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Review Article

A Scoping Review of the Effects of COVID-19 Medications on Pregnancy

Ahmed M Abbas[1,2]*, Islam H Ibrahim[2,3], Micheal Mikael[2,4], Safaa K Fathy[2,5], Lobna Ahmed[2,5], Dina B Ahmed6, Ahmed M Mahmoud[2,3], Sarah K Fahmi[2,3] and Nehal G Omar[2,3]

[1]*Department of Obstetrics & Gynecology, Faculty of Medicine, Assiut University, Egypt*

[2]*COVID-19 Research of Assiut University Association (CORAUNA) group, Egypt*

[3]*Undergraduate student, Faculty of Medicine, Assiut University, Egypt*

[4]*Resident physician, Ahmed Maher Teaching Hospital, Cairo, Egypt*

[5]*House officer, Faculty of Medicine, Assiut University, Egypt*

[6]*House officer, Mansoura University Hospitals, Mansoura, Egypt*

***Corresponding author:** Ahmed M Abbas, Professor, Department of Obstetrics and Gynecology, Assiut University, Women Health Hospital, Egypt.

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Abstract

COVID-19 is a pandemic disease caused by the SARS-CoV-2 which began to appear around in December 2019 in Wuhan, China and spread globally in the last few months. Currently, there is no specific treatment for SARS-CoV-2 which forced clinicians to use old drugs, chosen for their efficacy against similar viruses or their in vitro activity. The majority of information comes from small case series and single center reports which showed that COVID-19 infection in pregnant women can lead to intrauterine growth restriction, premature labor and spontaneous abortion. So, in the view of the urgency of COVID-19 pandemic and the uncertainties about its management during pregnancy, we aimed to provide a literature review on the effectiveness and safety of available medications for COVID-19 in pregnant women. Here, our overview may provide useful information for physicians to choose the best available medications for treatment a pregnant case with COVID-19.

Keywords: COVID-19; Pregnancy; Medications

Introduction

In Wuhan, China, coronavirus disease-2019 (COVID-19) began to appear in December 2019 [1]. It is caused by severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2), this is a new type of enveloped RNA viruses characterized by mild infection in upper respiratory tract and life-threatening pneumonia [2]. The number of the affected pregnant women is increasing as pregnancy is a special immunological case in which the immune system is exposed to great challenges involving maintaining and establishing adaptation to allogenic fetus and preserving fetus from any microbial challenges. The immune system in pregnancy undergoes three stages; pro-inflammatory state in the first trimester, anti-inflammatory state in the second trimester and second pro-inflammatory state in the third trimester [3].

During pregnancy the upper respiratory tract is swollen due to high levels of estrogen and progesterone which restrict lung expansion, and this increase the incidence of viral infection. Recent literature explains that COVID-19 infection is associated with cytokine storm in severe cases in which there is increased

plasma concentration of tumor necrosis factor alpha, macrophage inflammatory protein1 alpha, monocyte chemoattractant protein1, granulocyte-colony stimulating factor, interferon gamma inducible protein10, interleukins (IL-2), (IL-7), (IL-10). Based on the pro-inflammatory state in third and first trimester in pregnancy and cytokine storm in COVID-19 infection the pregnant women are exposed to severe inflammatory state which can affect the fetal brain and leads to several aspects of neuronal dysfunction [3,4]. Also, elevated levels of TNF alpha in mother's peripheral blood can be toxic to early embryo development and induce preterm delivery in non-human models [5].

Previous studies have explained that COVID-19 infection in pregnant women can lead to intrauterine growth restriction, premature labor and spontaneous abortion [6]. Therefore, treatment must be initiated when potential benefits outweigh potential risks and intra uterine development must be monitored closely during treatment and even after the treatment is stopped [7]. Due to the urgency of COVID-19 pandemic and the uncertainties about its management during pregnancy, we aimed to provide a literature review on the effectiveness and safety of available medications for COVID-19 in pregnant women. After we reviewed the guidelines and protocols from National institution of health (NIH), United Kingdom National Health Service (NHS), Egypt, Saudi Arabia, France, Italy, Spain and China, we limited our search on the most relevant medications mentioned in them. We also limited our search on English-language literature.

Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine are antimalarial and anti-rheumatoid drugs. They are weak bases and have deep volume of distribution and half-life around 50 days. These drugs cause defect in the lysosomal activity and autophagy, interfering with stability of cell membrane and causing defect in pathway of signaling and transcriptional activity leading to inhibition of cytokine production and modulating certain co-stimulatory molecules. Both drugs are enantiomers [8]. Chloroquine and hydroxychloroquine are category C according to FDA [9]. Studies showed that they have a broad-spectrum antiviral effect by increasing endosomal PH required for virus\cell infusion and causing defect in glycosylation of cellular receptors of SARS-COV. They also have anti-inflammatory effect plus their anti-viral effect which are responsible for their potent effect in treating COVID-19 [10]. Chloroquine can cross the placenta and accumulate in the fetal tissues as hydroxychloroquine which tend to accumulate in melanin containing tissues as retina and choroid leading to loss of vision [11].

On follow up of infants that their mothers took hydroxychloroquine during gestation and lactation, Hart and Naughton presenting that the main complication is preterm delivery (20.5%), no significant neonatal infections or congenital anomalies were observed, including infants that were breastfed. They concluded that hydroxychloroquine seems to be safe during pregnancy and preterm delivery reflects the state of maternal disease [12]. Suhonen reported a case receiving hydroxychloroquine phosphate in the first six weeks of pregnancy to control discoid systemic lupus erythematosus and fetus was born with no anomalies and grew without any mental or physical abnormalities [13]. Ross and Garotos examined autopsy from 14-week aborted fetus as his mother taking chloroquine showing no anomalies in oropharynx [14].

Additionally, eight patients who were presented to American Rheumatism Association, these patients had 28 pregnancies, they were receiving chloroquine, three of them underwent incomplete pregnancy or neonatal death as they came during period of activity of the disease, one had still birth fetus, four underwent spontaneous abortion and six had full term standard deliveries [15]. A meta-analysis conducted on hydroxychloroquine included seven cohort studies and one randomized controlled trial showed no significant increase in the rates of major congenital, craniofacial, genitourinary, cardiovascular, nervous system malformations, stillbirth or prematurity. Unfortunately, there is no data about the effect of chloroquine on pregnant women with COVID-19.

Remdesivir

Remdesivir is small molecule broad spectrum antiviral drug which act as RdRp inhibitor targeting viral genome process of replication. It is recommended to be safe during pregnancy in COVID-19 infection as in trials conducted of Marburg virus and Ebola virus [16]. In reproductive non-clinical toxicity, there is no adverse effects were noticed on embryo-fetal development in male infertility or pregnant animal with Remdesivir. In photoactivated localization microscopy study of acute Ebola virus disease, 26% of children and 3% of pregnant women received Remdesivir without any notable adverse effect [17].

Interferons (IFN-α and IFN-β mainly)

Type I interferons (IFN-α/β) have broad spectrum antiviral activities against RNA viruses by inducing an antiviral response across a wide range of cell types and stimulating the host adaptive immune response [18]. Data from several pregnancy registries showed no association between preconception or during pregnancy exposure to interferon-beta-1b and an increased risk of adverse birth outcomes [19]. A meta-analysis conducted to observe whether type I interferon has adverse effects on pregnant women with primary thrombocytopenia. The results showed that IFN-α did not significantly increase the risk of malformations, miscarriages, stillbirths, or premature births [20]. Another large systematic review included 50 studies that identified 761 pregnancies exposed to interferon β. Results reported that exposure to interferon β was associated with shorter mean birth length, lower mean birth

weight, and preterm birth (<37 weeks); however, there was no increased risk of serious pregnancy complications of spontaneous abortion, cesarean delivery or birth weight < 2.5 kg [21].

A recent study included data from 26 European countries evaluated pregnancy outcomes of 948 pregnant women with multiple sclerosis receiving IFN I-β during pregnancy or within one month before conception. Results did not show an increased risk of fetal malformations or spontaneous abortion [22]. Currently, IFN type I is classified as US FDA pregnancy category C.

