Review Article

Safety of pharmacological options for the management of COVID-19 in pregnant women: An Indian perspective

Kavita Manchanda[a], Jasbir Singh[b], Ranjeev Bhagat[c], Ilmjot Kaur Tiwana[d] and Harmanjit Singh[e,*]
[a]*Fellow in Reproductive Medicine, Milann Fertility Centre, Bangalore, India*
[b]*Associate Professor, Department of Pharmacology, Government Medical College and Rajindra Hospital, Patiala, India*
[c]*Assistant Professor, Department of Pathology, Government Medical College and Hospital, Chandigarh, India*
[d]*MBBS Intern, Government Medical College and Rajindra Hospital, Patiala, India*
[e]*Assistant Professor, Department of Pharmacology, Government Medical College and Hospital, Chandigarh, India*

Abstract. Coronavirus disease 2019 (COVID-19) is a viral illness caused by severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) presenting with pulmonary and extra-pulmonary manifestations. The first case was reported in Wuhan, China in December 2019 and it has rapidly progressed to the form of a pandemic. The presentation is mild in about 80 percent of the cases but the disease can also progress to a severe form of respiratory illness leading to acute respiratory distress syndrome (ARDS) and sometimes multi-organ failure, especially in people with other co-morbidities. Pregnant women also appear to be at a greater risk of acquiring a severe infection due to physiological changes during pregnancy. Many drugs with in vitro activity against the virus or an immunomodulatory effect have been considered for repurposing or have been tried as off-label drugs. The safety data regarding the use of newly approved or off-label or investigational drugs in pregnant women is limited and this poses a great challenge for clinicians. Therefore, it is important to know the utility and safety of the medications to avoid untoward adverse effects on pregnant women and fetuses. In this review, we aim to provide an overview of the approved, off-label, unlicensed, new and some promising pharmacological options for their use in the treatment of COVID-19 and the safety profile in pregnancy in an Indian scenario.

Keywords: Coronavirus, fetus, pregnancy, safety, teratogenic effects

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*Address for correspondence: Dr. Harmanjit Singh, Assistant Professor, Department of Pharmacology, Government Medical College and Hospital, Chandigarh, India. Tel.: +919968118472; E-mail: harman_gmcp@yahoo.com.

1. Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has emerged as a serious global health issue with high transmission rates affecting millions of people worldwide. It has been declared a pandemic by the World Health Organization (WHO) in March 2020 [1]. SARS -CoV-2 mainly affects respiratory epithelium and can result in symptoms varying from flu like illness to severe respiratory illness progressing to acute respiratory distress syndrome (ARDS) and other extra-pulmonary complications. Old debilitated people and those with other co-morbidities are thought to be at the risk of acquiring severe infection leading to need for hospitalization, intensive care unit (ICU) admission, ventilator support and, high mortality rates [2]. No highly effective antiviral drugs are available so far, which leaves us with the option of using old drugs which have shown some in vitro activity or effectiveness in previous coronavirus outbreaks. A few drugs have been proposed for the management to decrease morbidity and mortality, but none except for dexamethasone have been proven to make a significant impact [2].

Unsupervised use of the drugs which are primarily indicated for other conditions but are being investigated for treatment of COVID-19 or having off-label use in COVID-19 can lead to misuse of these drugs and safety issues especially in developing countries like India. This is because there is a lack of stringent regulatory control, a habit of self-medication and easy accessibility of drugs from pharmacy stores even without prescription, which may lead to serious consequences. This issue poses a greater risk to pregnant women as there is lack of safety data in pregnant women and there is no harmony on dosage and duration of use of such drugs for COVID-19. At present, the data on the safety and use of these medications is limited, with results of ongoing trials awaited. Globally, research is also ongoing for the development of a vaccine which are still in the trial phases [2].

