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REVIEW ARTICLE

Effectiveness and safety of available treatments for COVID-19 during pregnancy: a critical review

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ABSTRACT

Background: COVID-19 is a pandemic disease caused by the SARS-CoV-2 and it spread globally in the last few months. The complete lack of specific treatment forced clinicians to use old drugs, chosen for their efficacy against similar viruses or their *in vitro* activity. Trials on patients are ongoing but the majority of information comes from small case series and single center reports. We aimed to provide a literature review on the putative effectiveness and safety of available treatments for COVID-19 in pregnant women.

Methods: We reviewed all the available literature concerning the drugs that have been used in the treatment of COVID-19 during pregnancy and whose safe assumption during pregnancy had been demonstrated by clinical studies (i.e. including studies on other infectious diseases). Drugs contra-indicated during pregnancy or with unknown adverse effects were not included in our review.

Results and conclusions: Clinical trials are not often conducted among pregnant patients for safety reasons and this means that drugs that may be effective in general population cannot be used for pregnant women due to the lack of knowledge of side effects in this category of people .The choice to use a specific drug for COVID-19 in pregnancy should take into account benefits and possible adverse events in each single case. In the current situation of uncertainty and poor knowledge about the management of COVID-19 during pregnancy, this present overview may provide useful information for physicians with practical implications.

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Introduction

Pregnancy is a particular condition characterized by natural suppression of the immune system and higher susceptibility to infectious diseases. In particular, deep physiological changes in the immune and cardiopulmonary systems make pregnant women more vulnerable to severe responses to respiratory viruses [1]. Influenza A virus subtype H1N1 (A/H1N1), Severe acute respiratory syndrome coronavirus (SARS-CoV or SARS-CoV-1) and Middle East respiratory syndrome-related coronavirus (MERS-CoV) are known to cause severe complications during pregnancy, such as pulmonary insufficiency, disseminated intravascular coagulation, multiple organ failure and death [2–4]. In this respect, the pandemic caused by SARS-CoV-1 registered a 25% percentage of fatality rate among pregnant women [2].

On December 2019, a new coronavirus causing a severe acute respiratory syndrome (SARS-CoV-2) was identified in Wuhan (China). On March 2020, the World Health Organization (WHO) declared the Coronavirus disease 2019 (COVID-19) as outbreak pandemic [1]. Until now, 4 million cases worldwide have been reported, resulting in more than 300,000 deaths [5].

Basing on recent studies, there is no evidence that COVID-19 impairs pregnant women more than the general population and the clinical course of COVID-19 during pregnancy appeared to be less serious compared to SARS and MERS, with a fatality rate of 0, 18,

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and 25%, respectively [6,7]. The risk of vertical and peripartum transmission of SARS-CoV-2 to the newborn has not yet been clearly demonstrated [8], but the treatment of COVID-19 during pregnancy is a major problem for physicians due to potential adverse fetal and neonatal effects of different drugs. For example, Ribavirin, one of the most used antiviral against SARS-CoV-2, is contraindicated in pregnancy due to well-known teratogenic effects [9]. In addition, clinical trials are not often conducted among pregnant patients for safety reasons and this means that drugs that may be effective in general population cannot be used for pregnant women due to the lack of knowledge of side effects in this category of people [10]. Moreover, as stated by Costantine et al. [11], this "protection by exclusion" of pregnant women from clinical therapeutic trials may be misleading and unjustifiable, excluding pregnant women with COVID-19 from potentially beneficial interventions and making extremely difficult to assess safety and efficacy of drugs in pregnancy .

In addition to the paucity of data about effectiveness and safety of antiviral drugs during pregnancy, the therapy of viral infection is a challenge for clinicians because of the elusive biological behavior of viruses. Viruses mutate constantly as a part of their life cycle, and it is therefore difficult to develop curative drugs. For instance, since 2013 the Food and Drug Administration (FDA) has approved only 12 new antiviral drugs mainly for the treatment of Human Immunodeficiency Virus (HIV), Hepatitis C Virus (HCV), Citomegalovirus (CMV) and Influenza.

For all the above problems, the battle against COVID-19 is being fought by using old drugs and scientific community is moving to develop a vaccine rather than specific antiviral agents [12]. In view of the urgency of the COVID-19 outbreak and the uncertainties about its management during pregnancy, we aimed to provide a literature review on the putative effectiveness and safety of available treatments for COVID-19 in pregnant women.

Material and methods

A literature review was conducted by searching PubMed (National Library of Medicine, Washington, DC) and Embase (Elsevier) databases from 1st January up to 5th May 2020. The keywords for initial data bank searches included using a combination of the following key words: "COVID-19," "SARS-CoV-2," "pregnancy," and "therapy." We limited our investigation to English-language journals. We also reviewed the reference lists of retrieved articles to search for other pertinent studies. A narrative synthesis of data was finally undertaken, including 123 articles . The therapeutic drugs for SARS-CoV-2 were categorized according to the FDA classification. For our study purpose, we analyzed only drugs with a putative effects on COVID-19 whose safe assumption during pregnancy had been demonstrated by clinical studies (i.e. including studies on other infectious diseases). Drugs contra-indicated during pregnancy or with unknown adverse effects were not included in our review.

