

## C A S E R E P O R T

# Treatment of COVID-19 in pregnancy with hydroxychloroquine and azithromycin: a case report

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**Summary.** The combination of hydroxychloroquine (HCQ) and azithromycin could represent a suitable treatment for SarS-CoV-2 positive pregnancies. The authors report one of the first cases of COVID-19 positive pregnant woman successfully treated with HCQ in April 2020. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** Azithromycin, COVID-19, Hydroxychloroquine, pregnancy, SarS-CoV-2.

## Introduction

SARS-CoV-2 is the new coronavirus responsible of the rapidly spreading COVID-19 pandemic [1]. This is a novel disease with no standard proven treatment available. SARS-CoV-2 usually attacks the lungs causing a wide range of symptoms ranging from mild dyspnea to severe shortness of breath requiring intubation. The underlying pathogenic mechanisms of the virus on the cells are unclear and only few hypotheses are currently available. Moreover, data on COVID-19 in pregnant women are lacking and the management is challenging. To date, (April 7, 2020), hydroxychloroquine (HCQ) has emerged as the most promising choice with its relatively low side effects, drug interactions and low cost [2]. HCQ has an in vitro and in vivo effect on the replication of SARS-CoV-2 virus. In addition, HCQ presents itself as particularly appealing for its possible safe use during pregnancy. HCQ is commonly used for other pathologies affecting pregnancy such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and malaria.

The authors aim to report the successful use of HCQ in one pregnant symptomatic patient at 26 weeks of gestation, and hereby they present the details of the case, hoping to lead a new era in the response to this deadly virus.

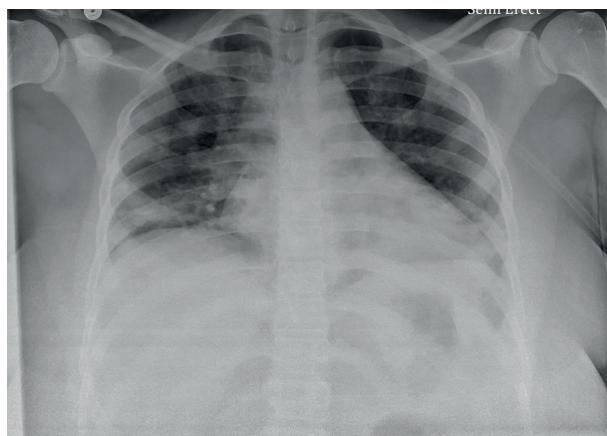
## Case Report

On 3/29/2020 a middle aged woman G6P4014 at 26 weeks of pregnancy came to the emergency room complaining of mild dyspnea. The nasopharyngeal swab for SarS-CoV-2 quantitative reverse transcriptase (qRT)-PCR resulted positive. She did not meet criteria for admission, and she was discharged home with azithromycin 500 mg for the first day and other 2 days of azithromycin therapy (250 mg po daily) as outpatient therapy. On 04/01/2020 she came back to the hospital with complaints of dyspnea, shortness of breath, cough, subjective fever. The vital signs were stable, with maternal body temperature of 102.8 °F. The chest X-ray showed bilateral patchy infiltrates (Fig. 1) and she was admitted to the hospital. On day 04/02/2020 HCQ 400 mg was started daily for other 5 days. In addition, Azithromycin 500 mg was prescribed on 4/01/2020 followed by 250 mg daily for other 4 days. On 4/02/2020 a repeated nasopharyngeal swab for SarS-CoV-2 qRT-PCR resulted negative. On 4/04/2020 a bedside chest X-ray was performed and showed persistent patchy infiltrates (Fig. 2).

The labs showed a normocytic anemia compatible with the pregnancy status, no increase of white blood cell, elevated platelet (PLT) (662 K at discharge) and elevated AST/ALT 261/391 U/L. Gallstones were



**Figure 1.** Chest ray in PA (a) and LL (b) projections, performed on 04/01/2020 showed bilateral patchy infiltrates.



**Figure 2.** Chest ray in PA, performed on 04/04/2020 showed persistent bilateral patchy infiltrates.

found during liver ultrasound examination. Daily fetal testing was negative, the patient did not exhibit any obstetrical complaint. On 4/05/2020 the EKG showed a prolonged QTc (479 ms), resolved with one dose of magnesium IV (1 gr/100 ml NS), with no chest symptoms.