Janus Kinase Inhibitors (e.g., Baricitinib)

Baricitinib is a potent and selective janus Kinase Inhibitor that is used for treatment of rheumatoid arthritis and currently being investigated for treatment of COVID-19 cases due to its anti-inflammatory and antiviral activities [23] as it would likely prevent the dysregulated production of pro-inflammatory cytokines in COVID-19 cases [24]. There are limited human data on the use of baricitinib to evaluate the drug-associated risk for major birth defects or miscarriage. In animal studies of embryo-fetal development, there was increased embryo lethality in some species that were given baricitinib at very high doses, above the maximum human recommended dose [25]. Baricitinib is not assigned in the US FDA pregnancy categorization. But It is classified as AU TGA (Australian categorization) pregnancy category: D.

Interleukin-1 Inhibitors (e.g., Anakinra)

Interleukin-1 is a pro inflammatory cytokine binds to IL-1 receptor and modulate its action so inhibitors of interleukin-1 are used to treat rheumatoid arthritis and currently being investigated for treatment of COVID-19 due to its potential effect to interfere with the cytokine storm in severe cases of COVID-19 [26]. There is limited evidence about the use of Interleukin-1 inhibitors(IL-1) in pregnancy but unintentional first trimester exposure is unlikely to be harmful [27]. According to an International multi-center study of the pregnancy outcomes in pregnant women exposed to interleukin-1 inhibitors, the use of interleukin-1 inhibitors may not significantly affect pregnancy outcomes or infant development. The study identified a total of 43 pregnancies with IL-1 inhibitors exposure in 7 countries, including 8 maternal from 14 with canukinumab and 23 maternal from 29 with anakinra. Seven healthy infants of normal gestational age and birthweight delivered from eight pregnancies exposed to canukinumab. Twenty-one healthy infants, and one baby with unilateral renal agenesis and ectopic neurohypophysis delivered from 23 pregnancies exposed to anakinra [28]. Anakinra is classified as US FDA pregnancy category B and AU TGA pregnancy category: B1.

Interleukin-6 Inhibitors (e.g., Tocilizumab)

Interleukin-6 (IL-6)is a pro-inflammatory cytokine that activates its downstream Janus kinase (JAK) signal by binding the transmembrane (cis-signaling) or soluble form (trans-signaling) of the IL-6 receptor [29]. Tocilizumab is a monoclonal antibody used for the treatment of rheumatoid arthritis and currently being investigated for treatment of some cases of severe COVID-19 with good results [30]. There are insufficient data to determine if there is a drug-associated risk for major birth defects or miscarriage [31]. A study analyzed pregnancy-related reports of 399 women with Tocilizumab exposure shortly before or during pregnancy. Pregnancy outcomes were reported in 288 pregnancies (72.2%) and showed no indication for a substantially increased malformation risk but the data do not yet prove safety [32]. Another Japanese retrospective study included 61 pregnancies with rheumatic disease exposed to tocilizumab during conception. Results showed no increased rates of spontaneous abortion or congenital abnormalities [33]. Tocilizumab is classified as US FDA pregnancy category C and AU TGA pregnancy category: C.

HIV Protease Inhibitors (e.g., Lopinavir/Ritonavir Darunavir/Cobicistat)

Lopinavir and Darunavir work as competitive inhibitors through binding directly to HIV protease and prevent subsequent cleavage of polypeptides, which in turn reduce viral replication and spread. Ritonavir and Cobicistat are metabolism-based enhancer to increase the exposure of Lopinavir and Darunavir [34]. Both drugs are used for treatment of HIV-infected women during pregnancy and prevention of mother-to-child transmission. In spite of their efficacy in vitro against SARS-CoV, they have poor selectivity index requiring higher than the tolerable level to achieve the clinically significant inhibition in vivo; however, based on systemic review and clinical studies found when given early to be associated with lower hospital stay and lower mortality rates [35-37].

Lopinavir is one of the main HIV protease inhibitors recommended in pregnancy with a good safety profile. Pharmacokinetics studies reported lower exposure of LPV in pregnancy [38] due to moderate decrease of total Lopinavir concentrations despite the dose increase [39]. However, the exposure of unbound LPV did not change significantly regardless of trimester or dose [40]. Two cohort studies of 21 women conducted with steady pharmacokinetic evaluations concluding that improving the oral bioavailability of the tablets may compensate for the reduction in exposure during the later stages of pregnancy [41]. Therefore, a population pharmacokinetic analysis conducted to assess the statically significance doesn't show clinically meaningful difference between Lopinavir exposure in pregnant women receiving the tablet and non-pregnant receiving the capsule and dose adjustment isn't needed [42]. However increased doses may be preferable in obesity (>100kg) and with a previous history of LPV/RTV use and/or compliance issues [43]. Bearing in mind that increasing the dose didn't correlate with frequent adverse effects

according to a random clinical trial [44] and didn't result in greater neurodevelopmental risks for HIV positive mothers or uninfected infants [45].