Results

Treatment options

Antivirals

Lopinavir/Ritonavir (LPV/r), used in Chinese treatment schemes against COVID-19, are also known as "anti-HIV drugs" [13]. Lopinavir inhibits the division of HIV Gag-Pol, whilst Ritonavir is a protease inhibitor. The combination of the two molecules reduces the replication of HIV by the production of immature particles that block viral replication [14]. LPV/r attaches *in vitro* to SARS-Cov-1 and, considering the high homology sequences between SARS-Cov-1 and SARS-Cov-2, LPV/r is currently employed in the treatment of SARS-CoV-2. During the SARS epidemic of 2004, Chu et al. [15] reported the utilization of LPV/r in addiction to Ribavirin showing a significative lower risk of adverse events such as ARDS or death compared to patients treated with Ribavirin only. LPV/r should be administered in the first 7–10 d, during the peak phase of the virus replication [16]. Data about the efficacy of LPV/r mostly come from small case series and retrospective, cohort studies [17,18].

Regarding pregnancy, there are no data available on the effects of LPV/r in the treatment of pregnant women with COVID-19. The available evidence regarding the efficacy and safety of this drug during pregnancy derives from studies on the treatment of HIV-positive pregnant women.

A randomized controlled trial by Koss et al. [19] involved 356 pregnant women infected with HIV, showing no significant risk of preterm labor, even if Berghella [20] reported that it crosses the transplacental barrier and may increase the risk of preterm delivery, but not the risk of teratogenic effects. These evidences seem to be confirmed also by Roberts et al. [21], in a study where 955 women with exposure to LPV/r during pregnancy were analyzed.

LPV/r are not assigned to any FDA category, while ritonavir alone is classified in B category. For relative

safety, LPV/r is a possible therapeutic option in pregnant women with COVID-19. A treatment protocol could involve an oral administration of LPV/r 200 mg/50 mg, two capsules every 12 h with alfa-interferon 5 million IU in 2 ml of nebulized physiologic solution [22]. Kim et al.[23] on the contrary recommend to avoid the nebulization of solutions for the risk of aerosolization of SARS-CoV-2 and, when possible, to administer inhaled medications by metered dose inhaler. If the nebulized therapy is necessary, it is important to use some precautions during the nebulization, such as the positioning of the patient in an airborne infection isolation room, the use of adequate PPE and not to reenter the room for 2–3 h after the therapy [24]. Side effects of this therapy are anorexia, nausea, abdominal pain, diarrhea, gastritis, liver and renal damage, pancreatitis, cutaneous manifestation [25,26] and hepatotoxicity, which is of particular importance considering that 20–30% of patients with SARS-CoV-2 have transaminase elevation [27].

Remdesivir (formally known as GS-5734), is a new nucleoside analog which appears to have promising antiviral activity against a wide range of RNA virus such as SARS/MERS-CoV and also against Ebola virus infection [26]. Currently, remdesivir could represent a promising therapy for COVID-19 due to its broad spectrum and it has demonstrated an *in vitro* activity against several novel CoronaVirus (nCOV), including SARS-CoV-2 [28,29]. Remdesivir acts by inhibiting RNA dependent RNA polymerase by reducing viral replication within the host cells and improving MERS/CoV induced lung damage as demonstrated in non-human primates. Remdesivir reduced the severity of disease, virus replication and damage to the lungs when administered as pre-exposure prophylaxis and therapeutic treatment in rhesus macaques [30,31]. Phase 3 clinical trials are now ongoing to evaluate the safety and antiviral activity of remdesivir in patients with mild to moderate or severe SARS-CoV-2 infection in United States and China [32] and it seems to be safe for the use in human pregnancies, as shown in trials conducted in Ebola and Marburg virus disease [33].

Early data from a randomized, placebo-controlled study by National Institutes of Health (NIH) reported that remdesivir helps to accelerates the time to recovery in severely ill patients with COVID-19. This trial showed that recovery was reduced from 15 to 11 d. Results included 1,063 patients from 68 sites (47 in the United States and 21 in European and Asian countries) are still awaiting a peer review. On 1st May 2020, few days after early data of the remdesivir trials were released by NIH, the FDA approved the emergency use (EUA) of the remdesivir for the treatment of COVID-19 in adults and children hospitalized with severe disease [34].

