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## REVIEW OF COVID-19 PANDEMIC IN PREGNANCY WOMEN

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### ABSTRACT

There are now more than 37 million confirmed cases and around 1.08 million deaths being reported of COVID-19 worldwide. The disease has reached 190 countries, with the USA has the extremely affected country in the world followed by India, Brazil. Pregnant women are referred to be endangered group owing to the immunologic and physiologic changes over expressed during pregnancy that can increase the risk of severe maternal disease could lead to incidence of preterm and caesarean births. However, the risk in pregnancy not well known more data should be needed. Vertical transmission might be possible in some theoretical model through ACE2 receptor widely expressed in the placenta. Few anti-viral drugs like lopinavir + ritonavir, remdesivir along with hydroxychloroquine has contained some efficacy but further proof needed through large number of clinical trials. Vaccines trail also should be specified in pregnant women because current studies excluded pregnant women.

### KEYWORDS

COVID-19, Pregnant Women, Vertical transmission, Anti-vital and Vaccines.

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### INTRODUCTION

COVID-19 is a global public health crisis arising from Wuhan city (30 January 2020, Hubei province). The name corona was acquired from a Latin word, meaning “halo” or “crown”. The virus is ball shaped structure with a diameter of 120nm-160nm. Genome comprises positive sense single stranded RNA (ssRNA+). Previously the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) embarked in 2002 and 2012. The World Health Organization (WHO) on March 11, 2020, has been stated the novel corona virus (COVID-19) a global pandemic.

The COVID-19 pandemic leads the way severe to severe acute respiratory syndrome. The virus could be transmitted either by COVID-19-positive persons (through airborne droplets from human to human or human to animal) or from a contaminated surroundings. During the invasion the virus passes in human cells by way of ACE-2 exopeptidase receptor. The likelihood of infection among pregnant women is similar to the general population; however, pregnancy is a condition of different respiratory function and immunological changes. The potential of the COVID-19 to effect maternal, fetal and neonatal morbidity and other poor obstetrical consequences severe maternal disease could lead to incidence of preterm and caesarean births. With a shortness of approved treatment options for infection, an advance to suppress the spread of disease is in urgent need. The WHO guidelines were common, suggesting management of sign and symptoms, advice well care of paediatric patients, pregnant women and patients with specific co-morbidities. There is no consent treatment for COVID-19; suggestion is to lay out supportive care depending on each patient's need (e.g. antipyretics for fever, oxygen therapy for respiratory distress). Antiviral treatment also available however it is not specific against COVID-19. WHO guidance did not recommend corticosteroids for COVID-19. Development of vaccine is under way among the development 11 vaccines are in phase 3 in clinical trials, however most of the trials did not include pregnant women for their trials hence, pregnant women has to wait more time even other population if eventually get vaccine.

### **VERTICAL TRANSMISSION**

There is a possibility of vertical transmission, much like that seen in SARS, as the ACE2 receptor has been widely expressed in the placenta. Even though the exact mechanisms of SARS-CoV-2 to cross the placental barrier are unknown, the following possibilities might be the mechanism: (i) Through infection of syncytiotrophoblasts and the syncytial layers by ACE2 and Fc receptor (FcR), (ii) Via

maternal circulation to extra villous trophoblasts or placental cells, (iii) Via maternal immune cells (iv) Ascending infection through maternal vaginal tract in recent research suggest SARS-CoV-2 mRNA or virions have been detected in syncytiotrophoblasts. After cross the placental barrier by vertical transmission it causes foetal effects involving birth defects, abnormalities of growth and development, neurological injuries, miscarriage, foetal death, preterm delivery and neonatal complications.

### **IMMUNITY IN PREGNANCY**

#### **Immunological changes**

Changes in a woman's immune system during pregnancy include,

Poor activity of NK cells ("natural killer" white blood cells), which kill cells that have been infected with a virus.

Poor activity of T cells, which help out to prevent infections caused by viruses.

#### **Immunology of COVID-19 in pregnancy**

The immunological condition at the time of pregnancy changes as pregnancy carries on initially via Th1 (pro-inflammatory response) at the first trimester subsequently modified to Th2 (anti-inflammatory response) by the second trimester, and again proceed to a Th1 phenotype in final third trimester association with initiation of parturition. Neutrophils, C-reactive protein and pro-inflammatory cytokines in serum (eg, IL1B, IL6, IL12, IFN $\gamma$ , IP10, and MCP1) have connection in pulmonary inflammation and deepen lung injury in SARS. Patients would match up with disease severity followed by death in serious ailment, same protein levels have been detected and inflammatory cytokines enhanced is correlated with T CD4<sup>+</sup> and T CD8<sup>+</sup> lymphocytes dipped and marginal IFN $\gamma$  production.

