


Pre-Exposure Prophylaxis for COVID-19 in Pregnant Women

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Abstract: Pregnant women are at higher risk for developing severe complications of COVID-19 including preterm delivery, respiratory failure, and death. Although vaccines to prevent COVID-19 are being developed, pregnant women are not included in the current COVID-19 vaccine trials and initially this population may not be eligible for COVID-19 vaccines due to lack of safety testing in pregnancy. As an alternate approach, we discuss the concept of pre-exposure prophylaxis (PrEP) using medications that are approved for use in pregnant women to prevent gestational problems and severe illness in this high-risk population. In particular, the use of hydroxychloroquine PrEP affords a safe and readily available means to avoid COVID-19 complications in pregnancy.

Keywords: COVID-19, SARS-CoV-2, pregnancy, pre-exposure prophylaxis, hydroxychloroquine, vaccine

Introduction

To date, SARS-CoV-2 has caused more than 96 million cases of COVID-19 and more than two million deaths worldwide.¹ The United States has witnessed a steady increase in cases, with a recent record of more than 500,000 cases reported in one week of October 2020. Despite such gloomy news, new COVID-19 vaccines have completed or are nearing completion of Phase 3 clinical trials. Although these vaccines may be available to the general population, there is a group of individuals who are likely to be left behind: pregnant women.^{2,3}

According to reports from the US Centers for Disease Control and Prevention, pregnant women have a significantly higher risk of severe COVID-19 complications compared to non-pregnant women, including admission to an intensive care unit, need for invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO), and death.^{4,5} A study from Sweden found that pregnant women with COVID-19 were five times more likely to be admitted to an intensive care unit and four times more likely to receive mechanical ventilation compared to women who are not pregnant.⁶ Risk factors for severe COVID-19 in pregnancy include hypertension, diabetes, cardiovascular disease, cerebrovascular disease, and obesity.⁷

COVID-19 may also affect the fetus. The rate of preterm delivery and stillbirths has increased significantly during the pandemic, and the rate of preterm birth was found to correlate with the severity of maternal disease.^{8,9} Significant placental pathology with fetal demise due to vascular compromise has recently been associated with COVID-19.^{10,11} Because the majority of pregnant women with COVID-19

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reported thus far experienced infection in the third trimester, ongoing surveillance is needed to assess the effect of infections in early pregnancy as well as longer-term outcomes of exposed infants.^{4,5} In a recent study of 594 primarily outpatient pregnant women, SARS-CoV-2 infection was associated with a prolonged disease course during gestation and in the six weeks after pregnancy.¹²

Since pregnant women are typically excluded from vaccine trials including the current ones for COVID-19, it is unlikely that this population will initially receive protection from a novel vaccine due to uncertainty over how it could affect pregnancy.^{2,3} A report of possible cross-reactivity between SARS-Cov-2 spike protein and a component of placental syncytin-1 has led to fears of infertility induced by the COVID-19 vaccines.¹³ Two of the vaccines utilize mRNA technology, a new platform when compared to historical vaccine delivery. Therefore, the effect of this novel technology in pregnant women is unknown and use of these vaccines in pregnancy will require extensive safety testing. Although some medical organizations have speculated that COVID-19 vaccines are safe and effective in pregnancy, clinical support for this speculation is lacking at present. The question then stands: How do we protect this vulnerable population from developing severe COVID-19 symptoms that could cause harm to both the mother and her unborn child? The answer lies in a controversial Food and Drug Administration (FDA)-approved medication that has been in clinical use for decades: hydroxychloroquine (HCQ).

History of HCQ

HCQ is an antimalarial medication that was developed after World War II as a replacement for atabrine, which was given to thousands of soldiers in the South Pacific to prevent the devastating effects of malaria. As an aside, in 1944 the United States produced more than 2.5 billion doses of atabrine, and a similar scale-up of HCQ could be achieved to combat COVID-19.¹⁴ HCQ has been the preferred drug for malaria prophylaxis due to its excellent safety profile when compared to other medications such as mefloquine, quinine, atovaquone, and chloroquine.¹⁵⁻¹⁷ It has also been used to treat Q-fever and Babesiosis.

