Management of pregnancy-related hypertensive disorders in patients infected with SARS CoV-2: pharmacological and clinical issues

Silvia Fogacci[a], Federica Fogacci[a], Elda Favari[b], Peter P. Toth[c], Claudio Borghi[a], Arrigo F.G. Cicero[a]

a. Hypertension and Cardiovascular Risk Research Group, Medical and Surgical Sciences Department, Alma Mater Studiorum University of Bologna, Bologna, Italy

b. Department of Food and Drug, University of Parma, Parma, Italy

c. CGH Medical Center, Sterling, IL, and Cicarrone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

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Abbreviations: ACOG= American College of Obstetricians and Gynecologists; AHA= American Heart Association; CCB= Calcium channel blockers; COVID-19= Coronavirus-19; CV= Cardiovascular; ESC= European Society of Cardiology; LMWH= Low molecular weight heparin; NSAIDs= Non-steroidal anti-inflammatory drugs; SARS-CoV-2= Severe acute respiratory syndrome Coronavirus 2.

Corresponding author:

Arrigo F.G. Cicero, MD, PhD

Medical and Surgical Sciences Department

Sant'Orsola-Malpighi University Hospital

U.O. Medicina Interna Borghi - Via Albertoni, 15

40138 Bologna - Italy

Tel.: ++39 512142224 - Fax: ++39 51391320

E-mail: arrigo.cicero@unibo.it

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Abstract

Aims: Coronavirus-19 infection (COVID-19) continues to spread throughout the world. It is known that among patients with hypertension, diabetes, chronic respiratory disease, or cardiovascular (CV) diseases, COVID-19 is associated with greater morbidity and mortality compared to patients without these conditions. This correlation is of great importance in pregnant women affected by COVID-19, since it usually leads to the development of a serious clinical complication. In particular, managing hypertensive disorders in pregnancy can be problematic because anti-hypertensive medications may interact pharmacologically with drugs used to treat COVID-19. This review focuses on the safety of drug treatment for COVID-19 in pregnant women treated with anti-hypertensive medication.

Methods and results: Several databases were searched to identify relevant literature. A few anti-hypertensive drugs and antithrombotic treatments are known for having a beneficial effect in the management of hypertension and hypertensive disorders in pregnancy. In this review, we focus on the expected drug-drug interactions with the experimental agents mostly used treat COVID-19.

Conclusions: The current indication for the management of hypertension-related disorders in pregnancy maintain their validity, while the risk of pharmacological interaction with the currently tested anti-SARS-CoV-2 medications is relatively low.

Keywords: SARS-CoV-2; Coronavirus-19; COVID-19; pregnancy; hypertension; antihypertensive treatment

1. INTRODUCTION

Coronavirus disease (COVID-19), caused by the highly transmissible severe acute respiratory virus Coronavirus 2 (SARS-CoV-2), continues to spread throughout the world [1]. The virus is primarily spread through close human contact via aerosolized droplets of saliva or mucus secretions [2]. Its main feature is infection of the respiratory system in association with cough, fever and typical changes in radiographic studies that can lead to acute respiratory distress syndrome, cardiovascular (CV) events such as myocardial infarction, myocarditis, fulminant heart failure and lethal arrhythmias, and such neurovascular events as ischemic stroke and encephalopathy. Pregnant women are considered a high-risk group due to their altered immunological and physiological status [3-5]. Viral respiratory illnesses frequently develop during pregnancy; hence, pregnant women have greater vulnerability for contracting a SARS-CoV-2 infection [6,7]. As a matter of fact, physiological hormonal changes in pregnant women, such as the progesterone-mediated action on nasal mucosa, have been demonstrated to increase the probability of contracting the disease compared to the general population [7].

Very few studies are available concerning the effect of COVID-19 on pregnancy and fetal outcomes [8]. The maternal-fetal interface was analyzed in different clinical settings, and no evidence of vertical COVID-19 transmission was seen in pregnant women in the third trimester of pregnancy [9-11]. Due to limited scientific evidence regarding pregnancy and COVID-19, some official statements have been made referring to SARS CoV-1 [12]. Some previous studies about SARS suggest women may need prioritized medical care sinceCOVID-19 infection during pregnancy may lead to maternal and fetal complications, such as spontaneous miscarriage, preterm birth, intrauterine growth restriction, premature rupture of membranes, fetal tachycardia and fetal distress, multiple organ injury and admission to intensive care units [10,12-14]. Nevertheless, what is clear is that more

studies are needed regarding COVID-19 and pregnancy, considering the fact that it affects the well-being of mothers and their babies [6]. For this reason, accurate hygiene and social information must be guaranteed to pregnant women and their families in order to prevent SARS-CoV-2 infection [2].

