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ORIGINAL RESEARCH ARTICLE

Efficacy and safety of hydroxychloroquine for treatment of mild SARS-CoV-2 infection and prevention of COVID-19 severity in pregnant and postpartum women: A randomized, double-blind, placebo-controlled trial

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Abstract

Introduction: Pregnant women have an increased risk of severe COVID-19. Evaluation of drugs with a safety reproductive toxicity profile is a priority. At the beginning of the pandemic, hydroxychloroquine (HCQ) was recommended for COVID-19 treatment.

Material and methods: A randomized, double-blind, placebo-controlled clinical trial was conducted in eight teaching hospitals in Spain to evaluate the safety and efficacy of HCQ in reducing viral shedding and preventing COVID-19 progression. Pregnant and postpartum women with a positive SARS-CoV-2 PCR (with or without mild COVID-19 signs/symptoms) and a normal electrocardiogram were randomized to receive either HCQ orally (400 mg/day for 3 days and 200 mg/day for 11 days) or placebo. PCR and electrocardiogram were repeated at day 21 after treatment start. Enrollment was stopped before reaching the target sample due to low recruitment rate. Trial registration EudraCT #: 2020-001587-29, on April 2, 2020. Clinical trials.gov # NCT04410562, registered on June 1, 2020.

Results: A total of 116 women (75 pregnant and 41 post-partum) were enrolled from May 2020 to June 2021. The proportion of women with a positive SARS-CoV-2 PCR at day 21 was lower in the HCQ group (21.8%, 12/55) than in the placebo group

Abbreviations: AE, adverse events; CQ, chloroquine; ECG, electrocardiogram; HCQ, hydroxychloroquine; ITT, intention to treat; MDES, minimum detectable effect size; OR, odds ratio; PCR, polymerase chain reaction; QTc, corrected QT; RR, risk ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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(31.6%, 18/57), although the difference was not statistically significant ($P = 0.499$). No differences were observed in COVID-19 progression, adverse events, median change in QTc, hospital admissions, preeclampsia or poor pregnancy and perinatal outcomes between groups.

Conclusions: HCQ was found to be safe in pregnant and postpartum women with asymptomatic or mild SARS-CoV-2 infection. Although the prevalence of infection was decreased in the HCQ group, the statistical power was insufficient to confirm the potential beneficial effect of HCQ for COVID-19 treatment.

KEYWORDS
COVID-19, hydroxychloroquine, pregnancy, randomized controlled trial, SARS-CoV-2, women

1 | INTRODUCTION

In the early stages of the COVID-19 pandemic, the World Health Organization (WHO) endorsed the use of hydroxychloroquine (HCQ) for treatment and prevention of SARS-CoV-2 infection.[1] This recommendation was based on the evidence of in vitro studies after the SARS 2003 epidemic showing that chloroquine (CQ) had a strong antiviral effect on SARS-CoV infection of primate cells and the inhibitory effect of CQ reported on SARS-CoV-2.[2–5] In addition, studies comparing CQ with HCQ on SARS-CoV-2 infected cells showed that HCQ had a more potent in vitro inhibitory effect than CQ.[2] Results of a French clinical trial in 20 infected patients showed a clearance of the virus in 75% of those treated with HCQ for 6 days compared with 10% in untreated controls.[6] These findings led to clinical studies in China with encouraging results and the inclusion of HCQ in the recommendations regarding prevention and treatment of the infection in this country.[4]

However, HCQ was not found to be efficacious in subsequent studies among COVID-19 patients admitted to hospital and as post-exposure prophylaxis.[7,8] As a result, two large clinical trials discontinued the evaluation of HCQ for treatment of severe cases.[9] However, these studies presented several limitations that make their results difficult to extrapolate to mild/moderate cases of SARS-CoV-2 infection and, importantly, they did not include pregnant or postpartum women.[10–12]

Pregnant women are considered a susceptible population for SARS-CoV-2 with increased infection severity that may lead to adverse pregnancy outcomes, including preeclampsia and preterm birth.[13,14] However, due to fears of potential embryotoxic effects, they were excluded from clinical trials during the pandemic.[11,15,16] On the other hand, the safety of CQ and HCQ in pregnancy is well established through their use for treatment of systemic lupus erythematosus and rheumatoid arthritis, as well as for malaria treatment and prevention in endemic regions.[17,18]

Key message

This study is the only completed clinical trial evaluating a drug for COVID-19 among pregnant women. Prevalence of infection was decreased in the hydroxychloroquine group but low recruitment led to insufficient statistical power to confirm the potential beneficial effect of HCQ.