Despite the high frequency of maternal adverse effects, they are mostly of low severity hence LPV is considered safe throughout pregnancy. It is not assigned in FDA pregnancy category, however; it's classified by AU TGA pregnancy category as: B3

Darunavir is not recommended to use in pregnancy due to the great diminished exposure in second and third trimesters of pregnancy leading to increase the risk of virologic failure during pregnancy and must be boosted by Ritonavir low dose [46]. A large non blind clinical trials of 28 women supported by pharmacokinetic studies has found that using DRV/COBI during pregnancy is associated with reducing the exposure of total DRV area under the curve by 33% and 48% and DRV trough concentrations were reduced by 71% and 75% [47]. Prevalence of birth defects for pregnancies of women on Darunavir-containing regimens in the first trimesters 0.4% higher than the control population according to the Antiretroviral Pregnancy Registry [48]. Preterm delivery and low birth weight have been noted as adverse outcomes, but correlation isn't established [49]. It is not assigned in FDA pregnancy category and classified by AU TGA pregnancy category as: B2

Ivermectin

Ivermectin is one of the most widely used anti-parasitic drugs for animals and humans. Its main action is to inhibit the importin family of nucleus-cytoplasmic transporters which is responsible for transmitting viral proteins into the host cell nucleus. A meta-analysis covering several animal studies showed its effectiveness against both RNA and DNA viruses but lack human studies [50]. Based on a systemic review of the safety of Ivermectin treatment in pregnant women conducted on five retrospective case control studies and one random clinical trial concluding the absence of evidence for excess abnormal birth outcomes in woman who received Ivermectin during pregnancy. Despite the serious unfavorable outcomes regardless of the dose, no correlation between adverse effects and Ivermectin administration can be assessed because the intended studies weren't designed to focus on the safety of Ivermectin use throughout pregnancy [51,52]. Further reproductive toxicological studies and randomized clinical trials are needed to reach conclusive results. The drug is already in clinical trials all over the world, but pregnant women are excluded as a vulnerable group making the assessment of safety and efficacy of drugs in pregnancy extremely difficult. Ivermectin has been classified as pregnancy category C by the FDA.

Convalescent Plasma and Immune Globulins

Plasma from convalescent patients and human immunoglobulin (IVIG) have been proposed by as alternatives containing the antibodies that could be able to reduce the viral load, decrease disease severity score and improve the oxygenation state of the transfused subjects. Available studies to support their use are limited to case reports and case series. according to a recent systemic review of five studies most of them conducted in china on small groups of patient exhibit improvement after plasma therapy in temperature and respiration [52]. Definitive conclusion can't be obtained due to high risk of bias, some weren't constant or performed on other RNA viruses [53-56] Although maximum dose of 2400ml is reported in 73 male patients in China [57], but optimal dose remained indefinite. Monoclonal antibodies are preferred due to their specificity, low risk of blood-borne pathogen infection [58]. FDA is permitting the emergency investigational use of convalescent plasma to treat COVID-19 under the criteria of the emergency IND.

Antithrombotic Therapy

There are two types of antithrombotic drugs anticoagulants and antiplatelet drugs. Anticoagulants slow down clotting, thereby reducing fibrin formation and preventing clots from forming and growing. Antiplatelet agents prevent platelets from clumping and also prevent clots from forming and growing [59]. In 1970, LMWH was produced chemically by splitting heparin into one-third of its original size. It has few side effects than heparin and has a more effect as an anticoagulant [59]. Aspirin is the first antiplatelet drug which used to relieve pain for more than 100 years. Then in 1960s, proven aspirin prevented platelets from clumping, and subsequent clinical trials showed that it reduces the risk of stroke and heart attack. In 1980, researchers showed that aspirin in very low doses (much lower than that required to relieve a headache) blocked the production of a chemical in platelets that is required for platelet clumping. During that time, better understanding of the process of platelet clumping allowed the development of designer antiplatelet drugs directed at specific targets [59,60].