Prior to this authorization the use was approved only in the context of compassionate use protocols (child $<$ 18 years and pregnant women) or in subjects enrolled in clinical trials [16], therefore it is not classified in any FDA toxicity category. The dosage currently proposed is a single iv 200-mg loading dose, followed by 100-mg daily infusion for 9 d [35,36]. At these dosages remdesivir does not appear to cause harmful side effects on the liver or kidney, however treatment should not be started in patients with a glomerular filtration fraction less than 30 l/min and in those with alanine aminotransferase level $>$5 times the upper limit of normal [16,23].

Antimalarials

Chloroquine/Chloroquine Phosphate/Hydroxychloroquine are antimalarial drugs with proven antiviral and immunomodulatory activities. The molecules differ in their chemical structures but have similar clinical effects, with hydroxychloroquine showing fewer side effects; currently, Chloroquine Phosphate and Hydroxychloroquine are the most utilized antimalarials in the clinical practice [37]. Evidence from clinical trials has confirmed the inhibitory effect of chloroquine on HIV/AIDS, MERS-CoV, SARS-CoV, and other viruses. The dose of drug required in the treatment of a viral infection is lower than in malaria infection, as well as the toxicity to host cells [38]. Importantly, Martin et al. [39] showed that the effect of chloroquine on cells of SARS-CoV infection can be demonstrated before or after the exposition of the cells to the virus, which means that chloroquine shows an effect both on prevention and treatment of SARS-CoV. This can be explained by the mechanisms of action of chloroquine in humans: firstly, chloroquine is an alkaline compound that enters the cells and concentrates in the acid organelles like Golgi vesicles, lysosomes, endosomes, increasing the pH in the nucleus and thus blocking the pH-dependent coronavirus replication [40]. Secondly, chloroquine can interfere with the terminal glycosylation of the cell receptor ACE2 (which is known to be the functional cell receptor of SARS-Cov [41]) and thus may inhibit the virus penetration in the organism. Thirdly, chloroquine has immunomodulatory effects that are beneficial in autoimmune disease such as rheumatoid arthritis and lupus erythematosus, by inhibiting the production and release of TNF-alpha and IL-6 [42]. These two cytokines are negatively correlated with the severity of the clinical course of

COVID-19, thus chloroquine can attenuate the damage due to inflammatory response through direct mechanisms. Additionally, it is reported a potential effect of chloroquine in reducing cytokines storm, by inhibition of lymphocytes differentiation in Th17 cells [43]. Wang et al. [28] demonstrated that chloroquine is beneficial both before and after the cell infection by SARS-CoV-2 in Vero E6 cells. For all the above, chloroquine has been proposed as treatment of COVID-19 and hydroxychloroquine showed a stronger ability to inhibit virus replication *in vitro* than chloroquine.

As specified for the other drugs, there are no data available on the use of these drugs in the treatment of pregnant women with COVID-19 and the available data regarding the efficacy and safety of chloroquine and hydroxychloroquine in pregnant women mainly derive from the studies on the treatment of malaria.

Consequently, even if this drug is not assigned to any FDA category, the effects of its administration during pregnancy are mild and there is no evidence of damage for the fetus or preterm delivery risk. Chloroquine is widely used in malaria areas, Klumpp et al. [44] report that, in 20 years of utilization, about 1 billion people have used chloroquine, including pregnant women and no fetal damages, or adverse effect on pregnancy, childbirth and newborns have been demonstrated. Hydroxychloroquine is commonly used for the treatment of LES and malaria in pregnant women [20] and it is reported that it passes the placental barrier and accumulates in fetal ocular tissues, but no toxicity or ocular damages have been found in human species.

The treatment scheme for Hydroxychloroquine is oral administration of 400 mg every 12 h for 5 d or 400 mg twice a day for the first day and then 200 mg twice a day for 4 d [26,45]. Chloroquine can be used at the dose of 1 g for the first day of treatment and then 500 mg daily for 4–7 d depending on clinical response [23,46,47]. Both chloroquine and hydroxychloroquine are well tolerated, and possible side effects are retinopathy, hyperglycemia, neurologic effects and QT prolongation (for which is recommended to perform ECG before and after the beginning of treatment) [48,49].

Anticoagulants

It is becoming clear that an increased risk of thromboembolic events is present in COVID-19 patients, as reported by Berghella et al. [20]. There have been several cases reported of pulmonary thromboembolism in COVID-19 patients and higher D-dimer levels and other coagulation markers. Considering that pregnancy is already a thrombotic condition, with increased production of thrombin and intravascular inflammation [50], it is strongly advised to immediately start prophylaxis in all pregnant women with COVID-19, unless there is a clear contraindication. Low molecular weight heparin should be preferred in women not close to delivery and in puerperium. It is recommended to continue this prophylaxis (4000 IU/daily) during the puerperium until the patient is still positive [20].