As the infection with COVID-19 continues to spread and with the number of cases on the rise, clinicians are likely to encounter a greater number of pregnant women with infection. The choice of medication should be balanced between reducing maternal morbidity and mortality while considering fetal risks as well. Hence, clinicians and pregnant women need to be aware of preventive as well as management strategies available to make appropriate decisions for the well-being of the mother and the fetus.

2. COVID-19 and pregnancy

Pregnant women are anticipated to be at a higher risk of acquiring severe respiratory infections due to physiological changes of pregnancy and a state of immune tolerance to avoid fetal rejection [3]. According to previous reports on SARS-CoV-1 infection in pregnancy, the prevalence of adverse maternal and fetal effects were found to be higher among infected pregnant women [4]. The maternal and fetal effects of COVID-19 in pregnancy are difficult to assess at present due to the paucity of evidence. Based on the initial reports the United Kingdom (UK) Royal College of Obstetrician and Gynecologists (RCOG), Royal College of Midwives and, Royal College of Pediatrics and Child Health, jointly issued guidance stating that pregnant women are no more susceptible to adverse health consequences than non-pregnant women [5]. On the contrary, the latest study conducted by the Center for Disease Control and Prevention (CDC) involving more than 8200 pregnant women, concluded that pregnant women might be at higher risk of acquiring severe illness and need for ICU admission than the non-pregnant counterparts [6]. So, we need to exercise caution while interpreting evidence available regarding the impact of SARS CoV-2 on pregnancy and management strategies to avoid adverse effects. Until the availability of a clear-cut evidence, it is better

to consider pregnant women in the clinically vulnerable group and, hence specific therapeutic measures are needed to ensure maternal and fetal safety.

The presentation of the disease can be mild to moderate in the majority of the cases. The mild cases mostly present with flu-like illness with symptoms such as fever, myalgia, nausea and dyspnea but the symptoms can also progress in severity leading to development of pneumonia and multi-organ involvement [6]. Patients with severe COVID-19 infection can present with complications like ARDS, cardiovascular compromise, disseminated intravascular coagulation and in terminal stages and multi-organ failure leading to death as has been seen in infection with other coronaviruses [4,7,8]. Limited data is available on the effect of COVID-19 on reproductive outcomes, as most of the studies involve a small group of patients. The available literature on other similar pathogenic coronaviruses like severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) can provide useful insights regarding impact on reproductive outcomes. According to previous studies on SARS infection in pregnancy, pregnant women with infection are at higher risk of miscarriage, preterm birth and, intrauterine fetal growth restriction [4]. However, the same has not been demonstrated in early reports from COVID-19 infection in pregnancy. In an analysis of 116 cases, mostly in the third trimester of pregnancy, COVID-19 infection was not found to be associated with increased rates of spontaneous miscarriage, spontaneous pre-term labor and feto-placental viral transmission [9]. The placentae from a small group of pregnant women infected with COVID-19 analyzed post-delivery have shown abnormalities such as fibrin clot deposition, decidual arteriopathy and mal-perfusion that has the propensity to cause fetal growth disorders [10,11]. However, it is premature to say whether these placental abnormalities are due to COVID-19 per se or due to other conditions associated with the pregnancy. These observations regarding presentation, course of infection during pregnancy, and its effect on the fetus however need to be validated in all three trimesters of pregnancy, and in a larger group of pregnant women before drawing clinical conclusions. Hence, we need to be cautious in making clinical decisions regarding management strategies based on the available evidence, which is limited by the small sample size and limited experience with the disease.