In Spain, HCQ was used in the early months of the pandemic to treat hospitalized patients with severe SARS-CoV-2 infection.[19] In this context, we aimed to evaluate the beneficial effect of HCQ to prevent disease progression among SARS-CoV-2-infected pregnant and postpartum women with asymptomatic or mild infection.

2 | MATERIAL AND METHODS

2.1 | Study design and participants

This is an individually randomized, double-blind, placebo-controlled multicenter clinical trial to evaluate the safety and efficacy of HCQ in reducing viral shedding and preventing COVID-19 progression in SARS-CoV-2-infected pregnant and postpartum women. The trial was conducted in eight hospitals and their corresponding referral primary health units in Spain: Hospital Clínic of Barcelona, Hospital Sant Joan de Déu, Hospital de la Santa Creu i Sant Pau and Hospital del Mar in Barcelona; HM Puerta del Sur, Hospital Universitario de Torrejón and Hospital Infanta Leonor in Madrid; and Hospital General de Segovia in Segovia. Women were invited to participate in the trial and sign an informed consent if they met the following inclusion criteria: (1) presenting with fever (≥37.5°C) and/or one

symptoms/signs suggestive of COVID-19 (cough, dyspnea, chills, odynophagia, diarrhea, muscle pain, anosmia, dysgeusia, headache) (2) >12 weeks of gestation (dated by ultrasonography) or being in the postpartum period (within 42 days after delivery). Exclusion criteria were: (1) known hypersensitivity to HCQ or other 4-aminoquinoline compounds, (2) history of retinopathy of any etiology, (3) concomitant use of digoxin, cyclosporin, cimetidine, (4) known liver disease, (5) clinical history of cardiac pathology including known long QT syndrome, (6) unable to cooperate with the requirements of the study, (7) participating in other intervention studies. Originally, the trial also aimed to assess HCQ efficacy as post-exposure prophylaxis in pregnant women reporting as being in close contact with confirmed COVID-19 cases.[20] The study protocol and subsequent amendment were approved by the *Comité de Ética en Investigación* of Hospital Clínic of Barcelona (Spain), with subsequent approval of local Ethics Committees, and the clinical trial was authorized by the Spanish Agency of Drugs and Medical Products (AEMPS; EudraCT number: 2020-001587-29; NCT04410562). Written informed consent was obtained from all participants. Patients were not involved in research.

2.2 | Procedures

Pregnant and postpartum women undergoing routine antenatal/postnatal care or attending maternity wards at the study health facilities, who reported symptoms and/or signs suggestive of COVID-19 or to be in contact with a COVID-19 confirmed case were screened for eligibility. At enrollment, an electrocardiogram (ECG) was performed with a mobile device (Kardia©); if the corrected QT Interval (QTc) interval was >500 ms, the woman was considered a screening failure and she was not included in the study. Nasopharyngeal and oropharyngeal swabs were collected for SARS-CoV-2 diagnosis by polymerase chain reaction (PCR). Participants' demographic, medical and obstetric information was registered on a study electronic case report form (eCRF). Information about their physical examination (weight, height, gestational age, axillary temperature) was also collected. Additionally, 5 mL of venous blood was collected for SARS-CoV-2 serologic analysis of all participants at baseline.