Heparin is a glycosaminoglycan not assigned to any FDA category; it works by preventing the formation of clots and the extension of existing clots within the blood. Heparin binds and activates the enzyme inhibitor antithrombin III (AT); the activated AT then inactivates thrombin, factor Xa and other proteases thus inhibiting coagulation. Due to its heavy molecular weight, heparin does not cross the placental barrier and its use is considered safe during the whole pregnancy and breastfeeding; in case of long-term therapy, we must mention two main potential side effects: osteoporosis and heparin-induced thrombocytopenia [51].

Steroids

Steroids are of common use during pregnancy. The usual prophylaxis for fetal lungs maturation with Betamethasone 12 mg i.m., two injections 24 h apart from the 23rd to 34th week of gestation, in case of risk of preterm delivery is indicated by Dashraad et al. [32] and the RCOG stated that there is no evidence of potential harms related to steroids administration for COVID-19 during pregnancy [52].

Furthermore, there are data demonstrating how SARS-CoV-2 infection in pregnancy (particularly in the third trimester) can increase the risk of premature rupture of membranes, preterm delivery and fetal growth restriction, and therefore the administration of betamethasone may be justified [1,22,32,53,54]. A very recent study, where a decision-analytic model was applied, showed that, in case of preterm, premature rupture of membranes, the administration of antenatal corticosteroids was an effective management strategy compared to no corticosteroid administration only at gestational ages less than 31 weeks [55]. However, we must quote that corticosteroids have diabetogenic effects and attention should be paid regarding those patients with preexisting diabetes or gestational diabetes, especially if under insulin therapy. Moreover, there are some reports about a potential worsening of the clinical conditions in already ill patient after betamethasone administration. For these reasons, a single

dose of 12 mg of betamethasone could be administered in order to minimize the effects on maternal blood sugar and on patient's clinical condition [56].

Betamethasone is not assigned to any FDA category. However, as there are few studies in the literature regarding the management of pregnant women with COVID-19, the use of corticosteroids in these patients should be assessed on a case-by-case basis, in relation to the patient's condition and with a multidisciplinary approach [1]. Intensive monitoring of infected patients during administration of betamethasone is also required [56].

Other steroidal drugs are not recommended by WHO, not only because they seem to delay the virus clearance without significant benefits on the survival [26], but also because (as well as betamethasone) they cause hyperglycemic status in the mother, although they do not cross the placental barrier (i.e. metilprednisolon) [32].

In a recent study, Liang et al. [22] reported a treatment scheme with a short-term administration of methylprednisolone 1-2 mg/kg per day in severe cases to reduce lung inflammation and prevent ARDS. Prednisolone and methylprednisolone are classified in category C/D and C of FDA, respectively. Some observational studies in patient with SARS and MERS showed that the addition of corticosteroids to standard care did not improve the survival rate, but on the contrary delayed the clearance of the virus from the body and exposed to complications such as hyperglycemia, psychosis and vascular necrosis. [57,58]. Therefore, due to the reduction of the host's inflammatory response in the lungs, the use of corticosteroids on the treatment of COVID-19 should be carefully evaluated.

Antibiotics

Antibacterial therapy should not be started by default, but only if a bacterial infection is suspected; it is mandatory to monitor the patient's condition with blood culture, urine microscopy and urine culture and to start the appropriate therapy only in case of positive cases [1]. Based on the patient's clinical manifestation, if the bacterial infection cannot be ruled out, it is possible to start a therapy for community-acquired pneumonia (amoxicillin, azithromycin) in mild COVID-19 patients; in severe patients until specific bacteria are identified, all possible pathogens should be treated [59]. For instance, intravenous ceftriaxone could be used while waiting for cultures [22], starting appropriate and specific antibiotic therapy, based on the specific infection, as soon as possible [1].

Amoxicillin belongs to the class of betalactam antibiotics, is a semi-synthetic penicillin that exerts a bactericidal action by inhibiting the synthesis of the bacterial cell wall. It has a satisfactory spectrum of action against both gram positive and gram negative bacteria; it is used to treat most bacterial infections, in many cases amoxicillin is the first choice drug compared to other betalactamic antibiotics, because it is much better absorbed after oral administration. Side effects are rare and in any case tend to resolve spontaneously and quickly with the suspension of the intake. The most common side effect is hypersensitivity to the drug which can manifest itself in various forms (skin rash, erythema, anaphylaxis). Other side effects that may occur during the use of amoxicillin, although rare, concern the gastrointestinal tract such as diarrhea, nausea, stomatitis and vomiting. Amoxicillin is classified as class B by FDA and commonly used in pregnancy and breastfeeding [60].

Azithromycin belongs to a family of macrolide-type antibiotics and it works by inhibiting the protein biosynthesis and consequently the growth of bacteria (bacteriostatic drug). Common side effects are nausea, vomiting, diarrhea, abdominal pain and, less frequently, a change in the electrical activity of the heart in particular by prolonging the QT interval. In fact, the addition of Azithromycin to the protocol with chloroquine it is not recommended as their combination may cause QT prolongation, with a greater risk of adverse cardiac effects [23]. Azithromycin is classified as class B by FDA and commonly used in pregnancy and breastfeeding [61].