HCQ has been used successfully as an anti-inflammatory agent (disease-modifying antirheumatic drug, DMARD) in certain autoimmune and rheumatic conditions such as systemic lupus, rheumatoid arthritis, Sjogren's syndrome, antiphospholipid antibody syndrome, and connective tissue disorders.^{15,16} Despite its recent

demonization in the media, HCQ when prescribed correctly and taken as directed is a relatively well tolerated and safe medication, even when taken for extended periods of time.¹⁶

Multiple studies demonstrate that HCQ has antiviral properties.^{1,17} Chloroquine analogs such as HCQ have been shown to exhibit non-specific antiviral activity in vitro against viruses such as Ebola, HIV, dengue, chikungunya, Zika, MERS, SARS and influenza, and more recently SARS-CoV-2.¹⁶ Additionally, HCQ has been shown to protect mouse fetuses from infection with Zika virus, a property that could prove beneficial during the SARS-CoV-2 pandemic.¹⁸

HCQ is recognized as being safe for use during pregnancy and breastfeeding, and this property is especially important for women in malaria-endemic regions.¹⁹⁻³³ A study of 133 pregnant women with connective tissue disease found that HCQ was safe when compared to a control group.²⁴ Historically, HCQ has been used by rheumatologists and obstetricians to treat women with autoimmune disease to minimize flares and improve pregnancy outcome. Reproductive immunologists have used HCQ to calm overactive immune systems with good outcomes in women who suffer from immunological pregnancy loss and/or failure.¹⁹⁻³³ Although HCQ has been criticized for prolonging the QT interval, numerous other medications are known to have a greater effect on this EKG parameter without significant clinical concerns, and the safety of HCQ in COVID-19 treatment trials involving nearly 3000 outpatients has recently been confirmed.³⁴⁻³⁶

HCQ Pre-Exposure Prophylaxis (PrEP)

A crucial aspect of HCQ treatment derives from the distinction between three populations at risk for COVID-19: hospitalized patients who are already infected with SARS-CoV-2, people with significant exposure to the virus who receive post-exposure prophylaxis (PEP), and people treated prior to viral exposure who receive pre-exposure prophylaxis (PrEP). HCQ treatment has met with failure in SARS-CoV-2-infected hospitalized patients, and HCQ PEP has also shown variable efficacy.¹ In contrast, HCQ PrEP prior to exposure or infection has shown positive safety and efficacy results. A recent British study of 120,075 healthcare workers (HCWs) found that these subjects had a 7-8 fold greater risk of developing severe COVID-19 compared to non-HCWs.³⁷ With this

background, four cohort studies of HCWs from India reported positive outcomes for HCQ PrEP.^{38–41} These case–control studies enrolled a total of 2160 high-risk HCWs and demonstrated significantly less SARS-CoV-2 infection in subjects who used HCQ PrEP compared to those who did not.^{38–41}

Additional population-based studies in more than 360,000 patients with rheumatic diseases from China, Portugal, and the United States found that HCQ treatment was associated with significantly less SARS-CoV-2 infection.¹ In a retrospective cohort study of 32,109 rheumatic disease patients from the United States Veterans Administration, the incidence of SARS-CoV-2 infection was extremely low regardless of chronic HCQ use (0.3% in users versus 0.4% in non-users), but mortality was significantly decreased in patients taking HCQ (odds ratio 0.70, $p=0.0031$).¹

The results of two randomized controlled trials (RCTs) of HCQ PrEP that enrolled 1615 HCWs were recently released, and among 1053 subjects who received HCQ PrEP there were no hospitalizations, no deaths, and no cardiac complications.¹ In addition, once-weekly dosing appeared to be as effective as twice-weekly or daily dosing for HCQ PrEP. Because the studies were terminated prematurely they were underpowered to show a treatment benefit, however, and additional RCTs of early HCQ treatment for COVID-19 have been recommended.^{42,43} Since RCTs require an average of 5.5 years for completion at an average cost of over a million dollars, it may take a long time to obtain conclusive results from these studies.¹