Once Aspirin reaches systemic circulation, it lacks antiplatelet activity. Aspirin achieve its maximum effect within 1 hour following an initial dose (325 mg), and to sustain its effect use very low dose (40mg/d). Its dose ranges from 50 up to 320mg/d [61]. The most dosage prescribed is (81mg/d) which called baby aspirin. Increasing dose of aspirin does not improve efficacy but increasing side effect especially gastrointestinal bleeding [62]. There are many roles of early use of aspirin in COVID-19 patients like inhibiting virus replication, anti-platelet aggregation, anti-inflammatory and anti-lung injury, is expected to reduce the incidence of severe and critical patients, shorten the length of hospital duration and reduce the incidence of cardiovascular complications.

Low-dose aspirin (150mg/d) is effective in prevention of placental complications during pregnancy like pre-eclampsia and fetal growth restriction. Additionally, this low dose not associated with an increased risk of congenital defects, bleeding or premature closure of the ductus arteriosus [63].

Antibacterial Therapy

Antibacterial therapy should not be started by default, but only if we suspect bacterial infection; it is mandatory to monitor the patient's status with blood culture, urine analysis and urine culture and to start the appropriate therapy only in case of positive cases [64]. Based on the patient's clinical manifestation, if the bacterial infection cannot be excluded, it is possible to start a therapy for community-acquired pneumonia (amoxicillin, azithromycin) in mild cases of COVID-19 disease; in severe patients until specific bacteria are identified, all possible pathogens should be treated. For instance, intravenous ceftriaxone could be used while waiting for cultures, starting appropriate and specific antibiotic therapy, based on the specific infection, as soon as possible [64-66].

Amoxicillin belongs to the class of beta lactam antibiotics, is semi synthetic penicillin that produce a bactericidal action by inhibiting the synthesis of the bacterial cell wall. It has a wide 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 beta lactamic group of antibiotics, because it is much better absorbed through the oral route. Amoxicillin is classified as class B by FDA and commonly used in pregnancy and breastfeeding [67,68].

Azithromycin belongs to a family of macrolide-type antibiotics and it works by inhibiting the protein biosynthesis and as a result the growth of bacteria (bacteriostatic drug). It has common side effects such as nausea, vomiting, diarrhea, abdominal pain and, less frequently some ECG changes as 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.68 Azithromycin is classified as class B by FDA and commonly used in pregnancy and breastfeeding [69].

Ceftriaxone is a beta-lactam agent which considered as a member of third generation cephalosporins group and it has a bactericidal action by interfering with the synthesis of peptidoglycans (i.e. bacterial cell wall constituents). Compared to first and second generation cephalosporins, it has lower efficacy against Gram-positive bacteria but it has a higher activity against Gram-negative bacteria. It has common side effects like 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 [70].

Proton Pump Inhibitors (PPIs)

Proton pump inhibitors (PPIs) remain central to management of acid-suppression disorders and are considered safe in the general population [71]. About two thirds of pregnant patients develop heartburn [72]. There are many factors which cause this, but the most significant one is a decrease in lower sphincter pressure of esophagus due to the female sex hormones, particularly progesterone. A prospective controlled cohort study was done on 295 pregnancies have deal with PPIs, 53 of them exposed to pantoprazole, and in comparison, with pregnancy outcomes with those of 868 control subjects. Rate of major congenital malformations in the group exposed to pantoprazole was 2.1% (1/48) compared with 3.8% in the control group (30/792) and no pattern of congenital anomalies [73]. PPIs have not a great teratogenic effect on pregnant women [74]. So pregnant women should choose an old PPI in a pharmacologic class that has the most fetal safety data that indicate the drug is effective. PPIs are classified as pregnancy category B.

Angiotensin Converting Enzyme Inhibitors (ACE inhibitors) & Angiotensin Receptor Blockers (ARBs)

Studies showed that COVID-19 uses ACE2 receptors in a way similar to SARS CoV. Poor outcomes in patient with diabetes mellitus and hypertension support this theory due to over expression of these receptors. Recent studies showed that patients receiving ACE inhibitors are in danger of poor outcomes due to up regulation of these receptors [75]. For pregnant women, ACE inhibitors can lead to injury or even more death of the fetus [76,77]. That's why the FDA put them in category C in first trimester and category D in the second. Thus, in turn, their use in pregnancy is not recommended and if it is necessary, the cardiologist must be cautious [77-78].