On 4/6/2020, at day 6 of admission, the clinical condition improved, and the patient was discharged in stable clinical condition on day 7, with no fever, no increase white blood cell, and reassuring fetal status.

## Discussion

During the COVID-19 pandemic, on 03/28/2020, FDA authorized the emergency use of HCQ and chloroquine to treat hospitalized patients with COVID-19 [3]. This case report represents one of the first patients successfully treated with HCQ and azithromycin for COVID-19 during gestation until today, (April 7, 2020).

On day 3 of admission, the nasopharyngeal SarS-CoV-2 qRT-PCR result was negative and on day 6 the upper respiratory symptoms disappeared. She was discharged home in stable condition on day 7 of hospitalization. To date, the efficacy of HCQ and chloroquine have been suggested in both in vitro and in vivo studies. Lai and colleagues have demonstrated that chloroquine inhibits the replication of coronaviruses in vitro [4,5]. Chloroquine increases intracellular pH [5,6] and inhibits the quinone reductase-2, inhibition of MAP-kinase, interfering with ACE2 receptor glycosylation [4]. HCQ and chloroquine share a very similar molecular structure and mechanism of action, but in the clinical studies HCQ has been used rather than chloroquine, based on proven benefits. Indeed, HCQ seems more potent than chloroquine and it allows lower daily dose of HCQ with the same efficacy; HCQ also carries a better safety profile compared to chloroquine [7,8] To the best of our knowledge, in the current English literature, there is only 1 in vivo clinical study [9] regarding the use of HCQ on COVID-19 positive patients. This study was conducted in France and it did not include any pregnant patients. Gautret and colleagues [9] conducted an open-label, non-randomized study evaluating the use

of HCQ on 20 COVID-19 positive patients admitted at “The Méditerranée Infection University Hospital Institute” in Marseille, France. Pregnant patients were excluded. The inclusion criteria comprised of being > 12 years of age and having a positive nasopharyngeal swab real-time reverse transcription-PCR for SarS-CoV-2. There were 20 patients treated with HCQ and 16 were control patients. Patients received 600mg daily of HCQ (200 mg TID) for a total of ten days. The primary endpoint was virological clearance at day-6 postinclusion. Of the 20 HCQ-treated patients, six patients received azithromycin (500mg on day 1 followed by 250 mg per day, the next four days) to prevent bacterial super-infection. The primary endpoint was viral clearance at day six. At day six, 70% of HCQ-treated patients achieved virological clearance compared to 12.5% in the control group, and 100% of HCQ and azithromycin combination-treated patients were virologically cured comparing with 57.1% in patients treated with HCQ only, and 12.5% in the control group. Details are shown in Table 1.

Gao and colleagues [10] in a recent research cite a “news briefing” on a large number of ongoing clinical trials in China. They state that more than 100 patients with COVID-19 had a better outcome with chloroquine compared to the control group, but these results have not yet been published in any peer-reviewed journal.

In our study we had the occurrence of prolonged QT interval at maternal EKG but the patient was asymptomatic and it promptly resolved with magnesium therapy. The association of HCQ with azithromycin is known to cause QTc prolongation and as a result routine daily EKG monitoring is necessary [11–14]. Daily EKG is recommended to monitor for increases in the QTc interval. Many international society guide-

lines [2,15,16] based on this limited in vitro and clinical evidence, considering the emergency need, already support the use of HCQ for COVID-19 patients, but there are not specifics for its use during pregnancy yet. HCQ has been used during pregnancy for rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and malaria with excellent outcome and a good safety profile for the mother and her fetus [17,18].

Liver dysfunction was found in severe COVID-19 disease [19,20] as a viral infection of liver cells but in our case, the increase of aminotransferase levels was mild and probably caused by gallstones.