It is known that among patients with hypertension, diabetes, chronic respiratory disease, or CV diseases, SARS-CoV-2infection is associated with greater morbidity and mortality compared to patients without these conditions [11,15]. This correlation is of great importance in pregnant women affected by COVID-19, since it usually leads to the development of a serious clinical complication [6]. Regarding hypertensive disorders in pregnancy there are very few drugs available with a controversial security profile, that sometimes pharmacologically interact with the ones tested to treat COVID-19 [16]. In particular, the anti-COVID-19 medications for which there are currently more evidence are low molecular weight heparin (LMWH), lopinavir/ritonavir, hydoxychloroquine and chloroquine [7,15].

The purpose of the current review is to highlight the safety of drug treatment for COVID-19 in pregnant women treated with anti-hypertensive medications.

2. MATERIAL AND METHODS

For the purpose of this review, authors identified trials in both MEDLINE (National Library of Medicine, Bethesda, Maryland, MD, USA; January 1980 to July 2020) and the Cochrane Register of Controlled Trials (The Cochrane Collaboration, Oxford, UK). The terms ‘SARS-CoV-2’, ‘severe acute respiratory syndrome’, ‘Coronavirus disease’, ‘COVID-19’, ‘lopinavir/ritonavir’, ‘chloroquine’, ‘hydroxychloroquine’, ‘aspirin’, ‘methyldopa’, ‘hydralazine, ‘beta-blockers’, ‘labetalol’, ‘metoprolol’, ‘atenolol’, ‘pindolol’, ‘calcium channel blockers’,

‘diltiazem’, ‘nifedipine’, ‘verapamil’, ‘magnesium sulfate’, ‘low molecular weight heparin’, ‘LMWH’, ‘hypertension’, ‘pre-eclampsia’, ‘preeclampsia’, ‘clinical trial’, and ‘human’ were incorporated into an electronic search strategy. The references of the identified studies and review articles were reviewed to look for additional studies of interest. The authors reviewed all of the citations retrieved from the electronic search to identify potentially relevant articles for this review.

3. RESULTS

A few anti-hypertensive drugs and antithrombotic treatments are known for having a beneficial effect in the management of hypertension and hypertensive disorders in pregnancy. In this review, we focus on the expected drug-drug interactions with the experimental agents most often used to treat SARS-CoV-2 infection (**Figure 1**).

.1 ***Aspirin.*** In accordance with the European Society of Cardiology (ESC) guidelines for the management of CV diseases during pregnancy, 100-150 mg/day acetylsalicylic acid (aspirin) should be recommended to pregnant women with a high or moderate risk to develop pre-eclampsia (class I; level of evidence A) [17]. Similarly, the American College of Obstetricians and Gynecologists (ACOG) recommends that these patients take 81 mg/day of aspirin (level of evidence A) [18].

In the general population, non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, are reported to negatively affect the lungs, worsening a pre-existing pulmonary infection [19,20]. For this reason, some investigators brought into question the safety of aspirin treatment in pregnancy during the COVID-19 pandemic [21]. Taking into account that significant data about aspirin intake and aggravation of COVID-19 symptoms in pregnancy are lacking, the same authors agree that the benefits of aspirin prophylaxis in high risk women for hypertensive disorders outweigh the potential dangers posed by the

virus [21]. In this perspective, it is also worth to evidence a possible effect of NSAIDs on induction of MAP Kinase Phosphatase 1, leading the inhibition of inflammatory gene expression [22]. Moreover, we have also to consider a possible interaction between aspirin and LMWH on risk of bleeding [23]. On the other side, there is no evidence that aspirin interacts with medications currently being evaluated for treating SARS-CoV-2 infection [24].

3.2 *Methyldopa*. Methyldopa is an alpha-2 adrenergic agonist with both central and peripheral nervous system effects. Together with labetalol and calcium antagonists, methyldopa is one of the drugs of choice recommended by ESC for the treatment of hypertension in pregnant women (class I; level of evidence B) [17]. In accordance with the American Heart Association (AHA) recommendations [25], methyldopa should only be prescribed in cases of severe hypertension during pregnancy, considering potential maternal and fetal side effects (class I; level of evidence A).

