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Management of COVID-19 in Pregnancy: A Review

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is currently a global health crisis across the world. The World Health Organization (WHO) declared COVID-19 as a pandemic on 11 March 2019. During this outbreak period, pregnant women were also afflicted significantly. Due to the adaptive changes during pregnancy, pregnant women could be more susceptible to COVID-19 infection than the general population. This paper presents a comprehensive review of current data concerning COVID-19 and its effect on pregnant women including symptoms and mechanisms. We also reviewed the recommended management of pregnant women with suspected or confirmed COVID-19 and drugs that are now under investigation to treat COVID-19 in pregnancy. The most frequent symptoms reported by COVID-19 infected pregnant women are fever, cough, myalgia, and shortness of breath. The diagnosis is based on epidemiological history, clinical manifestations, chest radiography, and etiological tests. Based on the available literature and guidelines recommendations for antepartum, intrapartum, and postpartum care are explained in this article. Appropriate and timely management is the key to safe motherhood and healthy offspring during this global pandemic. This paper aims to review the recommendations for the management of COVID-19 in pregnant women.

INTRODUCTION:

Coronavirus Disease 2019 (COVID-19) is currently the major public health concern around the globe. It is caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) [1]. The novel coronavirus (SARS-CoV-2) outbreak occurred in Wuhan (Hubei province, China) in December 2019. On 11 January 2020, the World Health Organization (WHO) issued a statement declaring the spread of the new coronavirus to be the sixth major public health emergency worldwide to pose a threat to all countries. On February 11, 2020, the new coronavirus disease received an official name from the WHO as Coronavirus Disease 2019 (COVID-19) [2]. The WHO declared COVID-19 as a global pandemic on 11 March 2020 [3]. As of 22nd December 2020, there have been 76,250,431 confirmed cases of COVID-19 with 1,699,230 confirmed deaths, reported to WHO [4].

Pregnancy is a physiological state that predisposes women to respiratory complications of viral infection due to the physiological changes in the immune and cardiopulmonary systems [1,5,6]. During this outbreak period, pregnant women and newborns were also afflicted significantly [7]. With immunocompromised status and adaptive changes during pregnancy, pregnant women could be more susceptible to COVID-19 infection than the general population. As COVID-19 is rapidly spreading, maternal management and fetal safety have become a major concern [8]. Obstetrics is an essential service and the provision of routine obstetric care must continue through pandemic to ensure optimal maternal and fetal health [9]. In response to the World Health Organization (WHO) statements and international concerns regarding the COVID-19 outbreak, several guidelines have been published by The American College of Obstetricians and Gynecologists (ACOG), The Royal College of Obstetricians and Gynecologists (RCOG), International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), Center for Disease Control and Prevention (CDC), International Federation of Gynecology and Obstetrics (FIGO), and Indian Council of Medical Research (ICMR) for the management of COVID-19 in pregnancy. Based on the available literature and the guidelines, this article intends to review the management of COVID-19 in pregnancy.

CHARACTERISTICS OF COVID-19

Coronaviruses are enveloped, non-segmented, single-stranded Ribonucleic Acid (RNA) viruses with a diameter of 80-120nm belonging to the family *Coronaviridae*, order *Nidovirales* [1,10,11]. There are four types: α-coronavirus, β-coronavirus, ẟ -coronavirus, and gamma-coronavirus [10]. Before SARS-CoV-2, six coronaviruses were known to cause

disease in humans, including Severe Acute Respiratory Syndrome Coronavirus-1 (SARS-CoV-1), and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [1,10.11]. Like the above two viruses, SARS-CoV-2 is also a β-coronavirus. It has a genomic similarity of about 80% with SARS-CoV-1 [1]. Furthermore, SARS-CoV-2 and SARS-CoV-1 share the same cellular receptor, Angiotensin-converting enzyme 2 (ACE2) despite amino acid variation at some key residues [12].

TRANSMISSION

COVID-19 spreads by respiratory droplets and direct contact (body fluids of an infected person touch another person's eyes, nose, or mouth, or an open cut, wound, or abrasion) [1]. The virus could potentially transfer to individuals within a distance of <2m (6 feet) of the infected person [6,11]. It should be noted that the coronavirus is viable on plastic and stainless-steel surfaces for up to 72 hours, whereas on copper and cardboard it is viable up to 24 hours [1]. As it can survive on non-living surfaces, it is very essential to clean the surfaces that are frequently touched [11].

CLINICAL MANIFESTATIONS OF COVID-19 IN PREGNANCY

The mean incubation period (from exposure to the appearance of clinical features) is 5 to 7 days, which can vary between 2 and 14 days [13,14]. The median duration of viral shedding is 20 days [13]. Most people who are infected will show features by 11 days of exposure [14]. The most frequent symptoms reported recently by COVID-19 infected pregnant women were fever, cough, myalgia, fatigue, and shortness of breath [13,15]. Less frequent symptoms are expectoration, nausea, headache, diarrhea, and ageusia [13]. The severity of infection may depend on the underlying health of the individual [11]. Pregnant women especially those with associated medical conditions like diabetes and asthma may present with severe pneumonia and marked hypoxia [14].