3. Treatment of COVID-19 in pregnancy: Challenges

The WHO issued interim guidelines for the management of COVID-19, which also include guidance for pregnant women based on experience with previous coronavirus outbreaks. These guidelines are being modified continually as the experience with the disease is increasing day by day [12]. The management of COVID-19 in pregnancy can pose various challenges for clinicians. There can be overlap between the symptoms of the disease and the symptoms due to physiological changes in the respiratory and cardiovascular system during the pregnancy and hence the delay in diagnosis, assessment of the severity and seeking health care. Though most of the cases are mild and can be managed by supportive treatment, it is the management of severe and critical cases that can be particularly difficult. Placental perfusion can be compromised due to development of ARDS and multi-organ dysfunction leading to fetal hypoxia jeopardizing fetal safety [13]. The management of such cases can create clinical dilemmas as the choice of treatment strategy has to make a balance between optimizing the health of the mother as well the fetal safety. Data regarding the safety of drugs used to treat COVID-19 in pregnancy and fetal effects is still limited. Many questions remain unanswered regarding the safety and efficacy of various pharmacologic interventions available due to exclusion of pregnant women from the clinical trials in general and those involving COVID-19 patients [14]. This excludes many drugs from use in pregnancy which are otherwise proven to be beneficial in the general population. Also, a few anti-viral drugs which have shown some

efficacy against SARS-CoV-2 are contraindicated in pregnancy due to their well-known teratogenic effects [15]. Hence, it is of utmost clinical importance to be well acquainted with the options available, and their efficacy and safety of use in pregnant women to optimize feto-maternal outcome.

4. COVID-19 and pregnancy: Pharmacological approaches and their safety profile

4.1. Hydroxychloroquine

Hydroxychloroquine (HCQ), a 4-aminoquinoline derivative with antimalarial and immune-modulatory properties, has been in use for many years for the treatment of malaria and immune conditions like systemic lupus erythematosus [16]. HCQ is more potent than chloroquine and has a better safety profile at higher doses [16]. In vitro studies during the SARS epidemic have demonstrated various anti-viral properties of HCQ like inhibiting virus entry into the host cells by modification of binding to ACE-2 receptors [17], preventing the release of virus in intra-cellular spaces [16], and dampening of the cytokine storm [16]. Initial studies showed a beneficial effect of the drug in reducing viral shedding and active disease period and hence it was recommended as one of the first off-label medications for the emergency treatment and/or prophylaxis of COVID-19 [18,19]. These studies had the limitation of small sample size and lack of proof of safety. As the experience with the disease increased, further studies failed to demonstrate any beneficial effect especially in severe cases of the disease, and hence based on interim observations of the SOLIDARITY trial being conducted by WHO, the HCQ arm has been withdrawn from further patient enrollment [20]. Further exploration into the safety profile raised serious concerns regarding the safety of its administration in patients with pre-existing cardiac disease and severe COVID-19 in which cardio-pulmonary function is already impaired [21] as one of the side effects of HCQ is the prolongation of QTc interval [22]. Pregnant women are another subset of patients, who need consideration regarding the safety of HCQ. The drug has been known to cross the placental barrier and a very small amount is also secreted in breast-milk. The levels of the drug in cord blood and maternal blood are found to be equivalent in a study conducted by Costedoat et al [23]. HCQ also has a propensity to cause ocular and ototoxicity as demonstrated in animal studies [13]. However, human studies based on the use of medication in the treatment of malaria and auto-immune conditions have not shown any teratogenic effects so far [13,23]. Though it has not been assigned any specific category by the U.S. Food and Drug Administration (US-FDA), it may be recommended to restrict its use to situations only where benefits outweigh the risks.

So, in view of mixed results obtained from the large clinical studies [24–27], currently the use of HCQ is not being encouraged for the prophylaxis or treatment of COVID-19. According to the current clinical management protocol issued by the Government of India and the Ministry of Health and Family Welfare (MoHFW), the use of HCQ is not backed by a firm evidence and its off-label use can be considered for management of mild cases with high risk factors and moderate cases based on the joint decision taken by patient and health care provider explaining the safety and efficacy of the medication after a baseline electro-cardiogram (ECG) [28]. The Indian Council of Medical Research (ICMR) has issued the recommendation regarding HCQ prophylaxis among health care workers, close contacts of patients with COVID-19 or suspected patients with COVID-19 and frontline personnel such as policemen and those involved in surveillance [29]. In view of lack of any conclusive data, the ICMR also warned against the misuse of HCQ by the lay public.