#### **The cytokine storm**

The interaction between immune cells and infective cells would result from the effects of many immune-active molecules like Interferons, interleukins, chemokines, Colony-stimulating factors and TNF-alpha present which are most

principal components involved in the development of the Cytokine storm.

### **SARS-COV-2 AND ANGIOTENSIN-CONVERTING ENZYME 2 IN PREGNANCY**

The rennin angiotensin aldosterone system (RAAS) is a hormonal cascade could functions as a key role in homeostatic control of arterial pressure, tissue perfusion, and extracellular volume. Many studies confirmed Angiotensin-converting enzyme 2 (ACE2) is a receptor of SARS-CoV-2. ACE2 receptor assists SARS-COV-2 transmission in human cells. Actually the role of ACE2 is converts angiotensin I to angiotensin 1-9 and angiotensin II to angiotensin 1-7 ACE2 is a negative regulator in the RAAS. Here the renin catalyzes the cleavage of the glycoprotein angiotensinogen, producing angiotensin I (Ang I). Ang I cleavage by the angiotensin-converting enzyme (ACE) to form angiotensin II (Ang II), the main effector in the RAAS, while neutral endopeptidases (EP) cleave angiotensin I to form angiotensin-(1-7), one more active peptide of this system that opposite action of the Ang II. Most of the well-known proliferative and pro-fibrotic effects of Ang II from angiotensin type 1 receptor (AT1-R), however it could also bind to the Ang II type 2 receptor (AT2-R) so opposite effects to those at the AT1-R. ACE2 provides a binding site for the S-protein in coronavirus. There was some structural evidence that the SARS-CoV-2 S protein which has a higher affinity to ACE2 than the SARS-CoV S protein. However, ACE2 is the receptor of SARS-CoV-2, it plays a safeguarding role in acute lung injury by local activation of the RAAS responses to viral infection in pregnancy may promote vasoconstriction, acute lung injury, adverse myocardial remodelling, preterm birth, intrauterine growth restriction, and miscarriage. Studies suggest that ACE2 has been transient over expression and overall higher activity during pregnancy, mainly in the placenta. Anyway, if pregnant women's are more common susceptible to SARS-CoV-2 is currently unknown.

### **CLINICAL FEATURES OF COVID-19 DURING PREGNANCY (Table No.1) AND MANAGEMENT OF COVID-19 IN PREGNANCY**

At the present movement, no properly approved drug available to treatment COVID-19 in either the pregnant or non pregnant population, and vaccines trails for COVID-19 is under fully fledged in many countries most probably it would be available in early 2021, so the main focus of treatment is supportive medications.

#### **ANTI VIRAL AGENT**

##### **Lopinavir + Ritonavir**

##### **Mechanism of action**

Most viruses are ability to synthesis proteins vital for their life cycle. The lopinavir and ritonavir combination inhibit the proteins synthesis process. For viruses to develop DNA or RNA (RNA in the case of SARS-nCov-2) the virus has to possess some of the proteins in the host cell.

##### **Indication and usage**

Lopinavir and ritonavir is traditionally indicated in combination with some other antiretroviral agents for the management of HIV-1 infection. Studies are going on at the movement it benefit against SARS-nCoV-2 virus.

##### **Dosage**

The recommended dose for pregnancy women 400/100mg of lopinavir and ritonavir twice daily.

#### **REMDESIVIR**

##### **Mechanism of action**

Remdesivir is an adenosine nucleotide pro-drug metabolism of remdesivir to remdesivir triphosphate. Remdesivir triphosphate react as an analog of adenosine triphosphate (ATP) and take part with the natural ATP substrate for incorporation to nascent RNA chains by SARS-CoV-2 RNA-dependent RNA polymerase, ended in delayed chain breaking off during replication of the viral RNA. Remdesivir triphosphate is a poor inhibitor of mammalian DNA and RNA polymerases with low capability for mitochondrial toxicity.

### **Indication and usage**

Remdesivir was traditionally tested to treat Ebola in a randomized clinical trial. Its anti-viral activities against SARS-CoV-2 have been some efficacy in both in vitro and in vivo studies. Remdesivir is used in several countries as an urgent drug for treating COVID-19, and few patients dramatically improved clinical benefit. Nevertheless, large-scale clinical trials need to be conducted to establish the full potency and efficacy of remdesivir in treating patients with COVID-19.

### **Dosage**

Administer single loading dose of 200mg on Day 1 followed by once-daily maintenance doses of 100mg from Day 2 via IV infusion.

### **HYDROXYCHLOROQUINE**

#### **Mechanism of action**

Hydroxychloroquine that inhibits endocytosis-mediated viral entrance, blocks endosomal acidification, and interferes with glycosylation of angiotensin converting enzyme 2 (ACE2).

#### **Indication and usage**

Hydroxychloroquine is indicated for the treatment of uncomplicated malarial infection due to *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. *In-vitro* studies have established that it is effective against SARS-CoV-2. But, randomised, double-blind, controlled studies are needed in humans to finalise its efficacy.