## Conclusion

Evidence is evolving regarding the treatment of SARS-CoV-2. Recent evidence supports the combination of HCQ and azithromycin treatment for COVID positive patients. Our successful treatment of a COVID positive pregnant patient with HCQ, during April 2020, indicates this drug might be a useful treatment for SarS-CoV-2 during pregnancy. Further studies are needed to establish the real effectiveness and safety during gestation. In view of the above, guidelines for treatment of COVID-19 during pregnancy are urgently needed by the clinicians fighting this virus on the field.

## Conflict of Interest

Each author declares that there are no commercial associations that might pose a conflict of interest in connection with the article.

**Table 1.** Clinical study on hydroxychloroquine treatment for COVID-19

Author, Country	Number of patients/controls	Study design	Daily dosage of HCQ (mg)	% of patients with negative PCR at day 6/% of controls with negative PCR at day 6	p-value
Gautret et al., France	20/16	Case control	600	70/12.5	0.001

HCQ = hydroxychloroquine

## References

- Kickbusch I, Leung GM, Bhutta ZA, Matsoso MP, Ihekweazu C, Abbasi K. Covid-19: how a virus is turning the world upside down. *BMJ*. 2020;369:m1336.
- Singh AK, Singh A, Shaikh A, Singh R, Misra A. Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries. *Diabetes Metab Syndr*. 2020;14(3):241–6.
- FDA. Coronavirus (COVID-19) Update: Daily Roundup March 30, 2020 [Internet]. <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-daily-roundup-march-30-2020>. 2020.
- Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). *Biosci Trends*. 2020;14(1):69–71.
- Colson P, Rolain J-M, Raoult D. Chloroquine for the 2019 novel coronavirus SARS-CoV-2. *Int J Antimicrob Agents*. 2020;55(3):105923.
- Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30(3):269–71.
- Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov*. 2020;6:16.
- Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis*. 2020;
- Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020;105949.
- Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*. 2020;14(1):72–3.
- Chen C-Y, Wang F-L, Lin C-C. Chronic hydroxychloroquine use associated with QT prolongation and refractory ventricular arrhythmia. *Clin Toxicol (Phila)*. 2006;44(2):173–5.
- Choi Y, Lim H-S, Chung D, Choi J-G, Yoon D. Risk Evaluation of Azithromycin-Induced QT Prolongation in Real-World Practice. *Biomed Res Int*. 2018;2018:1574806.
- Yang Z, Prinsen JK, Bersell KR, Shen W, Yermalitskaya L, Sidorova T, et al. Azithromycin Causes a Novel Proarrhythmic Syndrome. *Circ Arrhythm Electrophysiol*. 2017;10(4).
- Ehud Chorin, Matthew Dai, Eric Shulman, Lailt Wadhvani, Roi Bar Cohen, Chirag Barbhaya, Anthony Aizer, Douglas Holmes, Scott Bernstein, Michael Soinelli, David S Park, Larry Chinitz, Lior Jankel, Ehud Chorin, Matthew Dai, Eric Shulman, Lailt Wadhvani, R LJ. The QT Interval in Patients with SARS-CoV-2 Infection Treated with Hydroxychloroquine/Azithromycin. 2020;21(1):1–9.
- Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med*. 2020;
- multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. [Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia]. *Zhonghua Jie He He Hu Xi Za Zhi*. 2020;43(3):185–8.
- Ponticelli C, Moroni G. Hydroxychloroquine in systemic lupus erythematosus (SLE). *Expert Opin Drug Saf*. 2017;16(3):411–9.
- Fiehn C, Ness T, Weseloh C, Specker C, Hadjiski D, De-tert J, et al. [Safety management of the treatment with antimalarial drugs in rheumatology. Interdisciplinary recommendations based on a systematic literature search]. *Z Rheumatol*. 2020;79(2):186–94.
- Bangash MN, Patel J, Parekh D. COVID-19 and the liver: little cause for concern. *Lancet Gastroenterol Hepatol*. 2020;5(6):529–30.
- Liu C, Jiang ZC, Shao CX, Zhang HG, Yue HM, Chen ZH, et al. [Preliminary study of the relationship between novel coronavirus pneumonia and liver function damage: a multicenter study]. *Zhonghua Gan Zang Bing Za Zhi*. 2020;28(2):148–52.

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