4.2. Remdesivir

Remdesivir is a broad-spectrum antiviral nucleoside analog which is metabolized to the active triphosphate compound after intravenous administration drug and is considered as a potential breakthrough to curb COVID-19 pandemic [30]. It has been shown to inhibit viral replication in non-human primates, mouse, and human lung epithelial cells in various in vitro studies on SARS-CoV-1, MERS, Ebola, and recently, SARS-CoV-2 virus in micro-molar concentrations [30,31]. It acts by inhibiting viral RNA dependent RNA polymerase enzyme. Initial studies have shown promising clinical efficacy and tolerability so far [32,33]. In a randomized clinical trial conducted by the US National Institute of Health (NIH) involving 1062 hospitalized patients, compassionate use of remdesivir was found to shorten recovery time (11 days vs 15 days as compared to placebo) [32,33]. However, another randomized trial conducted by Wang et al. [34], remdesivir administration in severely ill COVID-19 patients did not show significant clinical benefit over placebo in terms of viral clearance and mortality. The most common adverse effects reported in the study were anemia, hyperglycemia, impaired renal function, and raised liver enzymes [34]. Recently, concerns have been raised regarding its potential to cause hepatotoxicity due to the interaction with P- glycoprotein inhibitors [35]. Hence, a close monitoring of the liver profile should be advised. Its use in pregnant women appears to be safe based on limited evidence available from small studies from use in Ebola virus disease and compassionate use in women with COVID-19 [32,36]. No data is available on possible teratogenic effects and secretion in breast milk. The decision regarding use in pregnancy has to be made based on a risk-benefit analysis. Currently, its use is not recommended in pregnant and lactating women according to MoHFW, the national clinical management protocol for COVID-19 [28].

Further larger studies are required to prove its efficacy and safety in clinical settings [34]. Based on the results of studies conducted to date and the promising effects of remdesivir, the US-FDA has broadened the emergency use authorization of remdesivir for use in all suspected or confirmed (mild, moderate and seriously ill) COVID-19 patients [37]. The Central Drug Standard Control Organization (CDSCO) of India gave emergency use authorization to remdesivir on 26 June 2020 for use in COVID-19 patients [38]. On October 22, 2020, remdesivir was approved (earlier approved under emergency authorization) by the US-FDA for the treatment of hospitalized adult and pediatric patients 12 years of age and older and weighing at least 40 kg [39].

4.3. Favipiravir

Favipiravir (T-705) is another broad-spectrum oral anti-viral drug approved for the treatment of influenza and re-purposed as a potential candidate for containing COVID-19 pandemic [40]. It is a nucleotide analog pro-drug which inhibits viral replication inside host cells by inhibiting RNA dependent RNA polymerase enzyme after being converted into active tri-phosphate [40]. The Efficacy and safety have been established in phase III clinical trials on favipiravir versus placebo in uncomplicated influenza [41]. It has shown promising results in early clinical trials and has been given emergency use authorization for treatment of mild to moderate COVID-19 in India by the CDSCO [38]. Also, China, Russia, and Japan [41] have approved its use in treatment of COVID-19 infection. In a randomized trial by Chen et al. comparing favipiravir versus arbidol (Umifenovir), favipiravir resulted in a faster recovery from symptoms of pyrexia and cough with mild adverse effects even in patients with co-morbidities like diabetes and hypertension [42]. Another clinical trial by Cai et al. [43] also showed its superiority over lopinavir/ritonavir. The results of these early studies are encouraging for use of favipiravir in COVID-19 to decrease the disease burden in the general population with mild disease which needs validation in

larger studies [42]. The most common adverse effects reported was hyperuricemia and no serious adverse events and no significant risk of QT interval prolongation, were reported. Based on the current data and clinical trials experience, favipiravir should not be used in pregnant and lactating women and effective contraception is to be advised before prescribing the medication in the women from the reproductive age group [44]. Favipiravir may cause the death of the embryo in peri- and pre-implantation period as well as shown to delay development of the embryo in all the species (dog, mice and rat) in drug development and authorization trials [44]. Hence, its use is not recommended in pregnant and lactating women, until we have conclusive evidence on its safety.