In vitro, chloroquine and hydroxychloroquine are aminoquinolone derivatives that have antiviral activity against the SARS-CoV-2 [26-29]; however, efficacy data in humans are still preliminary. Compared to chloroquine, hydroxychloroquine has a much better safety profile [30], and has demonstrated promising capacity to prevent pre-eclampsia [31]. In clinical practice, methyldopa is often prescribed to women affected by systemic lupus erythematosus treated with hydroxychloroquine to prevent flares [32]., The co-administration of methyldopa and hydroxychloroquine is considered to be safe in hypertensive pregnant women infected with SARS-CoV-2.

3.3 *Beta-blockers*. Among beta-adrenergic receptor blockers, ESC recommends the use of labetalol as first-line therapy in pregnant women with hypertension (class I; level of evidence C) [17], while AHA suggests atenolol (class III; level of evidence B), pindolol, metoprolol and labetalol as first-line therapies (class IIa; level of evidence B) [25]. ACOG

recommends labetalol therapy in urgent blood pressure control in pregnancy [18]. Third-generation beta-blockers have also been shown to prevent bronchial asthma attacks and respiratory dysfunction. The release of nitric oxide, antioxidant action and other mechanisms underlying the vasodilating action of these drugs may be responsible for the beneficial therapeutic effects of these agents [33]. However, these agents have never been tested in pregnant women.

In pregnant women, the combination of beta-blockers and LMWH is the recommended treatment for atrial fibrillation [34]. In this context, we can reasonably expect the combination of beta-blockers and heparin to be safely administered in hypertensive-treated pregnant women infected by SARS-CoV-2. This is certainly of great interest, since LMWH seems to mitigate the pulmonary coagulopathy often promulgated by the virus [35,36]. In contrast, the simultaneous administration of beta-blockers and hydroxychloroquine (or chloroquine) requires close electrocardiographic monitoring due to the risk of QT prolongation [37].

3.4 *Hydralazine*. Hydralazine hydrochloride is a hydrazine derivative vasodilator drug. In light of the ACOG recommendations, hydralazine is one of the drugs used for urgent blood pressure control in pregnancy [18]. AHA also recommends it in hypertensive-treated women (class III; level of evidence B) [25]. To date, there is a lack of validated studies evaluating the interaction between hydralazine and investigational drugs used for treating SARS-CoV-2 infection while NSAIDs could reduce its efficacy by inhibiting the prostacyclin-related vasodilation[38].

3.5 *Calcium channel blockers*. Calcium channel blockers (CCB) are another group of anti-hypertensive drugs recommended by ESC (level of evidence C) [17] and AHA (class I; level of evidence A) [25], whereas ACOG advises nifedipine administration only in the setting of hypertensive urgency [18].

During the current pandemic, questions have been raised about potential drug-to-drug interactions with treatments for SARS-CoV-2 infection. A variety of antiretroviral therapies are being tested to treat COVID-19 [3,39-41]. The co-administration of nifedipine and lopinavir/ritonavir is potentially toxic linked, to their common cytochrome P450 3A4 related metabolism [42,43], occasionally causing serious sides effects such as tachycardia, hypotension, headache and peripheral edema [43]. Considering the safety profile of combining nifedipine and lopinavir/ritonavir in non-pregnant women, we can reasonably expect a toxic effect in pregnancy as well [44].

3.6 ***Low molecular weight heparin***. LMWH has been shown to prevent pre-eclampsia in high-risk pregnant women by improving endothelial function in the vasculature [45,46]. Moreover, LMWH inhibits endothelial inflammation [47], making it potentially useful for treatment of SARS-CoV-2 infection.

In accordance with the latest ESC guidelines for the management of CV disease during the COVID-19 pandemic, drug-drug interactions should be considered before administering azithromycin in patients treated with LMWH [37], despite possible beneficial effects by azithromycin in patients infected with SARS-CoV-2 [48]. In contrast, chloroquine, hydrochloroquine and lopinavir/ritonavir do not have any clinically significant interactions with LMWH [37].

3.7 ***Magnesium sulfate***. Intravenous magnesium sulfate is recommended for preventing eclampsia and treating seizures as suggested by ACOG (level of evidence A) [18] and ESC [17] guidelines. According to a case-control study, its co-administration with LMWH shows better results than magnesium sulfate alone in treating severe pre-eclampsia [49]. There are no no contraindications to combined treatment in hypertensive pregnant women infected with SARS-CoV-2 [50].