Ceftriaxone is a beta-lactam agent which belongs to the family of third generation cephalosporins and it has a bactericidal action by interfering with the synthesis of peptidoglycans (i.e. bacterial cell wall constituents). It has lower efficacy against Gram-positive bacteria compared to first and second generation cephalosporins, but it has a higher activity against Gram-negative bacteria. Well known side effects are diarrhea, nausea or vomiting, pancreatitis, stomatitis, glossitis, and in general gastrointestinal symptoms. Ceftriaxone is classified as class B by FDA and commonly used in pregnancy and breastfeeding [62].

Host directed therapy

Host Directed Therapy (HDT) comprises a group of therapeutic approaches not acting directly against the virus but by modulating the immune system of the host in order to minimize damage due to excessive inflammation [9]. Clinical evidences show that patients with severe COVID-19 symptoms present a cytokines

storm with an excessive production of IL-2, IL-6, IL-10, granulocyte colony stimulating factor, TNF-alpha, which results in important organ damage [63]. HDT used in acute inflammation is safe and efficient and is composed by metformin, statins, glitazone [64].

Metformin improves the production of mitochondrial ROS and the macrophages autophagy [65], reducing the lung damage in murine models by reducing the mitochondrial complex I [66]. The use of metformin has been studied in the first trimester of pregnancy by Gilbert et al. [67] and seemed safe as concerning congenital malformations. Li et al. [68], studied the administration of metformin in patients with gestational diabetes and showed that it can reduce the risk of other complications such as gestational hypertension, hyperglycemia and the need of neonatal intensive care. Metformin is not assigned to any FDA category.

Statins induce autophagy and phagocytic maturation and are used for their anti-inflammatory role in lung infection diseases [69]. There is a limited amount of data on the effects of statins assumption during pregnancy, but they do not seem to cause major congenital malformations compared to the general population [70]. Statins are currently assigned as pregnancy category X by FDA, thus contraindicated in pregnancy; this decision was made according to animal models in which the dose administered was much higher than that normally used. A systematic review by Karalis et al. [71] concluded that better evidence is needed to declare that statins are safe in pregnancy. A major teratogenic risk is probably in the first trimester, thus its use should be avoided in this period of the pregnancy. As reported by Zumla [72], metformin and statins can be used as adjuvant in antiviral therapies, thereby reducing the needed dose of antiviral and consequently its side effects. No data are available regarding their clinical use with antiviral purpose in pregnant women.

Glitazones, the cytokines storm, as previously reported, has been recognized as a mediator of virus-induced lung disease, so an immunomodulatory therapy targeting the overproduction of cytokines is proposed for severe pulmonary diseases. A potential target is the peroxisome proliferator-activated receptor (PPAR)-γ, a member of the PPAR transcription factor family, known to inhibit the inflammatory process. PPAR-γ synthetic agonists the family thiazolidinediones (TZDs), like pioglitazone, with known ameliorating effects on severe viral pneumonia. TZDs, in particular rosiglitazone and pioglitazone are insulin-sensitizing drugs used in type 2 diabetes mellitus to increase tissues sensitivity to insulin and therefore improve the glucose uptake, stimulate adipocytes differentiation and lower the circulating levels of free fatty acids (FFA). Besides these well-known mechanisms, PPAR-γ activation also causes the reduction of pro-inflammatory genes like TNF-α and IL-6 and inhibits the expression of NF-κ reducing the inflammatory process. The use of PPAR-γ agonists has thus been proposed to reduce the cytokines storm.

Pioglitazone (30–45 mg/day for 3 months) showed to significantly reduce IL-6 and TNFα in insulin resistant individuals [73]. Zhang et al. reported that a 4 months treatment with pioglitazone (45 mg/day) reduced the monocyte gene and protein expression of IL-1b, IL-6, IL-8, and lymphocyte IL-2, IL-6, and IL-8 [74]. Other studies reported similar results on the cytokines production [75,76] and also on the reduction of lung disease [77–79].

Regarding the use of pioglitazone and other TZDs in COVID-19 patients, it is important to assess the efficacy and safety of this drug after short term administration and further studies are needed. The safety of the use of glitazones in pregnancy has not been studied and most information come from case report of inadvertent use or therapeutic use for PCOS which ended in normal outcome [80] or spontaneous abortion [81].

For these reasons pioglitazone has not been classified by FDA

Convalescent plasma

The possibility of using plasma of convalescent subjects to treat hospitalized subjects with critical stage of disease is under evaluation [26]. This therapeutic strategy has been used in the past to treat subjects with SARS, MERS and Ebola virus disease [82–84].