DIAGNOSIS

The diagnosis of COVID-19 in pregnancy is mainly based on epidemiological history, clinical manifestations, chest radiography, and etiological tests [12]. The CDC recommends a Reverse Transcription Polymerase Chain Reaction (RT-PCR) test for the detection of COVID-19 [14]. In the RT-PCR technique, viral isolates are used as a primary substrate to perform an assay that identifies a specific virus and its gene sequence [11]. The sample taken from throat swabs, urine, saliva, or stool can be used to conduct RT-PCR but CDC

recommends the collection of a nasopharyngeal swab specimen to test for COVID-19 [11,14]. If RT-PCR is not available, a serological test could also be used for diagnostic examinations.

Other laboratory findings include leucopenia, lymphocytopenia, mild thrombocytopenia, mild elevation in liver enzymes, and other acute infection markers like raised procalcitonin levels, raised C-reactive protein, and raised D-dimer level [14,15]. Computed tomography scan and other imaging modalities show patterns consistent with atypical pneumonia-like ground glassy appearance [14,15]. In cases where an X-Ray is taken or a CT scan is needed for a pregnant woman, there should be the provision of an abdominal shield to protect the fetus from radiation exposure. The ultrasound scan must be performed according to the ISUOG consensus statement on the provision of ultrasonography in the context of SARS-CoV-2 [16].

Criteria for COVID-19 testing in pregnancy

The criteria for offering a laboratory test for COVID-19 are the same for pregnant women and the non-pregnant population. As per the guidance issued by ICMR, pregnant women should be tested in the following circumstances [14].

1. A pregnant woman who has an acute respiratory illness with one of the following criteria:

- A history of travel abroad in the last 14 days. In addition to testing these individuals and there, household contacts should home quarantine for 14 days.

- Is a close contact of laboratory proven positive patient or

- She is a healthcare worker herself or

- Hospitalized with features of severe acute respiratory illness.

2. A pregnant woman who is presently asymptomatic should be tested between 5 and 14 days of coming into direct and high-risk contact with an individual who has been tested positive for the infection.

SEVERITY CLASSIFICATION OF COVID-19 IN PREGNANCY

Patients with COVID-19 can be classified according to the severity of the infection into mild, moderate, and severe cases. The CURB (Confusion, Urea, Respiratory rate, Blood pressure) severity scale can be used to assess the severity of the respiratory infection [13].

- Mild infection: The presence of local symptoms in the upper respiratory tract (cough, sore throat, rhinorrhea, or anosmia) with or without non-specific symptoms such as fever or myalgia and a CURB score of 0.

- Moderate infection: mild pneumonia, considered as pneumonia confirmed by chest X-ray, without presenting severity signs (basal SO_2 > 90%, no need for ventilatory assistance, and CURB score of ≤ 1).

- Severe infection: A) Severe pneumonia: when any of the following criteria are met: failure of ≥ 1 organ, basal SO_2 < 90%, respiratory rate ≥ 30 bpm, or need for vasopressors. B) Respiratory distress: suggestive clinical finding (cough, dyspnea, chest retraction) or radiological evidence of bilateral infiltrates. C) Sepsis: The Sepsis- Related Organ Failure Assessment (SOFA) Scale can be used to evaluate sepsis severity (consider if score > 2). Also quick SOFA with 2 of the 3 following criteria: Glassgow ≤ 13, systolic blood pressure ≤ 100mmHg or respiratory rate ≥ 22bpm. D) Septic shock: arterial hypotension that persists after resuscitation volume and requires vasopressors to maintain a mean arterial pressure ≥ 65mmHg and lactate ≥ 18mg/dl in the absence of hypovolemia [13].

CLINICAL CLASSIFICATION OF COVID-19

The clinical classification is based on the WHO's interim guidance, "Global surveillance for COVID-19 caused by human infection with COVID-19 virus" [1,6,17].

a) Suspected case:

- A patient with acute respiratory illness (fever and at least one sign or symptom of respiratory illness like cough, and shortness of breath) and with no other etiology that fully explains the clinical presentation and a history of travel to or residence in a country/ area or territory reporting local transmission of COVID-19 infection during the 14 days before symptom onset OR

- A patient with an acute respiratory illness and who has been in contact with a confirmed or probable COVID-19 case in the 14 days before the onset of symptoms.

- A patient with a severe acute respiratory infection and requiring hospitalization and with no other etiology that fully explains the clinical presentation.

b) Probable cause:

- a suspected case for whom laboratory testing for COVID-19 is inconclusive OR
- A suspected case for which the testing could not be performed.

c) Confirmed case:

- A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs, and symptoms [1,6,17].

IMPACT OF COVID-19 IN PREGNANCY

Pregnant women undergo a lot of physiological changes in their cardiovascular, immune, and respiratory systems [18,19]. The physiologic changes that occur in respiration during pregnancy are increased secretions and congestion in the upper airway, increased chest wall circumference, and upward displacement of the diaphragm. These can result in increased tidal volume and decreased residual volume decreased airway resistance, and increased oxygen consumption. Hemodynamic and cardiovascular changes include increased cardiac output, increased plasma volume of 20%-50%, and decreased vascular resistance [27]. All these changes along with alterations in the immune system could make pregnant women more susceptible to COVID-19 and other respiratory pathogens [19,27]. Due to these changes, even mild pneumonia is more likely to develop into severe pneumonia in pregnant women and this can be fatal for the fetus [12]. Therefore timely management must be undertaken for pregnant women with COVID19.

