Review Article
Volume 13:6, 2022

Journal of AIDS & Clinical Research

ISSN: 2155-6113 Open Access

The Effect of Azithromycin and 4-Aminoquinoline-Based Regimens in COVID-19 Positive Pregnant Women: A Systematic Review

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Abstract

Introduction: Worldwide the efficacy and safety of Azithromycin and 4-Aminoquinoline regimen in the treatment of COVID-19 has remained uncertain in both pregnant and other mothers. Pregnancy complications studies are still lacking, although a high preterm birth rate due to the combination of this regimen has been reported which is mostly caused by iatrogenic preterm birth owing to the diagnosis of COVID-19 principally preterm cesarean deliveries and perinatal transmission may occur but seems rare. There is lack of evidence reporting an increase in the incidence of congenital abnormalities, an increase in stillbirth or neonatal death (miscarriages), Fetal Growth Restriction (FGR) among pregnant mothers with COVID-19.

Aim: This study aimed at systematically reviewing studies regarding the use of Azithromycin and 4-Aminoquinoline based regimens in COVID-19 positive pregnant mothers.

Methods: This was asystematic literature review. A systemic search of articles was done on PubMed, TRIP, EPPI COVID Living Map, Web of Science, and medRxiv databases until 2020 using the keywords "COVID-19", "SARS-CoV-2", "coronavirus", "hydroxychloroquine", and "mortality". Relevant articles were chosen for further evaluation based on a review of their titles and abstracts. *In vivo* and *in vitro* studies were included assessing the safety and effectiveness of Azithromycin and 4-aminoquinline for treatment of COVID-19 pregnant mothers.

Results: A total of 438 articles were screened and 12 eligible clinical studies (seven peer-reviewed and published studies and five non-peer-reviewed studies from pre-print servers were included) selected. A number of studies have established very good virological and clinical outcomes with 4-Aminoquinoline in particular HCQ therapy alone or in combination with Azithromycin among COVID-19 pregnant mothers. However, some studies have shown negative results with combination of HCQ treatment and Azithromycin among COVID-19 pregnant mothers.

Conclusion: In this systematic review, we have found that the results of effectiveness and safety of Azithromycin and 4-aminoquinoline combination in COVID-19 pregnant mothers as obtained from 12 eligible clinical studies, is not satisfactory, although many of these studies had major methodological limitations. Stronger evidence from well-designed robust randomized clinical trials is required before conclusively determining the role of Azithromycin and 4-aminoquinoline combination regimen in the treatment of COVID-19. Clinical prudence is required to advocate of Azithromycin and 4-aminoquinoline combination regimen as an unmitigated therapeutic armamentarium in pregnant mothers with COVID-19. Also, the potential of HCQ as a chemo-prophylactic agent against COVID-19 needs to be explored.

Keywords: SARS-CoV-2 • Hydroxychloroquine • Azithromycin • Chloroquine

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Received: 26 March, 2022; Manuscript No. JAR-22-56004; **Editor assigned:** 28 March, 2022, PreQC No. JAR-22-56004 (PQ); **Reviewed:** 11 April, 2022, QC No. JAR-22-56004; **Revised:** 26 May, 2022, Manuscript No. JAR-22-56004 (R); **Published:** 02 June, 2022, DOI: 10.37421/2155-6113.2022.13.892

Introduction

The World Health Organization (WHO) identified a severe form of pneumonia in people being caused by a new corona virus leading to severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) on 31 December 2019 in Wuhan, China. Then on March 26, 2020, it was declared as a pandemic disease worldwide [1]. Corona virus disease 2019 (COVID-19) is defined as the disease of the respiratory tract caused by the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) [2].

It is a positive sense single stranded RNA (ssRNA) virus of order Nidovirales, family *Coronaviridae*, and subfamily *Orthocoronavirinae*, including four coronavirus genera (α,β,γ,δ): human coronaviruses (HCoVs) which are further classified under α-CoV and β-CoV [3]. SARS-CoV-2 is a β-CoV. There seven corona viruses are capable of infecting humans of which four of them HCoV-OC43, HCoV-HKU1, HCoV-229E, HCoV-NL63 causing mild respiratory infections and the three cause severe acute respiratory syndrome corona virus (SARS-CoV) (severe pneumonia), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2, [4,5] associated with severe respiratory diseases and with a high fatality rate [6]. COVID-19 has resulted in more than 210 million reported cases and 4.40 million deaths worldwide. Its severity resulted in death of more patients because of massive alveolar damage and progressive respiratory failure [7]. According to Phillipe Gautret (2020), COVID-19 has caused about 80% of patients present with mild disease and the overall case fatality rate is about 2.3% but reaches 8.0% in patients aged 70 to 79 years and 14.8% in those aged >80 years according to recent Chinese studies [8].