HCQ PrEP in Pregnancy

As noted above, HCQ works well for COVID-19 PrEP prior to infection or exposure to SARS-CoV-2. If HCQ is safe for treatment of pregnant women and effective in prevention of severe disease associated with COVID-19, serious consideration should be given to prescribing HCQ to this vulnerable population that will be neglected upon release of the highly anticipated vaccines. We propose using HCQ at weekly dosing of 400 mg during pregnancy, similar to dosing for malaria prophylaxis. This dose has been used safely in pregnant women, and it should avoid serious disease and maternofetal complications associated with SARS-CoV-2 infection.^{1,26}

While RCTs of HCQ PrEP in pregnancy would be desirable, these studies would be difficult to accomplish for several reasons: recruitment for HCQ RCTs has been impeded by negative publicity and political issues

surrounding use of the medication in PEP studies and hospitalized patients, and recent HCQ PrEP RCTs have been terminated prematurely due to recruiting failures, as noted above.¹ In addition, women are reluctant to participate in RCTs during pregnancy due to perception of harm to their unborn children.⁴⁴ Nevertheless, HCQ PrEP RCTs could be attempted in this population in conjunction with appropriate patient education about safety and efficacy of this FDA-approved medication.⁴⁵ In the face of a public health crisis, it is important to consider life-saving approaches based on scientific logic, safety considerations, and clinical availability even if definitive evidence is lacking.¹

Other Options for Pregnancy PrEP

Other FDA-approved medications have been touted as potential candidates for COVID-19 treatment.¹ Unfortunately, most are not considered safe during pregnancy and can cause serious side-effects in pregnant women. Atovaquone, ivermectin, nitazoxanide, tafenoquine, and mefloquine have all been suggested for COVID-19 treatment based on limited in vitro and in vivo studies. Atovaquone and ivermectin have questionable safety during pregnancy (Category C) and are therefore not ideal drug candidates for COVID-19 PrEP in pregnant women.^{46, 47} Nitazoxanide is safe to take during pregnancy (Category B), but proper dosing remains uncertain for purposes of PrEP.⁴⁸ Tafenoquine is contraindicated in pregnancy due to inadequate human data (no assigned pregnancy category) and potential risk of abortion based on animal studies.⁴⁹ A recent British study found that macrolides taken during pregnancy may be associated with an increased risk of birth defects.⁵⁰

Mefloquine was recently recategorized from a Category C to a Category B drug for malaria prophylaxis in pregnancy.⁵¹ Although this medication shows promise as a potential COVID-19 PrEP candidate, it possesses an unpleasant side effect: psychosis. As such, mefloquine is not advised for those who suffer from depression or any other mental health disease, conditions that are on the rise due to the effect of the COVID-19 pandemic. In contrast, neuropsychiatric complications are extremely rare even in elderly patients taking HCQ for treatment of rheumatic diseases.⁵²

Conclusions

Pregnant women initially may not be eligible to receive COVID-19 vaccines due to the unknown effects on mother and fetus, and these women urgently need an option for protection from COVID-19 when vaccine candidates are

not available to them. To address this issue, we propose the use of HCQ PrEP to attenuate or prevent SARS-CoV-2 infection in pregnancy. HCQ PrEP should have the same risk-benefit and safety profile in this population as in other high-risk populations. Based on the weight of evidence, HCQ PrEP should be implemented during pregnancy to save lives in the face of an expanding COVID-19 pandemic.

Ethics Statement

Institutional Review Board approval was not required.

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Author Contributions

Both authors meet the authorship requirements of the Committee on Publication Ethics and made significant contributions to the publication. MCF co-conceived the subject, acquired, analyzed and interpreted the original data and citations, and wrote the original draft. RBS co-conceived the subject, acquired, analyzed and interpreted additional data and citations, acquired funding and revised the submission for publication. Both authors agreed on the journal to which the article was submitted; reviewed and agreed on all versions of the article before submission and during revision; agreed on the final version accepted for publication and any significant changes introduced at the proofing stage; and agreed to take responsibility and be accountable for the contents of the article.

Disclosure

RBS is the owner of the Alan E. Beer Medical Center for Reproductive Immunology and reports no other potential conflicts of interest for this work. MCF has no conflicts of interest for this work to declare.

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