Host Directed Therapy (HDT)

Host Directed Therapy (HDT) is considered a group of maneuvers working through modulating the host immunity to decrease the damage resulting from excessive inflammatory process [79]. Evidences from clinical practice show that patients with severe symptoms of COVID-19 disease may present with which is called cytokines storm. Cytokines storm presents with an excessive increase in levels of IL-2, IL-6, IL-10, granulocyte colony stimulating factor, TNF-alpha, which lead to organ damage4. HDT includes metformin, statins and glitazone.

Metformin improves the production of mitochondrial ROS and the macrophages autophagy [80], decreasing the damage of the lung in murine models by reducing the mitochondrial complex I [81]. Gilbert et al. studied the use of metformin in pregnancy particularly in the first 3 months which seemed to be safe as concerning congenital malformations [82]. Li et al., studied the metformin administration in women with gestational diabetes and showed a risk reduction of some complications like gestational hypertension, increase of glucose level and the need of intensive care admission for the neonate [83].

Statins works by inducing autophagy and phagocytic maturation and are used as anti-inflammatory agents in pulmonary infections [84]. There is a limited data on the effects of statins administration

during pregnancy, but compared to the general population, they do not expect to result in major congenital malformations [85]. FDA assigned statins as category X in pregnancy, so it is contraindicated in pregnancy.

Glitazones target the cytokines overproduction. The main target is the peroxisome proliferator-activated receptor (PPAR)-c, which is considered a member of the PPAR transcription factor family, which causes inhibition of inflammatory process. PPAR-c synthetic agonists the family thiazolidinediones (TZDs), like pioglitazone, with known to have an ameliorating effect on severe viral pneumonia. Pioglitazone (30–45mg/day for 3 months) showed to significantly reduce IL-6 and TNF-alpha in people with insulin resistance [86]. The glitazones use in pregnancy has not been studied and most information come from case report of inadvertent use or therapeutic use for PCOS which resulted in normal outcome [87] or spontaneous abortion [88]. For the sake of that causes, pioglitazone has not been classified by FDA to be used in pregnancy.

Ambroxol

Ambroxol is secretolytic drug that has anti-inflammatory and anti-oxidant properties and can be used for cough and sore throat [89,90]. These symptoms are present in COVID-19 [91]. One of its great effects is reduction of pro-inflammatory cytokines 89. This effect is useful in cytokine storm and ARDS that happens in some of COVID-19 cases [24]. Despite all these advantages of Ambroxol, its use is not recommended in pregnancy and it is an FDA category C drug [92].

Codeine

Codeine is a narcotic used for pain relief, sedation and cough suppression [93]. It's an FDA class C pregnancy drug. Its use is not recommended during pregnancy. A small amount is metabolized into morphine in the body [93]. One of its dangers is neonatal narcotic withdrawal [94]. So, it can be used only of its use benefits overweight harms to the fetus [95]. It's better to be avoided in treatment of COVID-19 pregnant women but can be used if late cases in trial to save the mother.

Corticosteroids

Antenatal Administration of corticosteroid is relatively common among pregnant women as it has immunosuppressive and anti-inflammatory effects. In early pregnancy, steroids are used to treat recurrent miscarriage or fetal problems. Furthermore, the antenatal administration of corticosteroids to mothers who at risk of preterm delivery is one of the most significant developments in perinatal medicine; corticosteroids which are administered antenatal now the most important part of care for pregnancies of anticipation of premature delivery in developed countries. This because of improvement of neonatal outcomes following antenatal corticosteroid administration. However, prednisone does not represent a fatal teratogenic risk in humans at therapeutic doses, it does increase the risk of oral cleft by an order of 3.4-fold, which is consistent with the existing animal studies [96].

Prematurity abnormalities showed a good decline in antenatal exposure to Corticosteroids, including perinatal death, neonatal death, moderate/severe RDS, intraventricular hemorrhage (IVH), necrotizing enterocolitis and systemic infections in the first 48 hours of life [97].