4.4. Lopinavir/ritonavir

Lopinavir and ritonavir are anti-retroviral protease inhibitors, approved by US-FDA for treatment of HIV since September 2000 [45]. The proposed mechanism of action is inhibition of viral proteinase which plays a vital role in polyproteins processing required for viral replication [46]. Lopinavir is used in combination with ritonavir as ritonavir reduces its metabolism (by inhibiting enzyme cytochrome P450-3A4) in the liver and hence the dosage required [45]. This may also lead to drug interactions with other medications metabolized by the CYP450 enzyme and hence should be monitored [47]. This combination is generally well tolerated with minor side effects. Potentially serious adverse effect includes QT interval prolongation. Given the experience with SARS and MERS infections, the ICMR sought approval from CDSCO for its off-label use as an emergency medication in hospitalized COVID-19 patients [46]. A protocol was also proposed by researchers in ICMR to test the efficacy of this drug combination in symptomatic hospitalized patients with COVID-19 [46]. A retrospective cohort study reported efficacy of lopinavir/ritonavir combination as compared to HCQ in patients with mild to moderate disease [48]. However, the first-ever trial of lopinavir/ritonavir combination versus standard care in 199 recruited hospitalized patients with severe COVID-19, though there was numerical reduction in mortality by 5.8% as compared to standard care alone but the benefit did not reach statistical significance [49]. Similar preliminary results have been obtained in the RECOVERY trial, based on which, the lopinavir/ritonavir enrollment was closed in the SOLIDARITY trial [20]. Based on the present data, lopinavir/ritonavir combination does not seem to be a promising option for the management of COVID-19, and it needs to be confirmed in further well conducted, large clinical trials.

This combination is in use for many years for the treatment of HIV in all age groups including pregnant women [50]. Lopinavir has not been assigned any specific category by US-FDA, ritonavir belongs to category B and the combination has been assigned category C [50]. A systematic review involving 2675 women treated with combination medication did not show increased adverse pregnancy events like pre-term delivery, pre-eclampsia, and placental pathologies [51]. A small amount of drug crosses the placental barrier, but the odds of congenital malformations are not increased with the combination medication [51]. Hence, considering the safety profile in pregnancy it can serve as a useful alternative in pregnant women with COVID-19.

4.5. Dexamethasone

Dexamethasone is an orally administered corticosteroid, with potent anti-inflammatory and immune-suppressive properties [52]. It is one of the drugs in the WHO model list of essential medications since 1977 [53]. It acts by dampening the body's immune response to inflammation by inhibiting the release of a variety of cytokines which has been implicated in the worsening of COVID-19 leading to lung injury,

development of ARDS and other complications including multi-organ damage [52]. The results obtained from the RECOVERY trial have shown encouraging results so far in the management of patients with the severe COVID-19 on mechanical ventilation or oxygen support but not in patients who were not on oxygen support [54]. According to interim analysis, dexamethasone administration reduces mortality by one third in patients on ventilator support and by one-fifth in patients on supplemental oxygen [54]. However, it has a doubtful efficacy in mild and recovering cases in which it is supposed to reduce viral clearance rates and increase duration of viral shedding [54,55]. At present, according to the MoHFW, India, the use of dexamethasone is recommended in patients with moderate to severe COVID-19 patients showing progressive deterioration and those with evidence of hyper-immune response [28]. National Institute of Health (NIH) recommends its use in patients on mechanical ventilation and on supplemental oxygen but cautions against its use in patients who do not require supplemental oxygen [52].