In general, COVID-19 disease is said to be mainly transmitted through contact with respiratory droplets produced by an infected person and touching the mouth, eyes and nose and its clinical manifestations range from asymptomatic cases and mild upper airway infection, up to severe and fatal cases with pneumonia and acute respiratory failure [10].

Currently worldwide the efficacy and safety of Azithromycin and 4-aminoquinoline regimen in the treatment of COVID-19 has remained uncertain in both pregnant and other patients. Pregnancy complications studies are still lacking, although a high preterm birth rate has been reported which is mostly caused by iatrogenic preterm birth owing to the diagnosis of COVID-19 principally preterm cesarean deliveries and perinatal transmission may occur but seems rare [11]. Utero or intrapartum exposure evidence is little because most amniotic fluid, cord blood, neonatal plasma, and oropharyngeal and placental specimens have been reported to indicate negative results, but a case has been reported of a positive result for a Reverse Transcription Polymerase Chain Reaction (RT-PCR) in a nasopharyngeal swab from a neonate born by elective cesarean delivery and immediately isolated from the mother [12]. Postnatal exposure is said to be transmitted through respiratory and skin contact, but breast milk samples reported negative results in most studies.

A report from China, 33 neonates born to mothers with COVID-19, PCR test results reported 3 positive [13]. In pregnant COVID-19 mothers, pregnancy loss, including miscarriage and stillbirth, has been observed and also high fevers during the first trimester of pregnancy can increase the risk of certain birth defects (Control and COVID, 2020).

Chloroquine and its derivative hydroxychloroquine were rapidly identified as potential drug candidates because of their antiviral activity against less acute respiratory syndrome and severe acute respiratory syndrome *in vitro* in COVID-19 patients [14].

Chloroquine and Hydroxychloroquine is assumed to exert a direct antiviral activity by increasing intracellular pH resulting in decreased phagolysosome fusion, impairing viral receptor glycosylation and they significantly inhibits virus entry and at least five steps in the replication of SARS-CoV-2 [15]. Duration of fever, cough, clinical recovery, death and transfer to intesive care. It also has immunemodulating effect by inhibiting toll-like receptor signaling, decreasing production of cytokines especially IL-1 and IL-6. But also previous data suggests a potential anti-thrombotic effect [16].

Azithromycin, a macrolide antibiotic, presented antiviral properties *in vitro* such as decreased viral replication, blocking entrance into host cells, and a potential immunomodulating effect [17].

The *in vitro* studies shown synergistic activity of the combination of hydroxychloroquine and Azithromycin against SARS-CoV-2 [17]. These drugs appeared as low-cost treatment potentials for individuals with coronavirus disease (COVID-19). In france, a small non-randomized, open-label trial reported higher frequency of SARS-CoV-2 clearance after six days of treatment with hydroxychloroquine alone or hydroxychloroquine in combination with Azithromycin versus untreated control group (70% *vs*. 12.5%; P<0.001) [18]. Hydroxychloroquine and Azithromycin were tested in a study involving a group of old monkeys (macaques) being infected by SARS-CoV-2 and were they received either a high dose of hydroxychloroquine (90 mg/kg on day 1 then 45 mg/kg) or a low hydroxychloroquine dose (30 mg/kg on day 1 then 15 mg/kg). Hydroxychloroquine use with or without Azithromycin did not improve to viral clearance regardless of the stage of disease: prophylaxis, early treatment or late treatment [19].

Regarding pregnancy in sheep, Azithromycin crosses the placental barrier and with a maternal-fetal plasma concentration ratio of 3.2 after intravenous administration in non-human primate models. In a clinical study, placental transfer in humans was lower and in the human *ex vivo* cotyledon perfusion model [20]. Both Azithromycin and chloroquine have been safely administered individually in all trimesters of pregnancy, in Intermittent Preventive Treatment of Malaria in Pregnancy (IPTp) [21]