Some trials on children up to 12 years show that exposure to antenatal corticosteroids does not show any hinder or retard the somatic or psychomotor growth [98]. Antenatal corticosteroids are used for women at risk of premature birth and will decrease neonatal morbidity and mortality and save health care costs. A recent study, where a decision-analytic model was applied, showed that, in case of premature rupture of membranes in preterm, the administration of antenatal corticosteroids was an effective management plan when it was compared to no corticosteroid administration only at gestational ages less than 31 weeks [99]. There are some reports stated a potential worsening of the clinical conditions in already ill patient after betamethasone administration. As a result, a single dose of 12mg of betamethasone could be administered to minimize the effects on maternal blood glucose and on patient's clinical condition [100]. Therefore, the use of corticosteroids on the treatment of COVID-19 should be carefully evaluated because of the reduction of the host's inflammatory response in the lungs. FDA does not assign betamethasone in any category on the other hand, prednisolone and methylprednisolone are classified in category C/D and C of FDA, respectively but corticosteroids generally are classified as US FAD category D [101].

Non-Steroidal Anti-Inflammatory drugs (NSAIDs)

NSAIDs are one of the most commonly used over-the counter (OTC) medications for the treatment of pain, inflammation and fever. It's action by inhibiting the activity of cyclooxygenase enzymes (COX-1 or COX-2) in cell. These enzymes produce prostaglandins (PGs), lipids which cause pain and fever101. There are two types of NSAIDs non-selective (ibuprofen) and COX-2 selective (celecoxib and diclofenac) [102]. Paracetamol (acetaminophen) is generally not considered an NSAID due to its minor anti-inflammatory effect. It relieves pain mainly by blocking COX-2 and inhibiting endocannabinoid reuptake almost exclusively within the brain [103].

Ibuprofen used as the second most OTC analgesic after paracetamol [104] and consider as the mildest NSAID due to its fewest side effects which has been in clinical use for a long time [105]. Long term use of NSAIDs associated with higher rates of side effect like myocardial infarction, heart failure, stroke and nephrotoxicity [106-108]. Acute respiratory tract infections are

also associated with increased risk of stroke and myocardial infarction [106].

NSAIDs are associated with higher rates of complications after respiratory tract infections, including complicated pneumonia, pleural effusions, prolonged illness, peritonsillar abscess, dissemination of infection to more than one site, or suppuration. NSAIDs were also associated with delays in the prescription of effective antibiotic treatment for patients requiring hospital admission [107,108] so use of NSAID in patients who positive COVID-19 and has other comorbities may aggravate these symptoms [109]. However, NSAIDs are used in COVID-19 to relieve nighttime symptoms and aid sleep if paracetamol not enough as sleep is an important in immune defense. It also relieves musculoskeletal pain which annoying patients [110].

Ibuprofen is category (B,B,D) , paracetamol (B,B,B) and aspirin (D,D,D) according FDA (U.S. Food and Drug Administration) Pregnancy risk classification by trimesters (1st,2nd,3rd).

The placental barrier is permeable to paracetamol and its metabolites. Its metabolites detect in the infant's urine after the mother had taken a few hours before delivery [111]. There are no conclusion association between paracetamol exposure in utero and cryptorchidism according to Data from epidemiological and animal studies about risks of malformations [112]. There is no direct measurement of the ability of ibuprofen to cross the placental barrier and its subsequent plasma levels in human fetuses. Ibuprofen and its metabolites enter the fetal circulation [113] and found in the meconium of newborn infants [114].

In the third trimester of pregnancy, all NSAIDs are contra-indicated due to risks of severe cardiopulmonary toxicity and renal dysfunction in the fetus [115]. In the 1st trimester, non-selective COX inhibitors like ibuprofen decrease cell proliferation and increase cell death in human fetal ovaries mainly due to effects on fetal germ cells.115

Conclusion

COVID-19 is a pandemic disease caused by the SARS-CoV-2 which spread globally in the last few months. Currently, there is no specific treatment for SARS-CoV-2. Additionally, many of effective drugs in general population cannot be used for pregnant women due to the lack of knowledge of side effects so clinicians should take into account benefits and possible adverse effects and initiate treatment when potential benefits outweigh potential risks and intra uterine development must be monitored closely during treatment and even after the treatment is stopped.

Acknowledgment

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Conflict of Interest

None.

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