Because of the recency of the pandemic, many studies on the effect of COVID-19 in a pregnant woman is not published [18]. Based on the data from the previous two coronavirus outbreaks (SARS-CoV-1 and MERS-CoV), it is suggested that pregnant women are more susceptible to adverse outcome including preterm birth, need for endotracheal intubation, premature rupture of membranes (PROM), admission to intensive care units, preeclampsia, renal failure, and death [20,30]. On comparing with SARS-CoV-1 and MERS-CoV, it seems that COVID-19 is less lethal for pregnant women [21]. However, some cases of adverse outcomes due to COVID-19 in pregnancy were reported. A multinational retrospective cohort study conducted by Daniele et al found that SARS-CoV-2 in pregnant women are associated with 0.8% maternal mortality, 11.1% needed admission to ICU, 23% had a preterm birth, and the rate of perinatal death was 4.1% [22]. Various other studies showed fetal and maternal

complications including preterm delivery, fetal distress, respiratory distress, and PROM [23]. Yassamine et al reported a case of pregnant women infected with COVID-19 in her third trimester. Her condition gradually deteriorated leads to premature rupture of membranes, a premature birth via caesarian delivery, and neonatal death [7]. JE. Mongolia et al reported a case of coagulopathy developed in pregnant women infected with COVID-19 [24]. The pathological examination of placentas from COVID-19 infected mothers showed some abnormalities like maternal vascular malperfusion, increased fibrin deposition, and intervillositis [24,25]. These pathological changes may occur due to hypoxia in coronavirus infection [12]. Based on these reports, it can be speculated that COVID-19 may cause complications like intrauterine growth restriction, fetal distress, or miscarriage. Therefore pregnant women with COVID-19 should be strictly monitored. According to the Royal College of Obstetricians and Gynecologists (RCOG), the vertical transmission from mother to fetus may be possible but it is not yet confirmed.

MECHANISM OF COVID-19 IN PREGNANCY

The novel coronavirus SARS-CoV-2 enters the host cell through angiotensin-converting enzyme 2 (ACE 2) receptors [27]. The main target of SARS-CoV-2 within the lung is type 2 alveolar cells. Apart from the lungs, these receptors are also present in the kidneys, esophagus, and heart. A small percentage of monocytes and macrophages also present these receptors [26]. The ACE 2 receptors usually get upregulated in normal pregnancy [27]. The angiotensin-converting-enzyme plays a major role in the conversion of angiotensin 2, which is a vasoconstrictor to angiotensin- (1-7), a vasodilator [26]. The upregulation of ACE2 in normal pregnancy potentiates the conversion of angiotensin 2 (vasoconstrictor) to angiotensin- (1-7), which is a vasodilator and consequently lowers the blood pressure [32]. But in SARS-CoV-2 infected pregnant women, this high ACE2 expression poses them to a high risk for complications. The possible mechanism is that, when SARS-CoV-2 binds to ACE2, causes its downregulation and consequently lowers the level of angiotensin-(1-7). This reduced level of angiotensin-(1-7) could eventually worsen the vasoconstriction, inflammation, and pro-coagulopathic effects that occur in preeclampsia [27].

We all know that pregnancy is associated with immunological changes so to defend against infection, trauma, or acute inflammation the maternal body itself produces an exaggerated response to eliminate the damage. This exaggerated response is called Systemic Inflammation Response Syndrome (SIRS). This process leads to the release of some acute-phase proteins

and cytokines, known as a cytokine storm. The cytokine storm is an inflammatory process mediated by IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNF- α [26]. The cytokine storm is involved in the pathogenesis of COVID-19. Figure 1