Participants were randomized (1:1) to receive either HCQ (400 mg/day for 3 days, followed by 200 mg/day for 11 days) or placebo (2 tablets for 3 days, followed by one tablet for 11 days). Participants' allocation to study arms was done centrally by the sponsor (the Barcelona Institute for Global Health, ISGlobal) by block randomization. This method ensured balanced allocation to both arms. Participants, health providers, investigators and outcomes assessors were blinded to study group assignment. Study tablets (HCQ and placebo) were identically packaged in small opaque bottles. Participants received a bottle containing 19 tablets of study medication and were instructed to take two tablets for the first 3 days and one tablet for the following 11 days. Drug administration was supervised by study personnel on the first day of treatment. Participants were contacted by phone daily for the intervention period to assess general health condition, drug tolerability, potential adverse events (AE), treatment adherence and any concomitant medication intake. Information on any unscheduled study visit to hospitals was also registered.

Participants were assessed on day 21, 1 week after treatment completion, either at home or at the study health facility. During this visit, nasopharyngeal and oropharyngeal swabs for PCR-SARS-CoV-2 analysis were collected and a post-treatment ECG was performed. Study personnel monitored disease progression, drug safety and confirmed treatment adherence by counting the remaining tablets in the study medication bottle.

Pregnant women were followed up until the end of pregnancy. Participants enrolled in the postpartum period were followed up until day 21 after treatment initiation. A nasopharyngeal swab for SARS-CoV-2 analysis was collected from neonates born to study women in the first 24 hours of life.

2.3 | Outcomes

The primary outcome was the proportion of PCR-confirmed infected participants at day 21 after start of treatment. Secondary outcomes were: the proportion of participants progressing to severe COVID-19 in symptomatic participants at enrollment or developing clinical manifestations in women asymptomatic at enrollment; duration of COVID-19 symptoms; incidence of all-cause hospital admissions; incidence of outpatient visits; proportion of participants with obstetric complications such as preeclampsia or gestational diabetes and mortality; frequency of adverse pregnancy outcomes; and proportion of neonates with adverse health outcomes. Safety outcomes included incidence of AEs and prolonged QTc interval at day 21.

2.4 | Statistical analyses

A sample size of 200 infected women (100 asymptomatic and 100 symptomatic), was estimated necessary to detect an effect size of 18%, 23% and 27% in three scenarios of 3%, 10% and/or 30%, respectively, of curation rates (defined as a negative SARS-CoV-2 PCR test at day 21 of follow-up) in the control group, with 80% power and two-sided type-I error of 0.05. Quantitative variables were described with measures of central tendency and dispersion and qualitative variables using absolute and relative frequencies. In the analysis of contingency tables as well as the comparison of proportions and/or frequency distributions, the chi-square test (or Fisher's exact when appropriate) was used. Three populations of analysis were defined: (1) intention to treat (ITT), which includes all randomized women, (2) according to protocol (ATP), ie all women who fulfill inclusion criteria and took 14 days of HCQ or placebo, and (3) safety population, ie participants who received at least one dose of HCQ or placebo. Descriptive analysis was performed in the ITT population, and the efficacy analysis in the ITT and ATP

populations. Analysis of AE and safety outcomes was conducted in the safety population. Efficacy was determined by comparing the proportion of infected women at day 21 between study arms. In the comparative analysis, parametric tests (eg *t*-test) were used for variables that met the conditions for application and nonparametric tests (eg chi-square, Mann–Whitney U, Wilcoxon, etc.) for ordinal, categorical or other variables that did not meet parametric criteria. Risk ratios (RR) with 95% confidence intervals were estimated. Firth's logistic regression was used to estimate the odds ratio (OR) in case of separation. Kaplan–Meier curves were used to conduct a survival analysis on the duration of COVID-19 symptoms by study arm. All hypothesis tests were two-sided and with a significance level of 0.05. The statistical analysis was performed using R version 4.0.0.

2.5 | Ethics approval

A short trial proposal was approved on April 2, 2020 by the ethics committee (Comité de Ética en Investigación of the Hospital Clínic of Barcelona; trial code HCB/2020/0382, meeting reference 9/2020_Extraordinària) to allow the start of the clinical trial procedures in the COVID-19 emergency situation. The full trial protocol was approved as an amendment by the same committee at the ordinary meeting of May 14, 2020. The clinical trial was authorized by the Spanish Agency of Drugs and Medical Products (AEMPS) on April 8, 2020 (authorization tracking code FEPZKWTD4D) and the agency approved the full protocol on May 22, 2020 (authorization tracking code FBVJZBZ766; EudraCT number: 2020–001587-29). The trial was registered in Clinical trials.gov (NCT04410562) on June 1, 2020. Date of initial participant enrollment: May 2020. Written informed consent was obtained from all participants.