Indeed, the antibodies contained in the plasma of convalescent subjects could be able to reduce the viral load, decrease disease severity score and improve the oxygenation state of the transfused subjects. In a Chinese study, 10 patients with severe COVID-19 pneumonia were administered a single 200 ml dose of plasma from recently recovered donors, with the neutralizing antibody titers above 1:640 in addition to antiretroviral and symptomatic therapy. In transfused subjects, an improvement in clinical symptoms, in oxygen saturation within 3 d of infusion, a reduction in lymphocyte count and reactive protein C levels as well as varying degrees of absorption of lung lesions within 7 d were observed. The viral load was undetectable after transfusion in seven patients who had previous viremia and no severe adverse effects were observed [85].

In another case report, plasma from donors who had completely recovered from COVID-19 was

administered in 5 patients with severe respiratory impairment from the same infection. There was a significant reduction in nasopharyngeal viral load, an improvement in clinical symptoms and an improvement of oxygenation of transfused patients within 12 d [86].

It also appears that the administration of convalescent plasma is not associated with the onset of serious adverse effects [87].

Regarding the use of convalescent plasma for pregnant women suffering from COVID-19, no data are available. There are some studies regarding the treatment with convalescent plasma in Ebola virus disease and in particular a study conducted in Guinea in which 99 patients of various ages (including 8 pregnant women) with confirmed Ebola virus disease received transfusions of ABO-compatible convalescent plasma. There were no serious adverse reactions associated with the transfusion of convalescent plasma in this study (including pregnant women for whom no adverse effects were found for the patient or fetus), and the procedure was acceptable to both donors and patients [88].

In conclusion, further and larger studies are needed to evaluate the effective safety and efficacy of convalescent plasma in COVID-19 patients, in particular in COVID-19 pregnant patients, and a future major challenge may be to find available donors and to establish reliable test to confirm the neutralizing activity of plasma [23].

Immunomodulatory agents

Monoclonal antibodies directed against the specific cytokines responsible of severe forms of COVID-19 (IL-6, IL-2, TNFa) represent a further class of drugs with potential therapeutic usefulness. In particular, IL-6 seems to be a key molecule in the cytokines storm that cause the lung and organ damage [89].

Tocilizumab (TCZ) is a monoclonal antibody approved by FDA for the treatment of rheumatoid arthritis. It has been used in single dose of 400 mg in a small case series of severe COVID-19 with good results [90], and it is currently included in the Chinese treatment guidelines [47]. Data on the use of tocilizumab in pregnancy are limited and, in any case, not sufficient to determine whether there is a drug-associated risk for major birth defects and miscarriage. Based on the animal data, there may be a potential risk to the fetus but the estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In an animal study in which tocilizumab was administered to Cynomolgus monkeys during organogenesis, an increase in the incidence of abortion/embryo-fetal death was observed at a dosage 1.25 times higher than the maximum recommended human dose by the intravenous route [91]. A case series from the German Embryotox Pharmacovigilance Center investigated the effects of tocilizumab therapy as administered in early pregnancy in 16 women, reporting four spontaneous abortions (SAB), one induced abortion for personal reasons and 11 live-born infants. Congenital malformations were not recorded, but one SAB at week 15 + 3 d was complicated by hydrops fetalis of unknown origin. According to the authors, TCZ is not recommended for use during pregnancy due to limited data, but an incidental continuation of TCZ into early pregnancy does not justify an elective abortion. However, a detailed prenatal ultrasound at 20 weeks or before should be offered [92]. In another study Hoeltzenbein et al. [93] analyzed pregnancy outcomes of 288 women who were exposed to tocilizumab shortly before or during pregnancy. No indication for a substantially increased malformation risk was observed (the rate of malformations was 4.5% and compared to the general population, and an increased rate of preterm birth was observed, and also one stillbirth and three infants/fetuses with congenital anomalies were reported), but considering the limitations of global safety databases, the data do not yet prove safety. In another Japanese retrospective study of 61 pregnancies exposed to tocilizumab at conception and in the first trimester, no increased rates of spontaneous abortion or congenital abnormalities in patients with rheumatic disease was found. But limitations of this study include its small sample size, lack of data on disease severity of rheumatoid arthritis and of efficacy assessment in pregnant patients with rheumatoid arthritis, as well as missing information on tocilizumab dose and duration of exposure [94].

In conclusion, further studies are necessary to confirm the benefit-risk profile of tocilizumab treatment during pregnancy before its use can be recommended, therefore it is not classified in any FDA toxicity category and there are no ongoing studies investigating the use of tocilizumab in pregnant women with COVID-19.

Interferons

Type I interferons (IFN-α/β) have broad spectrum antiviral activities against RNA viruses by stimulating the host adaptive immune response.