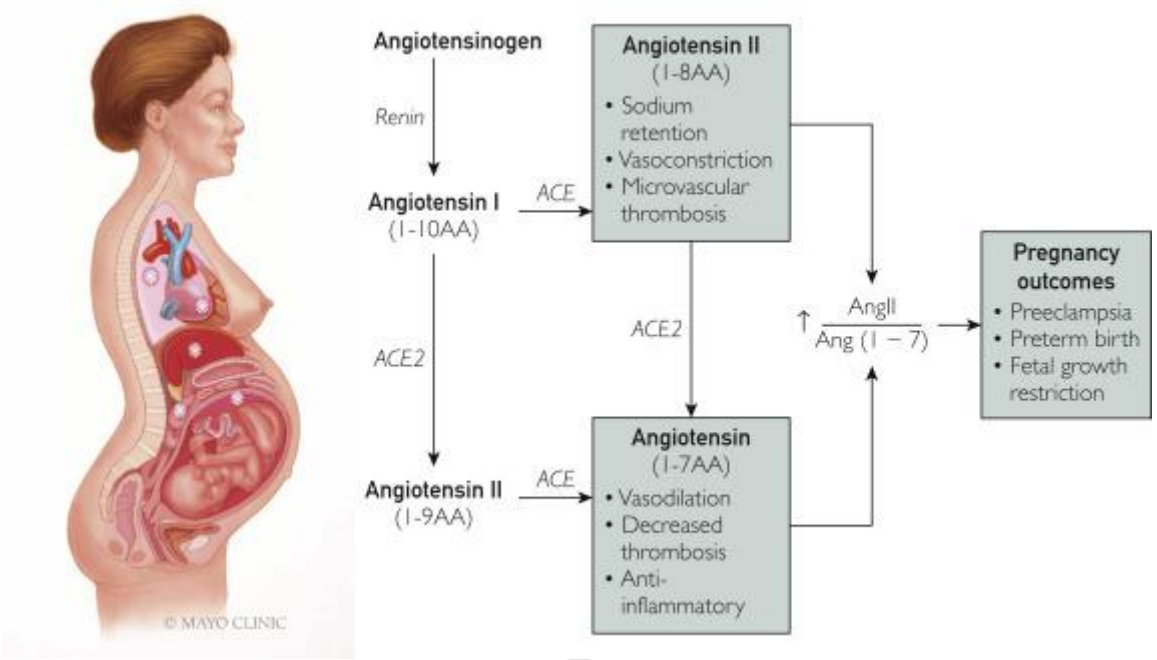

Figure no 1: Mechanism of vascular damage in pregnancy due to COVID-19 [27].

MANAGEMENT OF COVID-19 IN PREGNANCY

➢ Place of care:

Suspected, probable, and confirmed cases of COVID-19 infection should be managed initially by designated tertiary hospitals with effective isolation facilities and protection equipment [1,6]. Suspected or probable cases should be treated in isolation and confirmed cases should be managed in a negative pressure isolation room, when available. Otherwise, designated COVID-19 units can help to reduce the spread by cohorting affected patients with dedicated staffing [1]. Critically ill confirmed cases should be admitted to a negative pressure isolation room in an Intensive Care Unit (ICU). The designated hospitals should set up a dedicated negative pressure operating room and a neonatal isolation ward [6]. All attending medical staff should don PPE while providing care for suspected/ probable and confirmed cases of COVID-19 [1]. In areas with widespread local transmission of the disease, the health services may not be able to provide such levels of care to COVID-19 cases. Pregnant women with mild disease may not initially require hospital admission, and home confinement can be considered provided monitoring of the woman's condition can be ensured. If negative

pressure isolation rooms are not available, patients should be isolated in single rooms or grouped once COVID-19 has been confirmed [1,6].

➢ Treatment of suspected or probable cases:

General treatment includes maintenance of fluid and electrolyte balance, and symptoms should be treated for example with antipyretics, antidiarrheals, etc [1,6]. Close and vigilant monitoring of maternal vital signs and oxygen saturation level is needed to minimize the risk of maternal hypoxia. Repeated chest imaging should be performed. A complete blood count should be evaluated regularly, with renal and liver function testing [1]. Fetal surveillance includes performing cardiotocography (CTG) for fetal heart rate (FHR) monitoring when gestational age is beyond the limit of viability based on local practice (23-28 weeks). The pregnancy should be managed according to the clinical findings, regardless of the timing of infection during pregnancy [6].

➢ Treatment of confirmed COVID-19:

❖ Mild disease or non-severe disease:

a. The approach to symptomatic treatment and surveillance is the same as that for suspected or probable cases [6].

b. Conservative fluid administration is needed. Fluid balance should be evaluated regularly to minimize the risk of fluid overload. Isotonic crystalloid fluids should be administered [1].

c. Monitoring of bacterial infection (blood cultures, midstream or catheterized specimen urine microscopy, and culture) should be done, with timely use of appropriate antibiotics when there is evidence of secondary bacterial infection [6].

d. In pregnant COVID-19 patients with co-morbidities such as hypertension, diabetes seems to increase the risk for progression to severe disease. Therefore it is advisable to closely monitor pregnant patients with these comorbidities.

e. Fetal surveillance such as suspected or probable cases is required [1].

❖ Severe and critical disease:

Severe COVID-19 pneumonia is associated with high maternal and perinatal mortality rate, therefore aggressive treatment is required, including supportive measures with hydration and

oxygen therapy. The patient should be managed in a negative pressure isolation room in the ICU with the support of a multidisciplinary team consisting of obstetricians, maternal-fetal medicine subspecialist, obstetric anesthetist, internal medicine or respiratory physician, and infectious disease specialist, etc. The admission criteria to the intensive care unit (ICU) are outlined in the following table 1 [13].

Table no 1: Admission criteria to ICU [13]

MAJOR CRITERIA:
➢ Need for invasive mechanical ventilation
➢ Shock with the need for vasopressors
MINOR CRITERIA:
➢ Respiratory rate ≥ 30bpm
➢ PaO_2/ FiO_2 ratio < 250
➢ Confusion / disorientation ➢ Uraemia (blood urea nitrogen > 20mg/dl
➢ Leukopenia: < 4,000 cells/ cumm
➢ Thrombocytopenia < 100,000 platelets/cumm
➢ Hypothermia / central temperature < 36^{o}C
➢ Hypotension in need of aggressive fluid resuscitation
Admission criteria: 1 major criterion or 3 minor criteria. FiO_2- Fraction of inspired oxygen, PaO_2- Partial pressure of oxygen.

