be experienced by younger individuals and after the 2nd dose. Fever (17%), severe fatigue (10%), myalgia (10%). Surveillance for vaccine induced Bell's Palsy recommended |
| ChAdOx1 nCoV-19/AZD1222 (University of Oxford, `AstraZeneca, and the Serum Institute of India) | Replication-incompetent chimpanzee adenovirus vector that expresses the spike protein. | 2 doses IM, 4-6 weeks apart (DCGI approved regimen) | 70.4% at or after 14 days following the second dose. | Local and systemic reactions common including pain, feeling feverish, chills, muscle ache, headache, and malaise. One case of possible vaccine |

| | | | | |
|---|---|---|---|---|
| | | | | associated transverse myelitis. |
| BBV152 (Covaxin manufactured by Bharat Biotech) | Whole virion inactivated vaccine with a Toll like receptor 7/8 agonist molecule adsorbed to alum as adjuvant. | 2 dose IM, 28 days apart. | Phase III trials are in progress and interim analysis not yet reported. | Data from trials not yet published to provide accurate information. |
| Sputnik V (Gamaleya Institute) | Two replication-incompetent adenovirus vectors that express a full-length spike glycoprotein | 2 doses IM, 21 days apart. (Adenovirus 26 vector dose followed by an adenovirus 5 vector boosting dose) | 95% at 21 days after second dose. (Interim analysis data released as a press note. Not yet published in a peer reviewed journal) | Pain at injection site (58%), hyperthermia (50%), headache (42%), asthenia (28%), and muscle and joint pain (24%) as of data from Phase II trial. |

**It is amply evident that multiple vaccines are likely to be available with many more added in the near future. But do we really need so many options?**

If every single person on this planet has to vaccinated, multiple vaccine producers will be essential to ensure the swift production of the requisite number of doses. Moreover, every vaccine has its own unique transport and storage requirements making logistics planning easier if varied options exist. For instance, the BioNTech-Pfizer vaccine needs storage at ultralow freezing temperatures (–70° C) and the Moderna vaccine at low freezing temperatures (–20° C), which makes it unviable for rapid dissemination even in the most advanced nations. The Astrazeneca-Oxford vaccine and Covaxin are both transported and stored at refrigerator temperatures (2-8° C) and logistically easier to distribute even to remote areas. In effect greater options will allow greater flexibility in planning vaccination drives.

**The reward for work well done is the opportunity to do more - Jonas Salk**

**With such a plethora of vaccine options available, which one should be the preferred choice?**

With limited availability currently, a choice of vaccine is unlikely and you should consider taking whichever is available. It is mandatory that the entire vaccination series be completed with only one type of vaccine. Currently, none of available vaccines can be used interchangeably.

**Vaccine safety**
**Are the vaccines safe for use especially with regards to the neurological events? Considering which, is waiting for natural immunity advisable?**

Let's consider both choices scientifically. The risk of death with COVID 19 is 1-3 in 100. There is no vaccine related death documented till date. The risk of severe COVID 19 with resultant long term debility is 5-10 per 100. The incidence of 'possible' vaccine associated transverse myelitis in the interim data for the Astrazeneca-Oxford vaccine is about 1 in 11,000 and likely to improve as more data accumulates. The incidence of Bell's palsy in the Moderna and BioNTech-Pfizer vaccines was about 1 in 5,000 (this is lower than the estimated prevalence of Bell's palsy in the general population).

This clearly establishes the fact that the vaccines are safer and strongly advocated. Waiting for natural infection would be foolhardy. However, taking the vaccine is voluntary and should not be a forced decision. Knowing the benefits of the vaccine and the unpredictability of COVID-19 should form the basis for an informed choice to avail the vaccine.

Like any other virus, SARS CoV2 will also evolve over time. Extensive research and surveillance have uncovered multiple mutations in the viral genome during the duration of the pandemic. The most widely discussed UK variant (B.1.1.7 lineage), was isolated in the United Kingdom and has a transmissibility rate that is 50-75% higher. There is no conclusive data to suggest that this variant causes more severe illness or will escape the immunity provided by current vaccines. Another variant isolated in South Africa (B.1.351 lineage) is also believed to have increased transmissibility.

**Vaccine administration**
**Should individuals who have already had COVID 19 also take the vaccine?**

It is recommended that all individuals irrespective of past history of COVID 19 infection, be vaccinated. Persons who are currently suffering from COVID 19, should wait till they have completed their mandatory isolation period prior to considering vaccination. Persons who have received convalescent plasma or monoclonal antibody as part of treatment for COVID 19 should postpone vaccine for at least 90 days to preempt blunted vaccine immunogenicity. Those who have recovered from COVID 19 infection may postpone vaccination for up to 90 days (from recovery ) to allow other susceptible individuals to avail vaccination benefit as doses are likely to be in short supply. Antibody tests are not required prior to vaccination.

**Can these vaccines be recommended for pregnant women and children?**

None of these vaccines have been tested in pregnant women. However, vaccine trials involving 2nd and 3rd trimester pregnant women are to be undertaken. As the currently available vaccines do not use live virus, they are unlikely to pose a threat during pregnancy. Pregnant women are classified as a high risk group for COVID 19 adverse outcomes.

In the current situation, a suggested approach could be to test for Anti SARS CoV2 antibodies in the pregnant woman. If antibody is positive, then discussion about vaccination could be delayed till delivery and beyond. If negative, vaccination advice should be individualised based on perceived risk during pregnancy, patient preference, understanding risk to fetus and national vaccination guidelines.

There are no trials conducted on children below 12 years of age and hence vaccination cannot currently be recommended for that age group. Phase III data from the Covaxin trial will provide information on vaccine safety and efficacy in children above 12 years of age.

**Conclusion**

Life post-vaccine may not change substantially. Masks and social distancing will remain as societal norms for the foreseeable future. The wait for a sizeable population to achieve herd immunity should be a collective goal. When that is achieved, we may be in a position to lower our guard. Vaccines represent the hope that humanity clings on to. It is up to humankind to be aware and responsible and embrace this medical intervention (marvel) to reclaim the life and livelihood that we have substantially lost.

**This is like a world war, except in this case, we are all on the same side. There's no way we would be as far as we are if governments, companies, doctors and scientists were not working so closely together - Bill Gates**

**Quick fact sheet**

| **Should the vaccine be taken if** | |
|---|---|
| Healthy adult (>18 years of age)? | Yes |
| Children (less than 18 years of age)? | No |
| Pregnant or lactating women? | No |
| Chronic medical conditions (Hypertension, diabetes, dyslipidemia, cardiac, pulmonary, renal, hepatic, neurological, cancers)? | Yes |
| Immunosuppression including HIV, chemotherapy, steroid use | Yes |
| Complete recovery from COVID 19 infection more than 3 months ago? | Yes |
| Current COVID 19 infection or recovery less than 3 months ago? | No |
| Allergy to a previous COVID vaccine dose? | No |
| Immediate or delayed allergy to vaccines or injectable medications, pharmaceutical products, and food items? | No |
| Bleeding and coagulation disorders? | With caution |
| Second dose of vaccine is of a different make as compared to the first dose? | No |

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