Several human and animal studies showed that MERS-CoV infection was mediated by both virus

Table 1. Inhibition of viral replication, mitigation of host inflammatory response.

Active Principle	Drug Category	Putative Mechanisms of Action	DOSAGE*	Fda Pregnancy Category	References
Lopinavir/Ritonavir	Antiretroviral	*Inhibition of viral replication and release from host cells* -Lopinavir: Inhibition of viral enzyme 3-chymotrypsin-like protease (3CLpro) -Ritonavir: increases the half-life of lopinavir through inhibiting cytochrome P450 3A	400 mg/100 mg tablets, one tablet twice a day for up to 14 days or 200 mg/50 mg tablets, two together every 12 hours with alfa-IFN 5 millions IU in 2 ml of nebulized physiologic solution regardless to meals	Not assigned	Chu et al, 2020. [14] Koss et al, 2014. [19] Berghella, 2020. [20] Roberts et al, 2009. [21] Liang et al, 2020. [22] Dashraat et al, 2020. [32]
Remdesivir	Antiviral	*Inhibition of viral replication* -Viral RNA-dependent RNA polymerase blockage	5 mg/mL vial (reconstituted). Single i.v. 200 mg loading-dose, following by 100 mg daily infusion for 9 days	Not approved	Mulangu et al, 2019. [33]
Hydroxychloroquine	Antimalarial Antiprotozoal Antirheumatic	*Inhibition of viral host cell penetration, viral replication and mitigation of host inflammatory response* -Inhibition of terminal ACE-2 glicosilation -Endosomal pH increase -Inhibition of host TNF-α and IL-6 production	200 mg tablets: 400 mg oral every 12 h for one day, then 200 mg every 12 h for 4 days; or 400 mg daily 5 days; or 200 mg every 8 h for 10 days	Not assigned	Sanders et al, 2020. [16] Berghella,2020. [20] Klumpp, 1965. [44]
Chloroquine	Antimalarial Antiprotozoal Antirheumatic		500 mg or 250 mg tablets: 500 mg oral every 12-24 h for 5-10 days; or 1 g oral for the first day of treatment and than 500 mg daily for 4 to 7 days depending on clinical response	Not formally assigned to a pregnancy category	Sanders et al, 2020. [16] Berghella, 2020. [20] Klumpp, 1965. [44]
Heparin	Anticoagulant	*Inhibition of viral host cell penetration, prevention of endovascular thrombosis* -Factor Xa inhibition	4000 UI s.c. daily, also during post partum if still positive	Not assigned	Berghella, 2020. [20] Di Renzo et al, 2020. [50]
Betamethasone	Corticosteroid	*Mitigation of host inflammatory response* -Inhibition of host IL-1, IL-2, IL-6, IL-12, IFN-☒ and TNF-α production	12 mg i.m. two injection 24 h apart as prophylaxis for fetal lung maturation	Not assigned	Poon et al, 2020. [1] Liang et al, 2020. [22] Dashraath et al, 2020. [32] Kakoulidis et al, 2020. [56]
Prednisolone and methylprednisolone	Corticosteroid		1–2 mg/kg/day for 3–5 days	C/D and C	
Azithromycin	Antibiotic	*Inhibition of viral host cell penetration, viral replication and bacterial super-infection* -Inhibition of terminal ACE-2 glicosilation -Endosomal pH increase - Binding to the 50S subunit of the bacterial ribosome	500 mg/day for 3–5 days depending on clinical response	B	https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/050809s000_Lbl.pdf [61]
Amoxicillin	Antibiotic	- Bactericidal action by inhibiting the synthesis of the bacterial cell wall	1 gr p.os every 8–12 h depending on clinical response	B	https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/50-542S017_Amoxil_Prntlbl.pdf [60]

(*continued*)

Table 1. Continued.