Other treatment considerations for critical patients:

- Antibacterial treatment: appropriate antibiotic treatment for suspected or confirmed secondary bacterial infection.

- Appropriate blood pressure monitoring and fluid balance management. The WHO advises administration of 250-500ml crystalloid intravenous fluid in the first 15-30 min, as a bolus [6].

- Oxygen therapy: supplemental oxygen should be used to maintain oxygen saturation equal to or greater than 95%. Oxygen should be given promptly to patients with hypoxemia and or shock and the method of ventilation should be according to the patient's condition and following guidance from the intensivists and obstetric anesthetists [6].

- Fetal surveillance is the same as that for a suspected or probable cause.

- Prophylactic low-molecular-weight heparin (if maternal weight < 80kg: enoxaparin 40mg every 24hour equivalent; if maternal weight > 80kg: 60mg every 24 hour) is indicated during hospitalization and 2 weeks thereafter, due to the association of COVID-19 with deep vein thrombosis and pulmonary thromboembolism in patients with severe COVID-19 [13].

All the professional perinatal societies issued guidelines by dividing the management recommendations into 3 sections. They are antepartum, intrapartum, and postpartum care [3,27]. After reviewing all the available publications and guidelines this article intends to provide recommendations to preserve the health of mothers and their children during this pandemic. Figure 2.

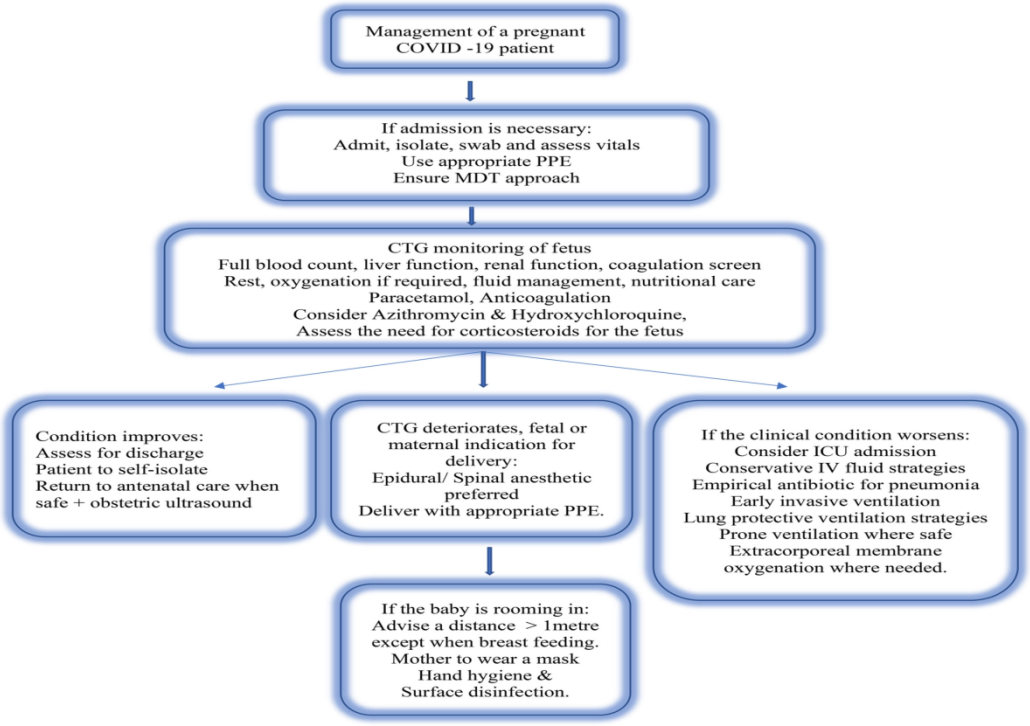

Figure no 2: A general algorithm for the management of COVID-19 in pregnancy

ANTENATAL CARE FOR OUTPATIENTS

All guidelines advise appointments to be taken before visits and screening at the entrances to the hospital. If appropriate telehealth should be encouraged for prenatal visits [3,28]. Providing advice via telephone or video conferencing to patients having an uncomplicated pregnancy with suspected/ probable/ confirmed COVID-19 can be considered to minimize the risk of transmission between pregnant women, healthcare provides, and other patients in the hospitals [1,6]. Women should be advised to check their blood pressure at home if possible and also provide appropriate instructions regarding when to seek medical assistance [6]. When the

patient has to be seen in the hospital, early triage and isolation measures should be applied. All the healthcare workers attending these patients should be appropriate PPE [1]. Screen the patients for symptoms or exposure before the arrival at the clinic. For the patients who have symptoms and if their visit is necessary for maternal or fetal reasons, then the visit can be deferred by at least 14 days. Advise the patient to monitor symptoms, and indications to present to the emergency room [6]. For women who are self quarantined because someone in their household has possible symptoms of COVID-19, an appointment should be deferred for 14 days. The algorithm for antenatal care for outpatients has been published in the FIGO guidelines [6].