Antenatal administration of dexamethasone (betamethasone may also be used) with blood glucose monitoring is recommended by the WHO to enhance lung maturity for the prevention of early neonatal morbidity and mortality due to premature delivery with recommended dose of 24 mg over 24 hrs [13]. Dexamethasone belongs to pregnancy category C and has the potential to cause defects in osteogenesis and fetal malformations on chronic use [56]. The administration of corticosteroids in small doses (dexamethasone 6 mg orally daily), for a short duration (over 10 days) in COVID-19 could be useful and relatively safer that it may not lead to any adverse maternal and fetal effects. The RECOVERY trial provides an example for giving a fair chance to include pregnant women in the trial as the investigators identified the need to adapt interventions, for example they substituted dexamethasone with prednisolone or hydrocortisone so that there is low placental transfer. This helped in avoiding the adverse fetal effects which have been reported with multiple courses of dexamethasone [54,57].

4.6. Interleukin-6 (IL-6) inhibitors

IL-6 inhibitors are monoclonal antibodies used in various inflammatory conditions that act by binding to membrane-bound and soluble IL-6 receptors and attenuate cytokine storm, a pathogenic mechanism responsible for acute lung injury and other complications [58]. IL-6 levels have been found to be raised in patients with severe COVID-19 and can serve as a predictive marker for severe respiratory disease [59]. Tocilizumab (recombinant humanized monoclonal antibody), Sarilumab (fully human IgG1 monoclonal antibody), and Siltuximab (chimeric human-murine immunoglobulin) are IL-6 inhibitors currently being evaluated for their possible role in the management of ARDS and other complications due to COVID-19 [58]. Administration of tocilizumab intravenously or subcutaneously in severely ill patients with elevated IL-6 levels brought down levels of inflammatory markers like C- reactive protein but failed to show improvement in mortality rates in an individual patient data systematic review [60]. In another retrospective cohort study, tocilizumab administration in patients with severe disease reduced the risk for mechanical ventilation or death [61]. However, the latest update from phase III COVACTA Trial comparing tocilizumab with standard of care (SOC) versus placebo with SOC reduced hospital stay but failed to show any improvement in clinical status or need for ventilator support [62]. One major concern with the use of IL-6 inhibitors is the risk of acquiring new infections. A retrospective analysis reported 14% infection rate with tocilizumab as compared to 4% with standard care alone [61]. Other adverse effects reported were mild such as elevation of liver enzymes and minor rash. According to the NIH guidelines, at present, the evidence is insufficient to recommend for or against the use of IL-6 inhibitors in the management of COVID-19 [63]. In the latest treatment protocol issued by MoHFW, India, off-label use of tocilizumab is restricted to patients with moderate disease showing progressive worsening [28].

The safety data regarding its use in pregnancy is limited. In a retrospective analysis of 61 pregnant women being administered tocilizumab for the treatment of rheumatoid arthritis, there was no evidence of increased rates of fetal malformations or spontaneous miscarriage [64]. It crosses the placental barrier and a very small amount of drug is secreted into breast-milk [65]. Based on the available data [63,65], its administration appears to be relatively safer in pregnant and lactating women. However, these studies have the limitation of very small sample size, further studies are required to make clinical decisions regarding the safety of administration after risk-benefit analysis. Although the data related to efficacy of tocilizumab in COVID-19 patients is mixed and inconclusive but in the recent trial (EMPACTA trial), administration of tocilizumab led to the reduced need for mechanical ventilation among COVID-19 patients with pneumonia which is an important outcome [66].

4.7. Ivermectin

Ivermectin is a broad-spectrum anti-parasitic medication with activity against a myriad of pathogens [67]. It has demonstrated in vitro antiviral activity against several RNA and DNA viruses such as HIV-1, West Nile virus, yellow fever, Zika virus, Influenza virus and HEV-1 [68]. The anti-viral action is thought to be by blocking the entry of viral proteins into the host cells by inhibiting the importin α/β receptor and ultimately, viral replication and it has been shown to reduce the viral load (of SARS-CoV-2) by approximately 5000 fold in in vitro Vero-hSLAM cell culture 48hrs post-infection [69]. However, the results in human studies are still awaited and its efficacy in vivo is still questionable. One important factor which discourages the in vivo use of ivermectin in COVID-19, is being the inability to decide on the right dosage for in vivo activity against virus, as the Cmax value attained with doses even up to 120 mg orally which is less than the effective concentration for in vitro activity [67]. The estimated plasma concentration would be several times higher than the concentration which is achieved even after the maximum approved dose in humans. This issue raises several questions regarding the efficacy and likely safety concerns with the use of ivermectin as the concentration required to inhibit the activity of SARS-CoV-2 is way higher and practically impossible to be administered to human beings [67,69].