3 | RESULTS

3.1 | Study participants

A total of 496 pregnant and postpartum women were approached and informed about the study from May 13, 2020 to June 30, 2021. Enrollment in the trial lasted for 12 months and was stopped before reaching the target sample size because of a low recruitment rate. Of the 496 omen approached, 247 (49.8%) refused to participate and 151 (30.4%) were eligible and screened for study inclusion. Trial profile is presented in Figure 1. After screening, 116 SARS-CoV-2-infected women were enrolled in the study, 75 women were pregnant (median gestational age 26.5 weeks) and 41 were in the postpartum period. Additionally, 13 uninfected women who reported being in close contact with a COVID-19 case in the previous 6 days were enrolled in the sub-study, which aimed to assess HCQ efficacy for post-exposure prophylaxis. However, this sub-study on COVID-19 contacts could not be completed due to difficulties in participant inclusion. The present work exclusively reports findings in the clinical trial conducted among SARS-CoV-2-infected women.

Baseline characteristics of participants are shown in Table 1. No significant differences in clinical and demographic characteristics were noted between study arms except for history of maternal immunization against influenza (18% in HCQ group and 13% in the control group, $P=0.014$). Mean QTc interval and rates of SARS-CoV-2 seropositivity were similar across study groups at baseline. Table 2 shows the reported symptoms among symptomatic women at baseline by study arm. The most frequently reported symptoms were headache, cough, muscle pain and anosmia. More women reported ageusia in the placebo group (18/35, 51%) than in the HCQ group (8/32, 25%; $P=0.044$).

3.2 | Study outcomes

The proportion of participants with a positive SARS-CoV-2 PCR on day 21 follow-up was lower in the HCQ group (12/55, 21.8%) than in the control group (18/57, 31.6%; Table 3) but the difference was not statistically significant ($P=0.499$). The minimum detectable effect size (MDES) was calculated, taking into account the actual sample size reached and the observed proportion of infection on day 21. Considering 80% statistical power, 61 participants in the control group and 55 in the HCQ group, the MDES was estimated to be 22.

Duration of COVID-19 symptoms was similar in the two study arms (Figure 2). Among asymptomatic women at enrollment, the proportion of them developing COVID-19-related symptoms and/or signs did not differ across groups: 13/23 (56.5%) in the HCQ group and 14/26 (53.8%) in the control group ($P>0.999$). Mean QTc interval was also similar in both study groups on day 21 of follow-up; there were no significant differences in this parameter between baseline and day 21 (Table S1).

In the safety study population ($n=115$), 37 of 55 (66.3%) women in the HCQ group and 40 of 60 (66.7%) women in the control group experienced at least one AE during follow-up. The proportion of reported AEs was similar in the two study arms (Table 4). The most frequently reported AEs were headache (12.8%) and cough (10.5%). Four women (2 in the HCQ and 2 in the control arm) were hospitalized due to severe COVID-19. One woman in the control group developed preeclampsia. No gestational diabetes was diagnosed among the study women.

No differences were found in the frequency of adverse pregnancy outcomes between groups. There were 113 live births, one stillbirth and one abortion because of chromosomal anomaly (Table 4). Eight neonates presented health problems at birth (lung immaturity, cyanosis, gastrointestinal disorders, hypertrophic pyloric stenosis, respiratory distress, meningitis, skull damage, extremely prematurity), with no differences between study arms.

Nasopharyngeal swabs were collected from 64 neonates (32 born to HCQ recipients and 32 to placebo recipients), yielding 63 negative results and one indeterminate SARS-CoV-2 PCR result in the placebo group.