Literature Review

Problem statement

Currently worldwide, COVID-19 is becoming so common which was declared a global pandemic by WHO. It has caused infections in over 210 million people characterized by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and billions have been affected socioeconomically (Control and COVID, 2020). Recent updates, cases and deaths were above 210 and 4.40 million respectively and despite the lack of conclusive evidence for safety and efficacy of chloroquine and its derivatives and Azithromycine, COVID-19 has led to increasing widespread use of these

medications. Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) has directly contributed to spontaneous preterm birth or preeclampsia. There is no approved, licensed effective therapy or vaccine for treatment of COVID-19 in pregnant mothers and other patiets, early identification of effective therapies before the disease becomes severe is optimal. There is currently no developed specific antiviral treatment recommended for COVID-19 in general or specifically for pregnant mothers, high costs emerged treatments and toxicity profiles in pregnancy and the placental transfer of medications under consideration as therapy against COVID-19. Chloroquine and its derivatives have acquired cardiac toxicities such as restrictive cardiomyopathy and the risk for hypotension and cardiac conduction disorder (prolongation of the QT space and enlargement of the QRS) when used in an over dose or in normal doses. It has also not helped in moderate to severe disease but has become the current standard for mild to moderate and early disease. In current studies, there is lack of strong evidence with strong trial design that Chloroquine and Azithromycin combination works for COVID-19 patients [22]. Approximately three times greater risk of preterm birth and an increased rate of caesarean birth has been associated with maternal COVID-19 (Wednesday, 2020). There is also lack of evidence reporting an increase in the incidence of congenital abnormalities, an increase in stillbirth or neonatal death (miscarriages), Fetal Growth Restriction (FGR) among pregnant mothers with COVID-19. Corona disease (COVID-19) transmission from a pregnant mother to her fetus or neonate by vertical transmission before, during, or after delivery is also still unknown (Control and COVID, 2020).

Justification

Due to the accelerating phase of the COVID-19 pandemic globally and the vaccines not yet fully approved in many nations, there is an emergency of Azithromycin and 4-aminoquinolines combination regimen in the treatment of moderate COVID-19 disease which has emerged into drug related problems and adverse effects in both pregnant mothers and other patients. Then the current review assessed whether 4-aminoquinolines and Azithromycin treatment outcomes or improved COVID-19 prognostic features in pregnant mothers, adverse effects and how to manage them [23].

Significance of the study

This review in particular, scientifically evaluated the anti-viral activity of Azithromycin and 4-aminoquinolines combination and therefore provides an alternative solution which would be safe, affordable and easily accessible to the local people. This information can then be applied in the health field to control the high deaths resulting from COVID-19 and can be provided to both government health facilities and in private pharmacies to be sold over the counter [24].

Findings from this systemic literature review contributed to the already known literature and highlighted more on how we can solve the drug adverse effects of Azithromycin and 4-aminoquinolines combination. It also helped in reducing the mortality in pregnant patients [25].

Objectives

General objective

To carry out a systematic literature review of studies regarding the use of Azithromycin and 4-Aminoquinoline based regimens in covid-19 positive pregnant mothers [26].

Specific objectives

- To assess treatment outcomes of Azithromycin and 4-Aminoquinoline combination in COVID-19 pregnant mothers.
- To assess safety of treatment of Azithromycin and 4-Aminoquinoline combination regimen on COVID-19 pregnant mothers [27].

Research questions in line with the specific objectives

- How effective is Azithromycin and 4-Aminoquinoline combination regimen on the growing fetus stages and on the mother?
- How safe is Azithromycin and 4-Aminoquinoline combination regimen on the growing fetus stages and on the mother?

Scope of the study

This study involved obtaining literature from specified search engines such as Google scholar and Pub Med concerning my systematic literature review study, particularly on effectiveness and safety of Azithromycin and 4-Aminoquinoline combination regimen on COVID-19 pregnant mothers, a minimum of 12 articles of interest was included in the study. Articles between December 2019 and up to date were included in the study. The study covered the whole globe [28].

Materials and Methods

Study design

This review represented an existing literature regarding the effect of Azithromycin and 4-aminoquinoline based regimen combination in pregnant mothers positive for COVID-19 [29].

Search words

The search words included Corona virus disease 2019 (COVID-19); SARS-CoV-2, positive pregnant mothers, foetus, Azithromycin and 4-aminoquinoline based combination, neonates.

Search engines

A systemic search of PubMed, TRIP, EPPI COVID Living Map, Web of Science, and medRxiv databases until 2020 using the keywords “COVID-19”, “SARS-CoV-2”, “coronavirus”, “hydroxychloroquine”, and “mortality” [30]to search for articles. Relevant articles were chosen for further evaluation based on a review of their titles and abstracts. *In vivo* and *in vitro* studies were included assessing the safety and effectiveness of Azithromycin and 4-aminoquinline for treatment of COVID-19 pregnant mothers [31].