#### **Dosage**

The beneficial impact of HCQ (200mg three times a day for 10 days) or HCQ plus azithromycin (AZM) (500mg on Day 1 followed by 250mg/day for the next 4 days).

### **CORTICOSTEROIDS**

Corticosteroids suddenly delay the inflammatory reaction; inflammation is a main factor for lung damage and acute respiratory distress syndrome in respiratory tract infection. But, previous research studies on corticosteroid therapy in SARS coronavirus and Middle East respiratory syndrome coronavirus established late viral clearance. Corticosteroid management may be worsening the

outcomes in COVID-19 patients. Because of this it is necessary that gynaecologist should carefully monitor fetal benefits with maternal risks. As a result, the risks and benefits ratio would be altered during corticosteroid therapy.

### **CONVALESCENT PLASMA THERAPY**

CPT application in pregnancy is useful in so many respects and further studies should be needed to find its efficacy in pregnant women. When in case of adaptive immunity, it suddenly appears poor in pregnancy, therefore using CPT in pregnancy with COVID-19 would be to provide the pregnant with specific antibodies against the virus assisting the immune system to fight against the pathogen via supportive immunity. It also wipes out the virus, furthermore, as IgG can cross the placenta, it may deliver the foetus with passive immunity. Finally, through its immune-modulatory and anti-inflammatory action, it looks that CPT has a vital property to arrest cytokine storm which is a crucial reason of ARDS and multi-organ damage.

### **VACCINES**

Vaccines require years of research and testing prior to reaching the public however, scientists are very keen to produce a safe and effective coronavirus vaccine as quickly as possible. Globally, researchers testing 44 vaccines are under clinical trials on humans among these 11 vaccines are in phase 3 in clinical trials, and at least 92 preclinical vaccines also under study. Moderna generated vaccines based on messenger RNA (mRNA) to make viral proteins in the body. In March, it was first COVID-19 vaccine into human trials which yielded favourable results. BioNTech collaborations with Pfizer, from New York, and the Chinese pharmaceutical maker Fosun Pharma to develop an mRNA vaccine. It produces antibodies against SARS-CoV-2 and immune cells called T cells that respond to the virus. Oxford-AstraZeneca which is developing the vaccine along with Oxford University currently in phase 3 clinical at more than 60 locations. Most of the vaccine developers excluded pregnant women in clinical trials due to safety. If vaccine would

available in coming days other population get easily, but not pregnant. Pregnant women also should be included in phase 3 trials of adenovirus-vectored vaccines and also protein-based vaccines (NVXCoV2373) a recombinant nanoparticle vaccine [NCT04368988] for COVID-19 there are even less safety concerns.

**Table No.1: Clinical features of COVID-19 during Pregnancy**

S.No	Characteristics	COVID-19
1	Total No. of cases	55
2	Age (y)	23-40
<b>Symptoms</b>		
3	Fever (%)	84
4	Cough (%)	28
5	Dyspnea (%)	18
<b>Other Investigation</b>		
6	CXR/CT evidence of pneumonia	76
7	Leukocytosis (%)	38
8	Lymphopenia (%)	22
9	Thrombocytopenia (%)	13
<b>Maternal Risk</b>		
10	Mortality (%)	0
11	Mechanical ventilation (%)	2
<b>Fetal Risk</b>		
12	Miscarriage/stillbirth (%)	2
13	IUGR (%)	9
14	Preterm birth (%)	43
<b>Neonatal Risk</b>		
15	Neonatal death (%)	2

**Leukocytosis described as a white blood cell count of >11,000/mm<sup>3</sup>. Lymphopenia described as a lymphocyte count of <1000/mm<sup>3</sup>. Thrombocytopenia described a platelet count of <150,000/mm<sup>3</sup>.**

**CONCLUSION**

There is a possibility of vertical transmission as the ACE2 receptor can expressed in the placenta. Few Changes in a woman's immune system like poor activity of NK cells and T cells during pregnancy may exaggerate the risk of COVID 19 infection. ACE2 has transient over expression and more activity during pregnancy, mainly in placenta. But if pregnant women are more susceptible to SARS-CoV-2 is currently unknown. Fever, cough, dyspnea were the major clinical features while the

Leukocytosis, Lymphopenia were common atypical findings. Pregnant women who contract coronaviruses incite the risk of adverse obstetrical outcomes. The infection outcome was commonly associated with higher rate of preterm birth, intensive care unit admission, miscarriage, neonatal death. Treatment is based on consensus and better practice, as clinical efficacy data regarding antiviral therapy is growing. Corticosteroid therapy looking contraindicated. So many obstacles will be expected in vaccine availability in pregnancy.

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## CONFLICT OF INTEREST

There is no conflict of interest.

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