Active Principle	Drug Category	Putative Mechanisms of Action	DOSAGE*	Fda Pregnancy Category	References
Ceftriaxone	Antibiotic	- *Bactericidal action by interfering with the synthesis of peptidoglycans*	1 gr i.m. or 1–2 gr i.v. daily depending on clinical response	B	https://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/050796s000_PRNTLBL.pdf [62]
Statins	Lipid-lowering agents	*Mitigation of host inflammatory response* -Inhibition of the MYD88 pathway	Lack of data in pregnancy	X	Pollack et al, 2005. [70] Karalis et al, 2016. [71]
Metformin	Oral antidiabetic	*Inhibition of viral host cell penetration* -AMPK activation, leading to ACE2 phosphorylation	500-850 mg day, during or after meals	Not assigned	Gilbert et al, 2006. [67] Li et al, 2015. [68]
Convalescent plasma		*Direct neutralization of the virus, mitigation of host inflammatory response and immunomodulation of a hypercoagulable state* -Virus neutralizing antibodies -Anti-idiotypic antibodies blocking autoreactive recipient antibodies -Saturation of FC receptors	Lack of data in pregnancy	Not assigned	van Griensven et al, 2016. [88]
Tocilizumab	Monoclonal Antibody	*Mitigation of host inflammatory response* -Soluble and membrane-bound IL-6 receptor blockage	400 mg IV or 8 mg/kg IV for 1–2 doses. Second dose after 8–12 h if inadequate response. Infuse in 60 minutes.	Not assigned	Weber-Schoendorfer et al, 2016. [92] Hoeltzenbein et al, 2016. [93] Nakajima et al, 2016. [94]
Pioglitazone	Oral antidiabetic	*Mitigation of host inflammatory response* -Inhibition of host IL-1b, IL-6, and IL-8 and TNF-α production	Lack of data in pregnancy	Not assigned	Yaris et al, 2004. [80] Ota et al, 2008. [81]
Interferon-I	Immunomodulants agents	*Inhibition of viral replication, mitigation of host inflammatory response* -Slowdown of cell metabolism -Inhibition of host IL-1b and TNF-α production	Variable dose, limited data avaible	C	Yazdani et al, 2012. [103] Romero et al, 2015 [104] Hiratsuka et al, 2000. [106] Thiel et al, 2016. [107] Hellwig et al, 2020. [108]

* Due to lack of data regarding COVID-19, the reported dosages refer to the therapeutic application for conventional pathologies

replication in the host's cells and both by the activation of host inflammatory response. The results of these studies inspired the use of the combination of type I and II interferons for MERS-CoV, as well as in other conditions including cancers, autoimmune disorders, and viral infections such as HBV and HCV [95].

There are few direct data evaluating the effect of interferon type I on SARS-CoV-2, but several studies have shown that I-IFN has antiviral effects on various animal cell models [57] and it has been proposed for the treatment of COVID-19 [96]. In particular IFN-beta effectively reduces MERS-CoV replication *in vitro* and has shown promising results in animal studies with MERS infection [97,98].

The antiviral activity of I-IFN against SARS-CoV-1 and MERS has also been demonstrated by human trials. Loutfy et al. conducted a study on 22 patients infected by SARS. Nine of these patients received intravenous I IFN and the study showed that all nine of these patients recovered from the infection [99]. Moreover, IFN-beta1 seems to have stronger antiviral activity than IFN-alpha and there was no significant difference in case fatality rate between IFN-β1a and IFN-α2a in patients infected with MERS [100,101].

In an *in vitro* study conducted by Mantlo et al. [102], Vero cells were infected by SARS-CoV-2 and then treated with human IFN-β1a and IFN-α at different concentrations for 16 h. As result they demonstrated that *in vitro* SARS-CoV-2 is sensitive to both IFN-α and IFN-β treatment and the virus replication is inhibited by IFN-α and IFN-β at concentrations that are clinically achievable in patients.

Therefore, I-IFN may be useful in clinical treatment of COVID-19, either alone or in combination with other antiviral therapies, and IFN beta may be preferable, but further studies are needed.

Regarding the use of IFN in pregnant women, Yazdani et al. [103] conducted a study to investigate the effects of I-IFN in a series of 63 pregnant women with primary thrombocytopenia. The results showed that IFN-α did not significantly increase the risk of malformations, miscarriages, stillbirths, or premature births. Safety of IFN treatment during pregnancy is also supported by larger studies on patients with multiple sclerosis treated by IFN type I (especially IFN beta) in early pregnancy, showing no increase of spontaneous abortion and birth defects [104–107].

Interestingly, a recent study [108] included data from 26 European countries on 948 pregnant women with multiple sclerosis receiving IFN I beta during pregnancy or within 1 month before conception. Results did not show an increased risk of fetal malformations or spontaneous abortion inherent to IFN I beta treatment. Currently, IFN type I is classified as US FDA pregnancy category C, namely there is no available evidence on the use of IFN during pregnancy for treating COVID-19.

Conclusion

COVID-19 is a pandemic disease caused by the SARS-CoV-2 and it spread globally from December 2019. The complete lack of specific treatment forced clinicians to use old drugs, chosen for their efficacy against similar viruses or their *in vitro* activity. Trials on patients are ongoing but the majority of information about therapy for COVID-19 comes from small case series and single center reports. The choice to use a specific drug for COVID-19 should take into account benefits and possible adverse events in each single case, as the emergent situation does not justify underestimation of issues related to medical therapy. In this complicated scenario, pregnant women represent a frail category of patients, systematically excluded from trials and thus candidate to compassionate treatments [109].

COVID-19 pandemic is ongoing and new evidences regarding its etiopathogenesis, diagnosis and therapy are emerging daily. Nevertheless, in the current situation of uncertainty and poor knowledge about the management of COVID-19 during pregnancy, this present overview may provide useful information for physicians with practical implications.

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