Data bases

The key word research was entered in popular data bases such as PubMed, Web of Science, Embase Cochrane Library, Google Scholar and MedRxiv databases using combinations of the

terms"COVID-19","SARS-CoV-2","coronavirus", Azithromycin, 4-aminoquinoline "hydroxychloroquine" and "mortality" [32].

Inclusion criteria and exclusion criteria

The articles which were included in this review were those that had the information of interest and in the year range of December 2019 and 2021 inclusive. Only articles written in English and containing information of patients of 18 years and above were included in this review. The journals which did not contain the information of interest and not in the year range were excluded from this systematic review [33].

Analysis plan

Data that was included in the study was qualitative and quantitative, experimental studies. A limit was placed on the publication dates and studies whose risk of bias was high were excluded

Ethical considerations

Unlike primary researches, in the systematic review the reviewer did not collect data from any participant instead obtained information from published accessible documents. The Kampala International University Western Campus Research and Ethics Committee provided the Ethical approval of this review study (Figure 1) [34].

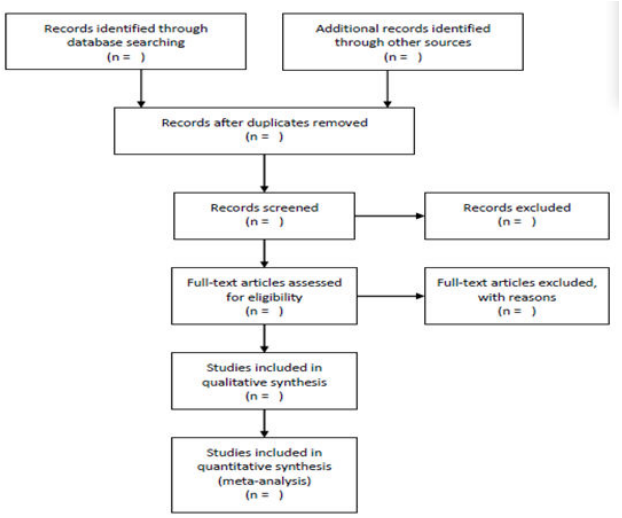

Figure 1: Reporting Findings

Results

This systematic review was conducted to investigate the outcomes and safety of Azithromycin and 4-Aminoquinoline-based regimens in COVID-19 positive pregnant mothers. This chapter shows the findings from the systematic review presented in form of Tables and narrations according to the specific objectives of the study.

Search results

A total of 438 articles with confirmed pregnant mothers with COVID-19 were screened and 12 clinical studies (seven peer-reviewed and published studies and five non-peer-reviewed studies from pre-print servers were included (Figure 1). The summary of the clinical studies is highlighted in (Figure 2) [35].

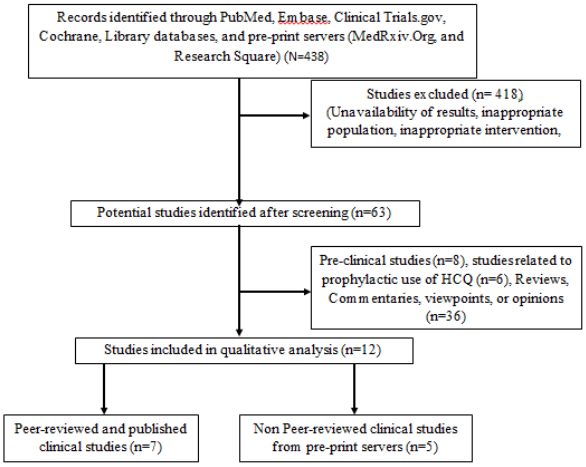

Figure 2: Reporting Findings.

The treatment outcomes of Azithromycin and 4-Aminoquinoline combination in COVID-19 pregnant patients

Have established very good virological and clinical outcomes with 4-Aminoquinoline in particular HCQ therapy alone or in combination with Azithromycin among COVID-19 pregnant mothers since 70.0% (treatment) *vs.* 12.5% (control) virologically cured (P<0.001) having used a sample size of [36]. Have also confirmed good virological and clinical outcomes with Azithromycin and 4-Aminoquinoline Combination in COVID-19 Pregnant mothers have shown negative results with combination of HCQ treatment and Azithromycin among COVID-19 pregnant mothers. Among the non-peer-reviewed studies included from pre-print servers, (2020) have revealed good virological and clinical outcomes (86.7% (treatment) *vs.* 93.3% (control) virologically cured (P>0.05)) with combination of 4-Aminoquinoline and Azithromycin treatment among the pregnant mothers with COVID-19. The results were negative or equivocal. Likewise, Mahevas et al. (2020) reported no significant effect of HCQ combined with Azithromycin on intubation or death in COVID-19 mothers who were pregnant [37].