ASSESSMENT OF WOMEN IN OBSTETRICAL TRIAGE:

Hospital admission might be required for pregnant patients with suspected/probable or confirmed COVID-19, either because of the disease itself or for obstetric reasons [1]. At arrival, screen them for symptoms or exposure relevant to COVID-19. In the case of a positive screen, necessary precautions should be taken [6]. A separate obstetric ward should be reserved for their patients, preferably with negative pressure rooms for confirmed cases[1]. Special attention should be given to women with associated co-morbidities like hyperglycemia and hypertension [6]. For women with mild symptoms with no risk factors for the severe disease may be discharged home after being advised to monitor symptoms and to seek care in case the symptoms worsen. For women with moderate symptoms or those who have comorbidities or other risk factors for severe COVID-19, should undergo detailed assessment including physical examination, laboratory testing, and chest radiography as indicated. Decisions regarding further management should be individualized based on the symptoms, risk factors, and the result of the assessment. Women with severe symptoms should undergo a detailed assessment by a multidisciplinary team [6]. Administration of antenatal corticosteroids for fetal lung maturation is recommended if gestational age is 23-33 6/7 weeks and delivery is anticipated in the next 7 days. But the risk/benefit balance needs to be discussed by the multidisciplinary team. The data regarding the use of steroids in the late preterm period >34 weeks is still controversial. This should be considered only on a case by case basis [3,27.28]. The algorithm for the management has been published in FIGO guidelines [6].

INTRAPARTUM CARE

Reviewed guidelines recommend a designated area for triaging, screening, and admitting SARS-CoV-2 positive pregnant patients or person under investigation (PUI) for suspected/probable/ confirmed cases of COVID-19 infection, delivery should be conducted in a negative pressure isolation room [3,6,27]. Always remember that COVID-19 infection is not an indication for delivery until there is a need to improve maternal oxygenation [6]. The number of staff members caring for the patient should be as low as possible. The timing and mode of delivery should follow routine obstetric indications [27]. The mode of delivery depends mainly on the clinical status of the patient, gestational age, and fetal conditions [6]. Vaginal delivery is not contraindicated in suspected/probable/confirmed COVID-19 patients. The use of operative vaginal delivery can be considered to shorten the second stage of labor, as active pushing while wearing a surgical mask may be difficult for the woman [3,6]. During labor excessive intravenous fluids should be avoided, especially when administering oxytocin, since this could worsen fluid overload. Oxytocin should be administered in an isotonic crystalloid such as 0.9% sodium chloride solution [1]. Emergency cesarean delivery (CD) should be performed in case of septic shock, acute organ failure, or fetal distress. It should be performed ideally in an operating room with negative pressure [6]. Always keep in mind that CD is not the only indication in COVID-19 unless there is fetal distress or deteriorating maternal clinical status [3,27].

Patients and healthcare providers should be appropriately gowned, gloved, and protective face masks; specifically, N95 should be used for aerosol-generating procedures such as forceful expiration during pushing, use of oxygen for intrauterine resuscitation, or intubation [3]. The use of birthing pools (water births) is contraindicated due to the inability to use adequate protective equipment for healthcare workers during water birth and the risk of fecal transmission [6,27]. Both regional and general anesthesia can be considered after consultation with the obstetric anesthetist. The algorithm for intrapartum management is given in the FIGO guidelines [6].

POSTPARTUM CARE

Postpartum is an important step that requires team management and coordination of care between gynecologists, neonatal specialists, midwives, and nurses for accurate delivery to ensure maternal and newborn safety [2]. Separation of mother and baby is not advised unless the mother is acutely ill [27]. If the mother is severely or critically ill, separation of mother and

baby is the best option [6]. Guidelines encouraged early discharge from the hospital to limit infection exposure in those who are not infected. The hospital length of stay should be decreased to 1 day for vaginal delivery and 2 days for CD [6,27]. As long as the patients do not have specific concerns that require in-patient examination, the postpartum visits can be conducted through telehealth [6]. The method of telehealth should be individualized based on resources and availability.

BREASTFEEDING (LACTATION)

In light of the current evidence, it seems that the virus is not transmitted via breastmilk [29,30]. As breast milk is the best source of nutrition and immunity for the infant, breastfeeding should not be discouraged [14]. The main risk for infants of breastfeeding is close contact with the mother, who is also likely to share infective airborne droplets [14]. However, the mothers are advised to follow appropriate respiratory hygiene by wearing a mask during skin-to-skin contact and breastfeeding [27]. For women and infants who are not separated and if they wish to breastfeed, the following precautions should be taken to limit spread to the baby:

- A pregnant woman should wash her hands before and after touching her baby.
- The mother should practice respiratory hygiene by wearing a three-ply surgical mask and not sneezing in front of the baby during breastfeeding [6,14].
- All surfaces should be kept clean and disinfect she has touched [14].

If a mother is confirmed with COVID-19 infection or who is symptomatic and separated temporarily from the infant should be encouraged to express their breast milk to establish and maintain milk supply [14,31]. If possible, a dedicated breast pump should be provided and it should not be shared between mothers [2,14,29]. Before expressing breast milk, mothers should wash their hands. After each pumping session, all parts of the pump that come in contact with breast milk should be thoroughly washed and the entire pump must be disinfected [2]. The recommendations for proper pump cleaning after each use have been explained by Welma et al [29]. This expressed breast milk should be fed to the new-born by a health caregiver [31]. In case of rooming-in, the cot of the baby should be kept at least 2m away from the mother's bed, if appropriate physical barriers such as glass or curtain can be used [1]. If the mother is too unwell to breastfeed her baby due to COVID-19 or its complications, she can be supported to safely provide breast milk to her baby in a way possible and acceptable to her.