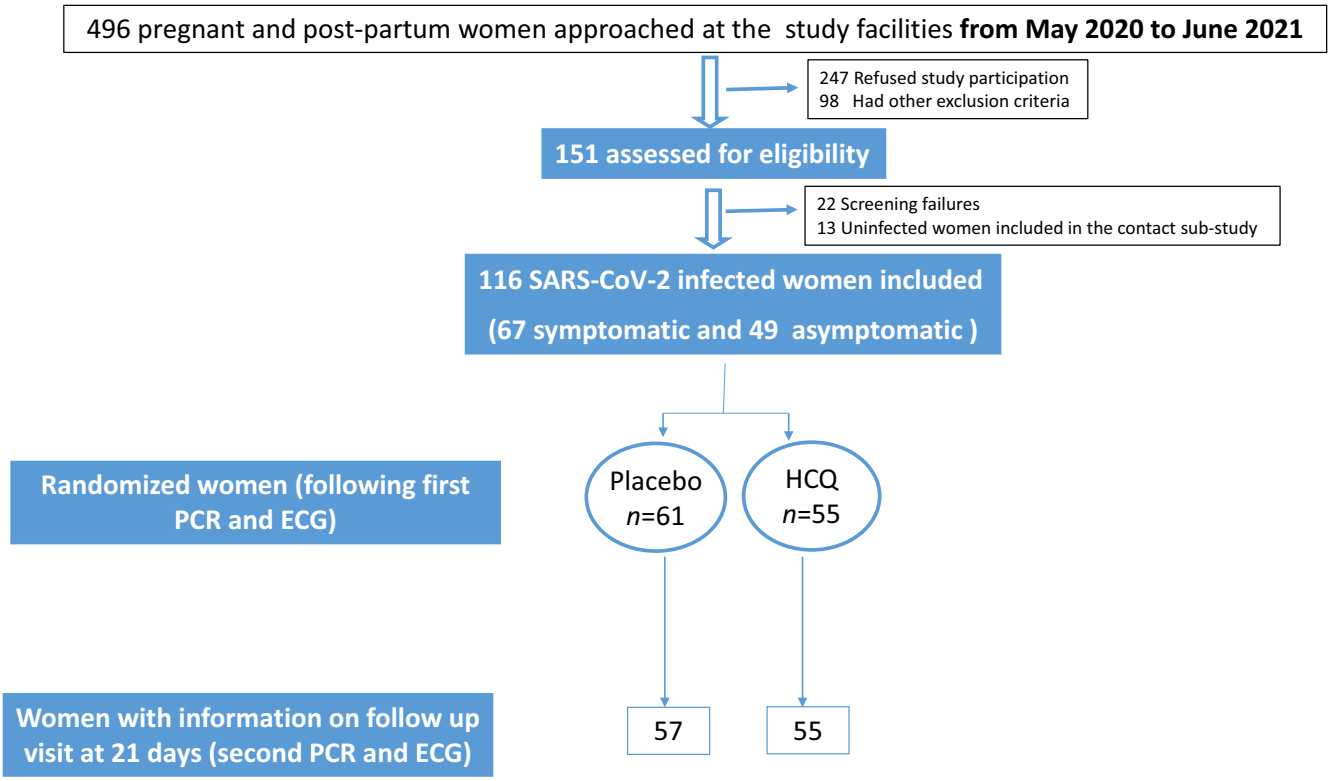

FIGURE 1 CONSORT Flowchart.

TABLE 1 Baseline characteristics of participants.

	HCQ ($n=55$)	Placebo ($n=61$)	*P*-value
Age (years), mean (SD)	30.8 (5.85)	31.6 (6.13)	0.470[a]
Gestational age (weeks), mean (SD)	25.9 (9.85)	26.7 (8.36)	0.747[b]
Gravidity, *n*/*N* (%)			0.206[c]
Primigravidae	11/55 (20.0)	19/55 (31.1)	
Multigravidae	44/55 (80.0)	42/55 (68.9)	
Postpartum women, *n*/*N* (%)	17/55 (30.9)	24/61 (39.3)	0.343[d]
Body mass index, mean (SD)	27.6 (4.6)	28.4 (6.0)	0.518[b]
Smoker, *n* (%)	4/55 (7.3%)	2 /55 (3.3)	0.421[c]
Health care worker, *n*/*N* (%)	3/55 (5.5)	4/55 (6.0)	0.999[c]
Country of birth, *n*/*N* (%)			0.829[c]
Spain	14/55 (25.5)	14/55 (23.0)	
Other	41/55 (74.5)	47/55 (77.0)	
Education, *n*/*N* (%)			0.242[c]
None	4/55 (7.3)	0 (0)	
Primary	6/55 (10.9)	7/55 (11.5)	
Secondary (High school)	28/55 (50.9)	34/55 (55.7)	
University	17/55 (30.9)	20/55 (32.8)	
QTc interval (ms), mean (SD)	383.9 (27.4)	384.5 (23.0)	0.899[a]
SARS-CoV-2 serology, *n*/*N* (%)			0.907[b]
IgG-positive	14/49 (28.6)	16/52 (30.8)	
IgM-positive	12/49 (24.5)	14/52 (27.5)	
Influenza vaccine in pregnancy	10/55 (18)	8/61 (13)	0.014[a]