The evidence for the safety of treatment of Azithromycin and 4-Aminoquinoline combination regimen on COVID-19 pregnant mothers

In the studies of a combination of Azithromycin and 4-Aminoquinoline regimen was found to be safe among pregnant mothers with mild adverse reactions, such as nausea, vomiting, and transient abnormal liver functions in their Prospective observational study having a sample size of 80 used 200 mg of HCQ thrice daily for 10 days; Azithromycin (500 mg on day 1, 250 mg on days 2–5). 97.5% improved clinically, 93% virologically cured by day 8, and mean length of stay in IDU was 5 days much as there were side effects of Nausea, vomiting, diarrhea, and blurred vision. (2020) in a Randomized controlled trial having a sample size of 40 used

Treatment: 400 mg of HCQ daily for 5 days plus conventional treatment [38].

Control: conventional treatment. Results showed that 86.7% (treatment) *vs.* 93.3% (control) virologically cured (P>0.05). The key adverse events were transient diarrhea, and abnormal liver functions have reported QT prolongation associated with combination of Azithromycin and 4-Aminoquinoline Regimen treatment of pregnant COVID-19 patients. A therapy comprising of combination of the 2 drugs was associated with serious adverse reactions, such as death, QT prolongation, first degree atrioventricular block, diarrhoea, and blurred vision in the non-peer-reviewed studies included from pre-print servers (Tables 1 and 2) [39].

Author (country)	Study design	Sample size (treatment/ control)	Age in years (mean ± SD or range)	Inclusion criteria	Study arms	Primary outcome	Results of the primary outcomes	Key adverse events with HCQ use
Gautret, Lagier, Parola, Hoang, et al. (2020)	Open-label non-randomized clinical trial	36 (20/16)	51.2 ± 18.7 (treatment) 37.3 ± 24.0 (control)	SARS-CoV-2 carriage in nasopharyngeal sample	Treatment: 200 mg of HCQ thrice daily for 10 days; six patients also received azithromycin (500 mg on day 1, 250 mg on days 2–5) Control: did not receive HCQSymptomatict reatment and antibiotics were provided	Outcome of a nasopharyngeal swab on day 6	70.0% (treatment) *vs.* 12.5% (control) virologically cured (P < 0.001)	Not reported
Gautret, et al. (2020) (France)	Prospective observational study	80	20–88	SARS-CoV-2 carriage in nasopharyngeal sample	200 mg of HCQ thrice daily for 10 days; azithromycin (500 mg on day 1, 250 mg on days 2–5)	Clinical outcome, outcome of a nasopharyngeal swab, and length of stay in IDU	97.5% improved clinically, 93% virologically cured by day 8, and mean length of stay in IDU was 5 days	Nausea, vomiting, diarrhea, and blurred vision
Chen, et al. (2020) (China)	Randomized controlled trial	30 (15/15)	50.5 ± 3.8 (treatment) 46.7 ± 3.6 (control)	Tested positive for COVID-19	Treatment: 400 mg of HCQ daily for 5 days plus conventional treatment Control: conventional treatment	Outcome of a nasopharyngeal swab on day 7	86.7% (treatment) *vs.* 93.3% (control) virologically cured (P>0.05)	Transient diarrhea, and abnormal liver function
Molina, et al. (2020) (France)	Prospective observational study	11	20–77	Tested positive for COVID-19	200 mg of HCQ thrice daily for 10 days; azithromycin (500 mg on day 1, 250 mg on days 2–5)	Outcome of a nasopharyngeal swab on days 5–6	20% virologically cured	QT prolongation, death, and ICU transfers
Mercuro, et al. (2020) (USA)	Retrospective observational study	90	60.1 ± 16.7	Tested positive for COVID-19	Treatment with HCQ alone (41.1%) or in combination with azithromycin (58.9%)	Change in QT interval and other adverse drug vents	HCQ and azithromycin prolonged the QTc interval significantly	Intractable nausea, premature ventricular contractions, right bundle branch block and hypoglycemia
Clancy & Nguyen, (2021) (USA)	Prospective observational study	1376	≥ 18	Tested positive for COVID-19 in nasopharyngeal or oropharyngeal sample	Treatment: 600 mg of HCQ twice daily on day 1; 400 mg of HCQ daily for 4 days; optional azithromycin (500 mg on day 1, 250 mg on days 2–5) Control: did not receive HCQ Symptomatic treatment and antibiotics were provided	Composite of time to intubation or death (time-to-event analysis)	No significant association between HCQ and intubation or death (hazard ratio, 1.04; 95% CI: 0.82–1.32)	Not reported
Million, et al. (2020) (France)	Uncontrolled non-comparative observational study	1061	43.6 ± 15.6	Tested positive for COVID-19	Treated for at least 3 days with HCQ and azithromycin and followed-up for 9 days	Worsening, viral shedding persistence, and death	91.7% had good clinical outcome and virological cure, 4.4% had	1.5% case fatality rate patients who among received HCQ and