3.8 *Vitamins*. Though vitamin D supplementation is not recommended by international guidelines, a recent meta-analysis shows it may prevent pre-eclampsia in pregnancy [51]. From the COVID-19 point of view, it seems to have a role in the pre-clinical phase in strengthening the immune system, especially in cases of deficiency [52]. Furthermore, several studies have shown antiviral effects of vitamin D, which can interfere directly with viral replication, but also can act in an immunomodulatory and anti-inflammatory way [53]. So far, low serum levels of vitamin D have been linked to increased morbidity and mortality in COVID-19 patients [54,55]. Ahmed et al. have reported the case of a 29-year woman with diabetes and vitamin D deficiency who died from thrombotic complications during SARS-CoV-2 infection [56].

In addition to vitamin D, vitamin C is not included in international recommendations, though its deficiency has been associated with an increased risk of pre-eclampsia [57]. Its role in preventing hypertensive disorders in pregnancy is still unclear and needs to be further investigated [58]. In the course of the SARS-CoV-2 pandemic, vitamin C serum levels are reported to decrease during infection and the requirement for supplementation increases accordingly [59]. A number of ongoing clinical trials will provide additional information on the impact of vitamin administration as a component of supportive care in SARS-CoV-2 infection [60,61].

4. DISCUSSION

The general advice for pregnant women is to avoid pharmacological treatments, in particular since rarely the safety profile of drugs has been systematically evaluated in this frail patient population [62].

Considering that available data on COVID-19 in pregnant patients do not provide a clear conclusion as regards clinical implications for mother and fetus [62], decision-making

processes in clinical practice need to be based on well-known similar prognostic models. In this context, in order to study the potential drug-drug interactions it is possible to refer to particular affections in pregnancy in which the anti-hypertensive treatment has just been tested along with drugs currently used against SARS-CoV-2. For example, cohorts of hypertensive pregnant women affected by HIV can be taken into exam to predict the clinical outcome of protease inhibitors and CCB association [63]. In the same way chloroquine and hydrochloroquine effect along with methyldopa can be usefully considered in cohorts of pregnant women with rheumatological diseases and gestational hypertension [32]. There is no doubt that data on long-term safety regarding all the above-discussed treatment combinations are needed, but until more evidence become available, it is necessary to rely on previous clinical experience and not prioritize the treatment of COVID-19over that of hypertension, as it can also result in potentially fatal complications [64]. On the other side, even if renin-angiotensin system inhibitors seem to improve the clinical outcomes of SARS-CoV-2 patients with hypertension [65,66], they are contraindicated during pregnancy because of teratogenesis risk [17]. Finally, it must be taken into account that even though several clinical trials have been initiated to assess potentially promising therapies for COVID-19, pregnant and breastfeeding women were excluded from almost all these studies [67]. Obviously, this will cause a delay in identifying the most appropriate treatment, though the choice is in some respects understandable.

Future research should focus on drugs protecting the endothelium from the damage induced by SARS-CoV-2 infection.[68] In particular, cell adhesion molecules (CAMs), including CD209L/L-SIGN and CD209/DC-SIGN, could be a relevant role in SARS-CoV-2 infection and other related viruses, consequently been possible therapeutic targets.[69] Inhibition of IL-6 and the Janus Kinase, signal transducer and activator of transcription proteins pathway (JAK/STAT), could be also favorable targets.[70]

To date, the only safe medical care showing benefit in treating the virus in pregnant patients is pressurized air enriched with oxygen, intravenous hydration, nutritional supports and electrolyte balance, which are supposed to help and improve the oxygenation in patients with much compromised respiratory system [29]. For this reason, people and in particular pregnant women with a weak immune system should take into account preventive measures to protect their health [6].

5. CONCLUSIONS

In conclusion, despite the scarcity of available data, current recommendations for the management of hypertension-related disorders in pregnancy remain valid since the risk of pharmacological interaction with currently tested anti-SARS-CoV-2 medications is relatively low.