[a]*t*-test.
[b]Mann–Whitney U-test.
[c]Fisher's Exact test.
[d]Chi-square test.

TABLE 2 Reported COVID-19 symptoms at baseline among symptomatic women.

	HCQ ($n=32$)		Placebo ($n=35$)		
Symptom/Sign	***n***	**%**	***n***	**%**	***P*-value***
Headache	18	56.6	13	37.1	0.145
Cough	16	50.0	16	45.7	0.809
Myalgia	13	40.6	18	51.4	0.464
Anosmia	11	34.4	19	54.3	0.141
Asthenia	10	31.3	9	25.7	0.787
Rhinorrea	10	31.3	9	25.7	0.787
Fever>37°C	9	28.1	10	28.6	>0.999
Ageusia	8	25.0	18	51.4	0.044
Dyspnea	6	18.8	7	20.0	>0.999

*Fisher's Exact test.

TABLE 3 Study outcomes at day 21 of follow-up.

	HCQ		Placebo		
	n/N	**%**	***n/N***	**%**	***P*-value***
SARS-CoV-2 PCR					0.499
Positive	12/55	21.8	18/57	31.6	
Negative	38/55	69.1	35/57	61.4	
Indeterminate	5/55	9.1	4/57	7.0	
SARS-CoV-2 serology					
IgG-positive	12/15	80.0	15/19	78.9	0.651
IgM-positive	11/15	73.3	11/19	57.9	0.839

*Fisher Exact test. ITT population.

4 | DISCUSSION

This study is the only completed clinical trial evaluating a drug for COVID-19 among pregnant and postpartum women. The present findings support previous evidence on the safety of HCQ in pregnancy. However, although the proportion of women with a positive PCR on day 21 after start of treatment was lower in those who had received HCQ compared with those who had received placebo, the statistical power was insufficient to confirm the hypothesis on the beneficial effect of HCQ in reducing SARS-CoV-2 infection in pregnancy.

The trial was conducted in the first year of the pandemic when HCQ was considered a promising drug for treating SARS-CoV-2 infection based on encouraging findings from in vitro studies and a few open-label clinical trials, which led the European Medicines Agency to provide emergency approval for HCQ use in COVID-19 patients.[3,19,21] The first study evaluating HCQ for COVID-19 was an open-label non-randomized clinical trial among 20 hospitalized French patients with COVID-19, which reported a statistically significant reduction of SARS-CoV-2 viral carriage at day 6 post-recruitment in patients treated with HCQ compared with controls.[6] That study also showed that the combination of azithromycin plus HCQ was more efficacious in clearing the virus than HCQ alone. In contrast, in another open label clinical trial among 667 hospitalized patients with COVID-19, HCQ administration with or without azithromycin did not improve disease progression.[22] A larger subsequent observational study reported inconclusive results on the effects of HCQ treatment for severe COVID-19.[23] More recently, another open label clinical trial in 293 non-hospitalized patients with mild COVID-19 found that HCQ treatment was not associated with viral load reduction or clinical recovery.[24]