							viral shedding persistence, 0.47% died	azithromycin

Table 1: Summary of the peer-reviewed and published clinical studies on the therapeutic role of Azithromycin and 4-Aminoquinoline Combination Regimen in COVID-19 among pregnant mothers.

Author (country)	Study design	Sample size (treatment/ control)	Age in years (mean ± SD or range)	Inclusion criteria	Study arms	Primary outcome	Results of the primary outcomes	Key adverse events with HCQ use
Z. Chen & Jiang S, (2020) (China)	Randomized controlled trial	62 (31/31)	44.7 ± 15.3	Tested positive for COVID-19	Treatment: 200 mg of HCQ twice daily for 5 days plus standard treatment Control: standard treatment	Time to clinical recovery	The time to clinical recovery was significantly shortened with HCQ treatment	Rash and headache
Mahevas, et al. (2020) (France)	Hospital record-based observational study	181 (84/97)	18–80	Tested positive for COVID-19	HCQ group: 600 mg of HCQ within 48 h of hospitalization Non-HCQ group: no HCQ	Transfer to the ICU within 7 days of inclusion and/or death from any cause	20.2% of patients in the HCQ group were transferred to the ICU or died within 7 days *vs.* 22.1% in the non-HCQ group	QT prolongation, first-degree atrioventricular block, right bundle branch block, ICU transfer
Magagnoli, et al. (2020) (USA)	Retrospective analysis of hospital records (observational study)	368	> 65 years	Patients hospitalized with COVID-19	HCQ alone or in combination with azithromycin	Death and the need for mechanical ventilation	Increased overall mortality with HCQ monotherapy, and HCQ alone or in combination with azithromycin did not reduce the risk of mechanical ventilation	Increased mortality following HCQ monotherapy
Wei Tang, et al. (2020) (China)	Randomized controlled trial	150 (75/75)	46.1 ± 14.7	Tested positive for COVID-19	HCQ group: 1200 mg daily for three days followed by 800 mg daily for 2 (mild/moderate patients) or 3 (severe patients) weeks plus standard treatmentControl: plus standard treatment	28-day negative conversion rate of SARS-CoV-2	The overall 28-day negative conversion rate was similar between the two groups	Upper respiratory tract infection, diarrhea, and blurred vision
Bessière, et al. (2020) (USA)	Retrospective analysis of hospital records (observational study)	98	62 ± 17	Tested positive for COVID-19, treated with HCQ alone or in combination with azithromycin, and with two electrocardiograms performed	HCQ alone or in combination with azithromycin	Baseline QTc and post-medication critical QTc prolongation	With the drug combination, the QTc prolongation was several-fold	QT prolongation

Table 2: Summary of the non-peer-reviewed (at the time of preparing this systematic review) clinical studies from pre-print servers on the therapeutic role of Azithromycin and 4-Aminoquinoline Combination Regimen in COVID-19 among pregnant mothers.

Critical appraisal of the included studies

It is relevant to mention that there were several major methodological limitations to these studies as evident from the high risks of bias in the majority of the included studies. The randomized controlled trials had mostly selection, performance, and detection biases, while the observational studies had predominantly comparability, exposure, and outcome biases [40-42]. The studies of patients with mild symptoms only and they were concomitantly treated with other antivirals. In the first study did not randomize the patients or include drop-outs in the final analysis. There were heterogeneities in terms of the viral load between the two groups at baseline and the investigators deviated from the registered protocol in terms of the outcome measures. Clinical outcomes, although extremely important, were not reported. In the second study neither included a control arm nor mentioned the eligibility criteria precisely. Likewise in the study of the HCQ-treated patients were more severely ill at baseline [43]. In the study of Chen et al., there was a small improvement in body temperature and cough with a higher dose of HCQ. However, the endpoints specified in the published protocol differed from those reported, the results of the low-dose HCQ group were not reported, and the trial was prematurely terminated. The largest observational study of with a sample size of 1061 patients also did not have a control arm. Further, no clinically relevant medium or long-term follow-up data are reported in any of these studies.