PSYCHOLOGICAL INTERVENTION

Pregnant women are at increased risk for anxiety and depression; once they have been diagnosed with COVID-19 infection. The patients may exhibit varying degrees of psychiatric symptoms that are detrimental to maternal and fetal health. The separation of the baby from the mother may destroy early bonding as well as the establishment of lactation [6]. These factors will inevitably cause additional stress to the mother. Therefore healthcare providers should pay attention to a patient's mental health, including assessment of sleep patterns, and sources of anxiety and depression. Consult a perinatal psychiatrist if necessary [6].

DRUGS USED FOR THE MANAGEMENT OF COVID-19 IN PREGNANCY

At present no specific drugs or vaccines are available in the market for the treatment of COVID-19. However, several clinical trials are being conducted every day in the medical field. The pregnant populations are usually excluded from the clinical trials due to safety reasons. Based on the clinical experiences and clinical trials, some drugs are being used to treat COVID-19 in pregnancy. Additional treatment options may emerge as the clinical understanding of COVID-19 improves. The choice of drugs for COVID-19 in pregnancy should take into account the benefits and possible adverse events in every single case. Those drugs which are safe during pregnancy, demonstrated by clinical studies are included in this paper.

1. Hydroxychloroquine :

Hydroxychloroquine is an antimalarial agent with proven antiviral and immunomodulating activity [32,33]. It has an inhibitory effect on SARS-CoV-1, MERS-CoV, and other viruses [33]. Recent studies found that it can inhibit the proliferation of SARS-CoV-2 *in vitro* [12]. The mechanism by which hydroxychloroquine block the coronavirus infection is by increasing the endosomal pH required for cell fusion and by interrupting the glycosylation of cellular receptors (ACE-2 receptors) and thus inhibit the virus penetration [32,33]. Also, it can reduce cytokine storm, by inhibiting the differentiation of lymphocytes [33]. Although the drug and its metabolites can pass through the placenta, it is safe in all trimesters of pregnancy with no risk for the fetus [32]. Chloroquine can also be used as an alternative but hydroxychloroquine has a stronger ability to inhibit the virus replication in vitro than chloroquine [14,33]. The recommended dosage regimen for hydroxychloroquine is 400mg per oral for every 12 hours

for one day, then 200mg 12 hours for 4 days or 400mg daily for 4 days or 200mg every 8 hours for 10 days [33]. The dose of chloroquine is 5oomg twice a day for 7 days [14].

2. Antiviral therapy:

Antiviral therapy has been used to treat COVID-19 during pregnancy in China [34]. Lopinavir-Ritonavir was the first combination of antiviral agents used to treat COVID-19. It can also be considered for patients who have a chronic disease, immunocompromised, or uncontrolled diabetes [14]. Lopinavir and Ritonavir are proteases inhibitors and show *in vitro* activity against all the three coronaviruses (SARS-CoV-1, MERS-CoV, and SARS-CoV-2) [9]. During the previous two coronavirus outbreaks, this combination reduced the viral load and had decreased the death rate or acute respiratory distress syndrome (ARDS) [12]. The rationale behind this combination is that Lopinavir inhibits viral replication by inhibiting the enzyme 3-chymotrypsin- like protease. While Ritonavir increases the half-life of lopinavir by inhibiting cytochrome P4503A [33]. The data regarding the safety and efficacy of these drugs in pregnancy were derived from the studies on the treatment of HIV- positive pregnant women [9,33]. The recommended dose is two capsules of lopinavir or ritonavir (200mg/50mg per capsule) orally together with nebulized α- interferon inhalation (5 million IU in 2ml of sterile water for injection) twice a day [34].

Remdesivir is a novel, broad-spectrum nucleoside analog which shows significant antiviral activity against RNA viruses such as SARS/MERS- CoV and also against Ebola virus infection [9,33]. Currently, it is found that the remdesivir has *in vitro* activity against SARS-CoV-2. The remdesivir acts by blocking the viral RNA dependant RNA polymerase enzyme and thus inhibit the viral replication [33]. The data regarding safety during pregnancy is not confirmed, but it seems to be safe in pregnancy based upon the trial conducted in pregnant women with Ebola virus disease [33]. The currently proposed dose of remdesivir is a single IV 200mg loading dose, followed by 100mg daily infusion for 9 days [33]. However, the administration of antivirals in pregnancy requires further research.

3. Anticoagulants:

COVID-19 is associated with an increased risk of thromboembolic events including pulmonary thromboembolism and venous thromboembolism [9]. We all know that pregnancy is already a thrombotic condition due to the increased production of thrombin. Therefore it is necessary to provide prophylactic therapy for pregnant women with COVID-19 unless there

is a clear contraindication. Low molecular weight heparin is considered in pregnant women who are not close to delivery and in the puerperium. It is recommended to continue this prophylaxis until the patient becomes negative. Heparin does not cross the placental barrier owing to its high molecular weight and therefore heparin is safe during the whole pregnancy and breastfeeding [33]. The recommended dose is 4000 IU subcutaneous (SC) per day. Heparin should be continued in the postpartum if the patient is still positive.