In the present study, although not statistically significant, the proportion of women with a positive SARS-CoV-2 PCR at day 21 of follow-up was lower in the HCQ group (21.8%) compared with the placebo group (31.6%). However, the sample size reached by the study arms and the observed proportion of infection on day 21, resulted in 22% of the MDES, indicating that this sample size was underpowered to detect effect sizes below this figure that could be potentially clinically relevant. The study target sample size could not be met, mainly due to low participant acceptability.[25] In addition to the general factors affecting pregnant women participating in clinical research, during the course of this study the WHO withdrew the recommendation of CQ and HCQ for severe COVID-19 treatment, which may have further discouraged their participation.[9] Furthermore, negative publicity regarding HCQ administration in COVID-19 patients, spread in the news media in May 2020, noticeably influenced pregnant women's participation in the study. Although this information proved to be false, the damage was done and recruitment dropped noticeably after this event.[26]

The main limitation of this study is the lower than estimated sample size reached, which does not allow conclusive results on the efficacy of HCQ in the treatment of mild COVID-19 in pregnant and postpartum women. However, the present findings provide useful information regarding drug options for COVID-19 in this susceptible group to the infection, in whom the risk–benefit ratio of drug exposure must be considered with extreme caution. Additionally, the study provides insights on the difficulties on undertaking clinical trials in pregnant women, especially in the midst of a pandemic with constantly changing protocols often based on limited scientific evidence that is constantly evolving.

No differences in the proportion of AEs or adverse pregnancy and perinatal outcomes between study arms were observed in the study, which confirms the safety of HCQ use in pregnancy. Additionally, ECG monitoring before and after HCQ treatment did not show any safety concerns in the QTc interval. These findings support the safe use of HCQ in pregnancy. This reports also highlights the need to include pregnant women in COVID-19 treatment trials to allow the development of evidence-based recommendations for this vulnerable population.[11]

5 | CONCLUSION

In conclusion, HCQ treatment was found to be safe and well tolerated among pregnant and postpartum women with asymptomatic or mild SARS-CoV-2 infection. Larger randomized controlled