Another major factor to be considered is that very few studies have focused on the safety aspect of azithromycin and 4-Aminoquinoline based regimens in covid-19 positive pregnant mothers.

Discussion

Two specific objectives guided the present study. A systematically reviewed the literature and compiled the available evidence of the therapeutic role of azithromycin and 4-Aminoquinoline-based regimens in COVID-19 positive pregnant mothers from clinical studies. This chapter presents the discussions based on the findings of the systematic review of studies [44].

The treatment outcomes of Azithromycin and 4-Aminoquinoline combination in COVID-19 pregnant mothers

Studies have shown the disruption of the interaction of the S protein of SARS-CoV-2 with the host cell membrane following the application of a combination therapy of HCQ and Azithromycin, as well as the role of HCQ that can complement an evolving SARS-CoV-2 main protease. A good *in vitro* efficacy of HCQ alone or in combination with Azithromycin against SARS-CoV-2 was shown *in vitro* pre-clinical studies as well. Some other authors have also demonstrated the *in vitro* efficacy of HCQ against SARS-CoV in Vero cellsww (viral production medium and Crandell-Reese feline kidney (CRFK) cells. However, the translational value of the pre-clinical studies to clinical ones is of concern. Despite showing good *in vitro* efficacy, HCQ showed poor *in vivo* efficacy in earlier studies with Zika virus, Ebola virus and Chikungunya virus, as well as poor clinical outcomes in dengue fever and influenza. This *in vitro* and *in vivo* disparity may be partly because of the complex pharmacokinetics of 4-aminoquinolines and hence, the same applies to HCQ [45]. This warrants further clarification about COVID-19 pathogenesis before using a combination of HCQ and Azithromycin among COVID-19 positive mothers who are pregnant despite promising *in vitro* results.

Likewise, although some of the clinical studies have shown a good efficacy of HCQ alone or in combination with Azithromycin in achieving virological as well as clinical endpoints in pregnant mothers with COVID-19, the studies had major methodological limitations. A majority of the included studies had high risks of bias. Some studies showed negative results with HCQ along with serious concerns of HCQ-related toxicities. None of the studies included critically ill pregnant COVID-19 patients with multiple co-morbidities and the treatment period was very short. Hence, the real clinical benefits of HCQ combined with Azithromycin in pregnant COVID-19 mothers are still elusive. It is important to mention that although viral clearance is important, medium and long-term clinical outcomes are much more relevant, and these need to be studied [46].

The daily divided dose of HCQ studied in COVID-19 was between 400 mg and 1200 mg for 5–10 days. The dosing recommendations for HCQ in the special population, such as pregnant mothers, obese patients, and pediatric population or patients with systemic co-morbidities diagnosed with COVID-19 are unavailable. Based on the 50% maximal effective concentration (EC50), the therapeutic dose of HCQ can be calculated as well as the dose of a combined HCQ and Azithromycin regimen. A physiologically based pharmacokinetic modeling study recommended a loading dose of HCQ of 400 mg twice daily for 1 day followed by 200 mg twice daily for the treatment of COVID-19. Through simulation, it was found that a loading dose of 800 mg of HCQ followed by 600 mg in 6 h and then 600 mg daily for 4 days achieved a daily through concentration above EC50 in >50%of the subjects.

The evidence for the safety of treatment of Azithromycin and 4-Aminoquinoline combination regimen on COVID-19 pregnant mothers

From the safety point of view, short-term HCQ treatment has been considered safe, even in pregnancy. However, the addition of azithromycin may lead to QT prolongation, as well as bundle branch block. Nonetheless, these issues could be tackled with the inpatient use of ambulatory telemetry monitors. The use of HCQ was found to be safe in some of the included clinical studies, while in the other it led to serious adverse reactions, including death. HCQ treatment might warrant monitoring of blood counts, serum electrolytes, blood glucose, and liver and renal functions. In an earlier systematic review, the authors recommended that HCQ is worthy of treatment as an experimental drug in COVID-19 [47]. However, because of the lack of robust data on the efficacy and safety of HCQ, other authors have vouched for clinically relevant medium and long-term follow-up results and safety data from well-designed robust studies before advocating the routine use of HCQ in COVID-19. The need for a robust antimicrobial stewardship program to fight the COVID-19 pandemic has also been stressed. Two recent editorials in the British Medical Journal and New England Journal of Medicine have highlighted the need for well-designed, adequately powered, randomized controlled trials of chloroquine or HCQ combined with Azithromycin among COVID-19 pregnant mothers, and a recent article in the Lancet has also raised concern on the use of combination therapy of HCQ and Azithromycin in critically ill COVID-19 patients. Likewise, a recent systematic review in JAMA has stressed the safety and efficacy of HCQ alone or in combination with Azithromycin in COVID-19, although the authors have highlighted the importance of randomized clinical trials before the widespread use of these drugs.