At present ivermectin appears to be a viable option that is widely available, low cost, with ease of oral administration and excellent safety profile [70], however, it needs further stringent evaluation in clinical trials. The data for safety in pregnancy is mainly obtained from the analysis of inadvertent mass administration of the drug to pregnant women (pregnant women given ivermectin erroneously as it is very difficult to screen all patents during mass drug administration) for filariasis [71]. It is categorized into pregnancy category C by the US-FDA. Animal studies conducted in rats, rabbits, and mice have reported fetal neurotoxicity [72,73]. However, similar results have not been reported from human studies [71,72], the probable explanation for which can be the presence of P-glycoprotein in the placenta and blood-brain barrier which develops as early as 8 weeks of gestation and prevents the passage of drug to the fetal circulation [74]. A systematic review and meta-analysis analyzed pregnancy outcomes in 496 women, of whom 17.3% had exposure in the first trimester during mass drug administration, reported that there is inconclusive evidence regarding the safety of ivermectin during pregnancy and lactation and further randomized trials are recommended to establish its safety [73]. The authors also pointed out that despite this wide experience with use of ivermectin, there is a lack of convincing evidence regarding the safety of ivermectin in order to expand its benefits to special groups like pregnant women and children with weight less than 15 kg and lack of safety data among these groups led to exclusion of ivermectin from mass drug administration campaigns [73]. The issue linked to the dosage of ivermectin seems to be serious and further discourage its use in special groups like pregnant and lactating women. Such higher

doses may lead to multiple adverse effects which can be detrimental to mother and child health and can lead to poor pregnancy outcomes [75]. The use of ivermectin in COVID-19 treatment is not encouraged in India, however, the Utter Pradesh government has started using it (in place of HCQ) for the prophylaxis and treatment of COVID-19 [76].

4.8. Azithromycin

Azithromycin is a class of macrolide antibiotic which is used in the treatment of respiratory, gastrointestinal, and cutaneous bacterial infections [77]. The therapeutic effect in COVID-19 is thought to be exerted by inhibition of viral replication due to inhibition of protein synthesis by ribosomes and immune-modulation [77]. In earlier studies, it has shown a synergistic effect with HCQ in inhibiting viral replication [19,78]. In a French study, co-administration of azithromycin with HCQ in six patients cleared viral load in 100% of cases mostly by day 6 as compared to HCQ alone [19]. But this effect could not be demonstrated in further studies [79,80]. Rather, concerns were raised regarding the possibility of development of drug resistance and increased risk of cardiac events as both the drugs lead to prolongation of QTc interval [19,77]. Due to these adverse effects, the combination of azithromycin and HCQ has been withdrawn from the protocol given by MoHFW, India [28]. Currently, it can only be used for treatment of other new superimposed bacterial infections.

Azithromycin belongs to category B of the pregnancy category by the US-FDA. Many small observational studies have demonstrated the safety of azithromycin in pregnancy with no increase in risks of fetal malformations [81]. Its use also appears to be safe in lactating women [81].

4.9. Doxycycline

Doxycycline belongs to the tetracycline group of antimicrobials with activity against a wide range of gram-positive and gram-negative bacteria [82]. It has shown in vitro activity against RNA viruses such as HIV and Dengue in Vero cell cultures [83,84]. It inhibits viral replication into the host cells by increasing the pH and by upregulating intracellular zinc finger antiviral proteins [85] and has demonstrated anti-inflammatory properties as well [82]. The combination of doxycycline with ivermectin has shown remarkable recovery rates in sixty hospitalized COVID-19 patients, in a study from Bangladesh [86]. Based on these results the ICMR has started investigations to test the efficacy of combination medication in patients with COVID-19 [87].