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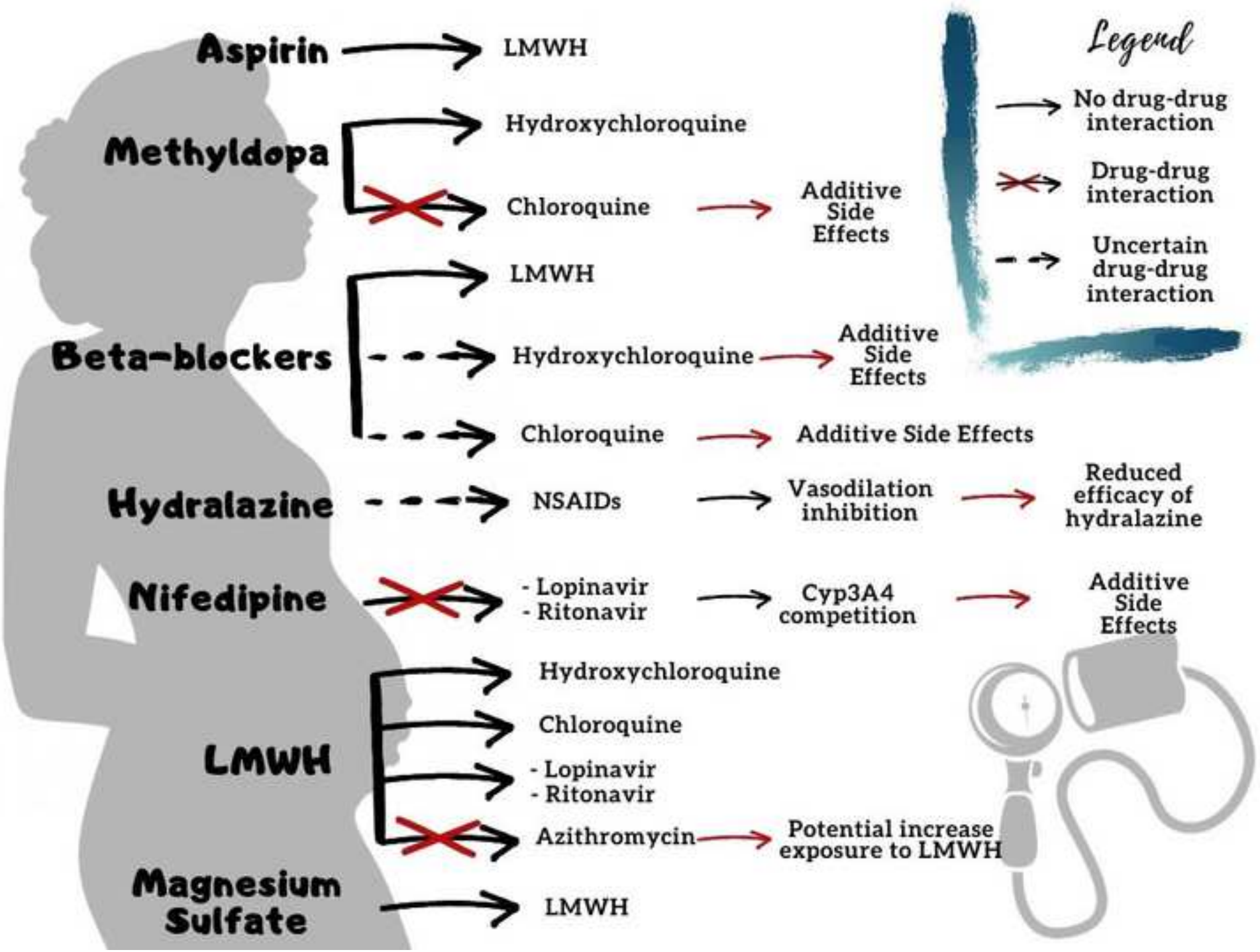
Figure legends

Figure 1 - Anti-hypertensive drugs interaction with anti-COVID-19 medications.

LMWH= Low molecular weight heparin; NSAIDs= Non-steroidal anti-inflammatory drugs.

Figure


Aspirin
LMWH
Methyldopa
Hydroxychloroquine
Chloroquine
Additive Side Effects
Beta-blockers
LMWH
Hydroxychloroquine
Additive Side Effects
Chloroquine
Additive Side Effects
Hydralazine
NSAIDs
Vasodilation inhibition
Reduced efficacy of hydralazine
Nifedipine
- Lopinavir
- Ritonavir
Cyp3A4 competition
Additive Side Effects
LMWH
Hydroxychloroquine
Chloroquine
- Lopinavir
- Ritonavir
Azithromycin
Potential increase exposure to LMWH
Magnesium Sulfate
LMWH
Legend
No drug-drug interaction
Drug-drug interaction
Uncertain drug-drug interaction