It is pertinent to mention here that HCQ has been also advocated to be used as a prophylactic agent against COVID-19 for some specific high-risk population like asymptomatic healthcare workers involved in the care of suspected or confirmed cases of COVID-19 and asymptomatic household contacts of laboratory-confirmed cases [48]. In a previous systematic review, it was shown that although pre-clinical results with HCQ are promising, there is a dearth of evidence to support the clinical efficacy of HCQ in preventing COVID-19 but they further stressed that a combination therapy of HCQ and Azithromycin could be safe and more effective even among pregnant mothers diagnosed with COVID-19. Similar views were published in other journals. Several ongoing clinical trials are evaluating the prophylactic and therapeutic role of combination therapy of HCQ and Azithromycin in COVID-19 with much focus on pregnant mothers. The results, including the interim ones, of these trials are awaited.

However, in this ongoing challenging scenario, considering the absence of any other definitive therapy in COVID-19, the mixed efficacy, and the safety profile of combination therapy of HCQ and Azithromycin among COVID-19 positive pregnant mothers, I feel that

clinicians should carefully weigh risks and benefits of HCQ alone or in combination with Azithromycin. Considering that COVID-19 itself can have cardiac manifestations periodic QT interval should be monitored in COVID-19 patients on HCQ. At the same time, it is necessary to define when a treated patient can be considered as no longer contagious after treatment with HCQ and the viral load can come handy [49].

Conclusion

In this systematic review, we have found that the results of effectiveness or outcomes and safety of Azithromycin and 4-Aminoquinoline combination in COVID-19 pregnant mothers as obtained from 12 clinical studies, is not satisfactory (not enough to give conclusive remarks about the topic under study), although many of these studies had major methodological limitations. Stronger evidence from well-designed robust randomized clinical trials is required before conclusively determining the role of Azithromycin and 4-Aminoquinoline combination regimen in the treatment of COVID-19. Clinical prudence is required to advocate of Azithromycin and 4-Aminoquinoline combination regimen as an unmitigated therapeutic arm amentarium in pregnant mothers with COVID-19. Also, the potential of HCQ as a chemo-prophylactic agent against COVID-19 needs to be explored.

Recommendations

There is enough rationale to justify the continued investigation of the efficacy and safety of combination of HCQ and Azithromycin regimen in COVID-19 pregnant mothers given the fact that both the mother and the unborn baby need to be safe. Based on the preliminary trial results, some countries, in fact, have already incorporated HCQ and Azithromycin into their treatment protocols for certain patients with COVID-19. But more caution needs to be taken regarding the use of these drugs among COVID-19 pregnant mothers.

Limitations and Strengths

There are certain limitations to this review. To date, there is a dearth of adequate data from well-designed studies on this topic of interest. There was some heterogeneity in the combination of HCQ and Azithromycin treatment regimens across the clinical studies. Some non-peer-reviewed studies from pre-print servers were included, the final version of which are likely to change after publication. Pre-clinical and clinical studies are ongoing, and most likely new information will be rapidly be added to the existing literature shortly. As of 5 May 2020, 171 and 107 clinical studies on HCQ in COVID-19 have been registered in Clinical Trials. Government and the International Clinical Trials Registry Platform (ICTRP) of the World Health Organization (WHO). Notwithstanding these limitations, this systematic review included a large sample size of COVID-19 pregnant mothers and the results of this study will add to the knowledge of the treating clinicians who are using a combination of HCQ and Azithromycin regimen in COVID-19 patients in their care.

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How to cite this article: Vian Namanya and Amza Kalema Bashir . "The Effect of Azithromycin and 4-Aminoquinoline-Based Regimens in COVID-19 Positive Pregnant Women: A Systematic Review ." *J AIDS Clin Res* 13 (2022) : 892