Doxycycline has been given pregnancy category D by the US-FDA and it is also secreted in breastmilk. The tetracyclines are known for their teratogenicity affecting the bone formation and tooth enamel staining and hence, are contraindicated in pregnant and lactating women and children less than 8 years of age [88]. However, based on limited human studies available doxycycline has not shown an increased risk of teratogenicity but the risk of tooth enamel staining and enamel damage remains there [88,89]. Hence, its use in pregnancy and lactation is not advocated.

4.10. Other therapies

Convalescent plasma. Transfusion of plasma with neutralizing antibodies obtained from recovered patients is under investigation for the management of critically ill patients not responding to other therapies [90]. A systematic review of 5 studies, has shown promising results with decrease in viral load, improvement in symptoms and reduced mortality rates in critically ill patients with no major adverse

effects [90]. The initial promising results however, have been contradicted in the interim analysis of a trial which compared convalescent plasma with standard of care (SOC) to SOC alone which could not find any significant difference in mortality or clinical improvement parameters between the groups [91]. Currently, it is recommended for off-label use in patients with moderate disease not responding to oxygen therapy by MoHFW [28]. The data regarding safety in pregnancy is limited to case reports on use in COVID-19 and small number of patients in Ebola virus disease [92,93]. According to these studies, there are no reported maternal and fetal adverse effects with the use of convalescent plasma in pregnant women.

Itolizumab is an anti-CD6 monoclonal antibody in use for treatment of moderate to severe psoriasis has recently been approved for treatment of cytokine release syndrome in moderate to severe ARDS in patients with COVID-19 [94]. This drug has been used in India for the last 7 years for the treatment of psoriasis and due to its anti-cytokine properties, and now it has been repositioned for the managing ARDS in COVID-19 patients [94]. The mechanism of action is thought to be inhibition of cytokine storm which plays a pathophysiological role in development of ARDS and other complications [95]. The main concern with the use of itolizumab appears to be risk of acquiring other infections due to suppression of natural defense mechanism in already compromised patients and hence the need for further exploration regarding safety profile [95]. Its safety in pregnant ladies has not been ascertained and need further studies [95].

Umifenovir is an antiviral drug, approved for treatment of Influenza in Russia and China [96] that has shown in vitro activity against SARS [97]. The efficacy of umifenovir in COVID-19 is questionable at present, as initial studies have failed to demonstrate any effect on viral clearance or prognosis in patients with mild disease [41,97,98]. Its safety in pregnant ladies has not been studies and need further work. A phase III randomized, double blind, placebo-controlled trial has been approved by for assessing the utility and safety in COVID-19 by Central Drug Research Institute, India [99].

5. Conclusion

COVID-19 is a serious health concern that has emerged as a pandemic in a short span of time and is still ongoing with evolving knowledge on its pathogenesis, complications and treatment strategies. No highly effective pharmacological therapy has been developed so far and the line of treatment includes isolation, symptomatic treatment and few specific drugs depending on the stage of the disease. The pregnant women constitute a special group of patients due to various physiological changes of pregnancy and risk of adverse fetal effects. Few agents such as doxycycline and favipiravir are known to cause potential adverse fetal effects and hence should be avoided in pregnant and lactating women while rest of the agents may only be considered after weighing the risk benefits and urgency. Use of such drugs in pregnant women should be based on a shared decision of clinicians and patients and their relatives. The choice of medication in pregnant women should be based on the sound knowledge of the pharmacological effects of the particular drug and its potential to cause fetal harm. In the absence of a clear-cut evidence on efficacy and safety, the treatment should be individualized and guided by risk-benefit analysis which would differ according to the severity of the disease.

Conflict of interest

None to report.

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