4. Antibiotics:

The lung damage caused by the virus can increase the risk of secondary bacterial pneumonia [34]. If the secondary infection is suspected, appropriate antibiotics should be initiated without any delay [26]. The antibiotics which are considered to be safe during pregnancy should be administered [14]. It is mandatory to monitor the condition of a patient with blood culture, urine microscopy, and urine culture to start appropriate antibiotic treatment [33]. Ceftriaxone can be administered while waiting for culture and sensitivity results [33,34]. The antibiotics which are safe during pregnancy are Amoxicillin (1gm per oral every 8-12 hours), Azithromycin (500mg/day for 3-5 days), and Ceftriaxone (1gm IM or 1-2 gm IV daily).

5. Other drugs:

The symptomatic relief of fever and myalgia in COVID-19 infected pregnant women can be achieved with paracetamol. Ibuprofen and other NSAIDs must be avoided in pregnant women.

MEASURES FOR PREGNANT WOMEN TO PREVENT COVID-19 INFECTION

The greatest tool against COVID-19 is to maintain social distancing. Following are the important aspects for pregnant women to prevent COVID-19 infection:

a. Maintain good personal hygiene and social hygiene.

b. Frequent hand washing and use of hand sanitizer (with 70% alcohol concentration) should be encouraged.

c. Disinfection of surfaces to reduce formalities related to spread.

d. Refrain from excessive outdoor activity unless an emergency occurs.

e. Avoid non-essential travels. If travel is undertaken, it is preferable to use a private vehicle than that of public transport.

f. Avoid gatherings and functions.

g. Minimize visitors from coming to meet pregnant ladies.

h. A three-ply surgical mask should be worn while visiting a hospital or other high-risk areas.

PRECAUTIONS FOR HEALTHCARE WORKERS

COVID-19 pandemic is a prodigious global war and here we are facing the same enemy, novel coronavirus. In this war hospital is the first battlefield and medical workers are our soldiers. The risk of acquiring COVID-19 infection in healthcare workers is high as they care for the patients [14]. Contact with a large number of patients, close contact, and procedures where there is aerosolization (resuscitation, ventilation) or a splash of body fluids (labor, delivery, surgical procedures) are the main causes of transmission to healthcare workers. But appropriate use of PPE and other protective measures can avoid the transmission to healthcare workers [6,14]. Distancing, use of appropriate PPE, and chemoprophylaxis are the 3 principles that every healthcare worker should follow while meeting and examining the patients [14]. Following are the general precautions for the healthcare providers and obstetricians:

- Maintain a distance of about at least 1 meter from patients and other healthcare workers if possible.
- Remove non-essential items from the consulting or examination room to facilitate cleaning and disinfection and reduce the risk of fomites related spread.
- Regularly clean hands with soap and water or alcohol-based rub for at least 20 seconds.
- Patients should be encouraged to wear surgical masks if they have respiratory symptoms.
- The procedure of wearing (donning) and removing (doffing) of PPE should be strictly followed.
- Educational information including posters or brochures should be provided in the waiting area.

- To screen the patient's triage areas should be set up and all the staff must use appropriate PPE.

- All pregnant patients who present to the hospital and for the outpatient visits should be assessed and screened for symptoms and exposure relevant to COVID-19.

- For pregnant patients with known exposure to COVID-19 and those with mild symptoms, the antenatal visits should be postponed by 14 days.

- The number of visitors in the department should be reduced.

- Pregnant patients with symptoms should be placed in an isolation room for further evaluation on presentation to the triage area.

- It is very important to closely monitor the medical staff who care for the patient with suspected/probable or confirmed COVID-19 cases. If they show fever or any other symptoms of COVID-19, then they should be quarantined or self-isolate for 14 days.

- Obstetricians should follow risk assessment and infection control guidelines following exposure to patients with suspected or confirmed COVID-19.

As per the Indian Council of Medical Research (ICMR) guidelines, hydroxychloroquine can be taken as prophylaxis for asymptomatic healthcare workers who care for the suspected or confirmed COVID-19 infected patients. The recommended regimen is to take 400mg tablet twice a day on day 1 and once weekly for 7 weeks [14]. The medicine should be taken with meals.

SUMMARY

At the moment no specific drugs are available in the market for the treatment of COVID-19. Because of the physiological and immunological changes, pregnant women are a highly vulnerable population during this pandemic. All pregnant women have the right to a safe and positive childbirth experience, whether or not they have confirmed COVID-19 infection. Based on the studies conducted during this pandemic, it is concluded that COVID-19 in pregnancy is a complicated situation so a multidisciplinary team of medical experts consisting of obstetricians, infectious diseases experts, anesthetists, pediatricians, nosocomial infection control experts, and psychologists is required to manage and treat pregnant women and their newborns. Appropriate and timely management is the tool for safe

motherhood and healthy offspring during this global pandemic. Finally and above all, cooperation between nations is essential to tackle the problem of COVID-19. Healthcare professionals and other experts should share important and useful information to control the spread of COVID-19.

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