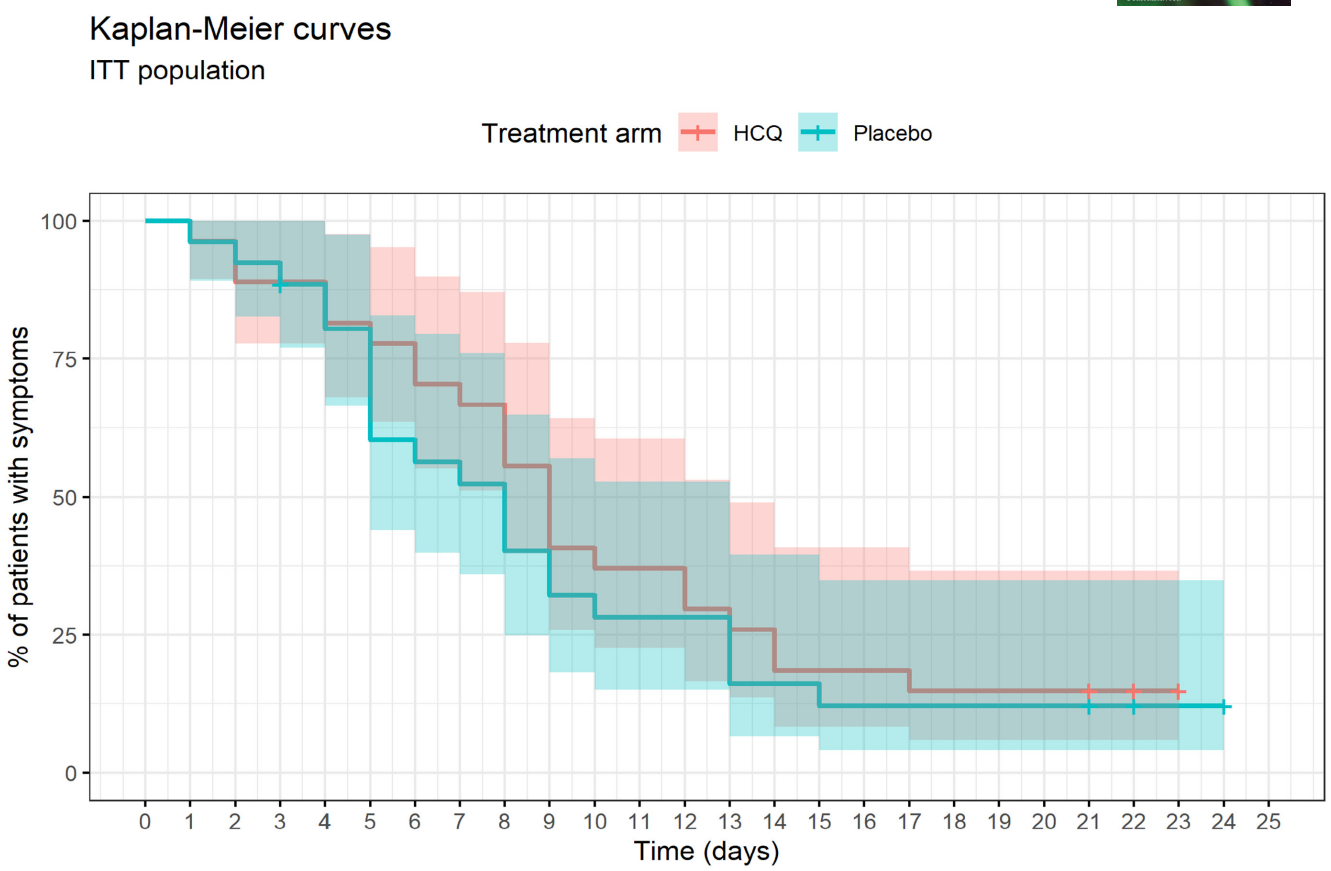

FIGURE 2 Duration of COVID-19 symptoms by study arm. Kaplan–Meier curves for the proportion of patients with symptoms for each treatment group for the ITT population. The 95% confidence intervals are represented as shaded areas and censored patients are marked with "+" symbols.

TABLE 4 Adverse events and pregnancy outcomes by study arm.

	HCQ		Placebo		
	n/*N* %		*n*/*N*	%	*P*-value**
Adverse events*					
Mild	89/113	78.8	81/102	79.4	>0.999
Moderate	22/113	19.4	18/102	17.7	0.263
Severe	2/113	1.8	3/102	2.9	>0.999
Hospitalization due to COVID-19	2/40	5.0	2/38	5.3	>0.999
Type of delivery					0.783
Vaginal	41/55	74.5	43/57	75.4	
Cesarean	14/55	25.4	14/57	24.6	
Pregnancy outcomes					
IUGR	4/42	9.5	7/45	15.6	0.522
LBW	4/55	7.3	4/59	6.8	>0.999
Preterm birth	2/55	3.6	5/59	8.5	0.440
Legal abortion[a]	0/55	0	1/59	1.6	>0.999
Stillbirth	0/55	0	1/59	1.6	>0.999

*N refers to the total number of reported adverse events (113 in HCQ group and 102 in the placebo). Safety population ($n = 115$). **Fisher's Exact Test.

[a]Abortion due to chromosomal anomaly detected (trisomy 21); IUGR: intrauterine growth restriction; LBW: Low birthweight.

double-blind trials would be needed to draw conclusions on the potential beneficial effects of HCQ on decreasing viral burden and improving disease progression.

AUTHOR CONTRIBUTIONS

CM, RG, LG-O and CP-D conceived the study. AG, MdelMG, EM, EF-P, PT, EL, ES, MARZ, ML, BS, AP, SA, MC-L, CP-D, LG-O, LBH, MÁR and RG contributed to the recruitment, clinical care and follow-up of participants. LQ and RG analyzed and managed data. RG and CM wrote the first draft. All authors participated in critical revision of the paper and had final responsibility for the decision to submit for publication. All authors read and approved the final paper.

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CONFLICT OF INTEREST STATEMENT

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

DATA AVAILABILITY STATEMENT

De-identified individual data will be made available upon reasonable request to the corresponding author. A data transfer agreement will be signed between the COVID-Preg consortium and the requesting institution before data sharing. The Study Protocol and Statistical Analysis Plan will also be shared upon request. Data will be available beginning 6 months and ending 12 months following article publication.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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