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Hydroxychloroquine - safety in pregnancy

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ABSTRACT

Hydroxychloroquine (HCQ) is an antimalarial drug containing a 4-aminoquinoline radical, with immunomodulatory, antioxidant, anti-inflammatory and vascular protective effects, which is widely used in the treatment of various rheumatological conditions and is also compatible with pregnancy. It is well known that hydroxychloroquine crosses the placental barrier and hence it can protect against adverse perinatal outcomes, such as congenital heart block in fetuses of anti-SSA/Ro positive mothers.

When it is administered at daily doses inferior or equal to 400 mg, HCQ is not associated with augmented risk of perinatal morbidity and it has also been found to prevent disease flares among pregnant women with systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA), improving maternal outcomes and being protective toward fetal health as well. However, the concerns about its safety in pregnancy are still present because studies on the risks of perinatal defects associated with HCQ administration arise sparse and have controversial results.

The purpose of the current article is to make a review of the medical literature concerning the safety of HCQ in pregnancy. For this purpose, scientific research in online medical publications such as Elsevier, PubMed, and The Lancet, was conducted.

Keywords: hydroxychloroquine, pregnancy, rheumatology, lupus, antiphospholipid syndrome, preeclampsia, malformations, prematurity, low birth weight, ocular toxicity

INTRODUCTION

From "The history of lupus throughout the ages", published by Felten R. et al in 2020, in the Journal of the American Academy of Dermatology, we find that the history of hydroxychloroquine is supposed to begin by the year 1600 with the Incas in Chile, from whom the cinchona bark properties were learned by the Jesuits (9). The main alkaloids of quinine and cinchonine were isolated in 1820 and subsequently the first antimalarial drug widely used was quinacrine, a derivative of quinine, which was dispensed to American soldiers in Second World War, malaria being an important cause of morbidity, especially among soldiers fighting in the South Pacific (9,10,11,12). On this occasion there was noted an improvement of inflammatory arthritis and skin rashes, on soldiers affected, but with the disadvantage of numerous side effects (10). Sustained research efforts to develop a better tolerated alternative, led to the discovery of one of its chemical derivative substance - chloroquine in 1943, and after that, HCQ, was introduced in 1955 (10). Nowadays, HCQ is used for its antimalarial action, only for uncomplicated malaria caused by susceptible strains of Plasmodium infection, in those geographic areas where chloroquine resistance was not reported.

MECHANISM OF ACTION

It is commonly known that antimalarial drugs produce their therapeutic effect using different molecular pathways, such as anti-inflammatory, antithrombotic, and antioxidant mechanisms, according to the target cells and physiopathology of each disease. More exactly, at therapeutic concentrations, they inhibit the production of reactive oxygen

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species (ROS) by neutrophils, and at higher concentrations, can themselves scavenge reactive oxygen species (13). The potent immunomodulatory and anti-inflammatory action is exerted, mainly, by accumulating in lysosomes (where its basic pH modifies the normally acidic milieu, inhibiting the phagocytosis and antigen presentation), by inhibition of matrix metalloproteinases, and by binding and stabilizing DNA (14-16). Nevertheless, it has been shown recently, that HCQ inhibits toll-like receptor signaling, this way, decreasing the production of proinflammatory cytokines (17).

USE IN PREGNANCY

According to 2020 American College of Rheumatology (ACR) Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases, the treatment with HCQ is strongly encouraged during pregnancy for patients with systemic lupus erythematosus (SLE), positive for antiphospholipid antibody, or positive for anti-Ro/SSA or anti La/SSB antibodies, and there are many studies supporting fetal-maternal benefits and low risks associated for both mother and fetus (4,6,7,8,18–23).

As standard good practice suggested that women with rheumatic and musculoskeletal diseases (RMD) who are taking in consideration having a baby, should enter pregnancy with low or quiescent activity disease, maintaining also complementary care with specialists in maternal-fetal medicine, obstetrics-gynecology, neonatology, and other specialists, if necessary (8).

In pregnant women with SLE, or those who are considering pregnancy, the guide strongly recommends testing for lupus anticoagulant (LAC), anticardiolipin (aCL), and anti–β2-glycoprotein I (anti-β2GPI) antibodies once, before or early in pregnancy and do not repeat these tests during pregnancy (8). It is also recommended that women with SLE take HCQ all along the pregnancy, if possible, continuing it if they are already taking it and if they are not taking HCQ, it is recommended to start its administration, in the absence of potential contraindications including intolerance, allergy or adverse side effects (8). Besides HCQ, treatment with low-dose aspirin (81 or 100 mg daily), should be initiated in the first trimester of gestation (8).

Pregnancies in aPL positive patients or antiphospholipid syndrome (APS) present specific challenges and may require additional surveillance and therapy. The standard recommendation of ACR, is addition of HCQ to prophylactic-dose heparin or low molecular weight heparin, in patients who meet criteria for APS (obstetrics or thrombotic), together with low-dose aspirin, because it may decrease complications linked with thrombotic events (8,23).

Neonatal lupus erythematosus (NLE) is characterized by several fetal and infant manifestations as a consequence of exposure to maternal anti-Ro/SSA and/or anti-La/SSB antibodies during pregnancy. Prospective studies of infants born to women with anti-Ro/SSA and/or anti-La/SSB antibodies show that 20% develop transient cytopenia, 30% develop mild transient elevated transaminases and approximately 10% develop a neonatal lupus rash, but these complications are spontaneously remitted as the maternal antibodies disappear (8,24).

Complete fetal heart block (CHB) occurs in approximately 13–18% of pregnancies of women with anti-Ro/SSA and/or anti-La/SSB antibodies, if they had a prior child who have had either cardiac or cutaneous neonatal lupus erythematosus, and in approximately 2% of pregnancies of women who have not had a prior infant with neonatal lupus (8,25). When present, complete fetal heart block rarely appears after 26 weeks of gestation, it is irreversible and require management by pediatric cardiologists (8,26). Approximately 20% of fetuses diagnosed with complete fetal heart block die in utero or in the first year after birth, and in the majority of cases they will require a pacemaker (8,26).

The PATCH study (Preventive Approach To Congenital Heart Block with Hydroxychloroquine) evaluated the use of HCQ in dose of 400 mg per day, started before the end of the 10th week of pregnancy and maintained throughout delivery, between 2011 and 2018, in 54 women from across the United States (excepting a single patient from the United Kingdom), who have previously had a pregnancy complicated by third degree heart block (3). Results from this prospective clinical trial, published in 2020 in *Journal of The American College of Cardiology* suggest that treatment with HCQ in dose of 400 mg per day, reduces the recurrence of CHB in anti-SSA/Ro exposed pregnancies by more than 50% and should be considered for secondary prevention of fetal cardiac disease (3).

In addition, retrospective studies demonstrate that women with a prior infant with cardiac NLE, have a lower risk for a future fetus to develop complete fetal heart block if they are treated with HCQ during pregnancy (2,8).

Present recommendation of ACR Guideline from 2020, suggest that all women who are positive for anti-Ro/SSA and/or anti-La/SSB antibodies should be treated with HCQ during pregnancy (27).

HCQ AND PREECLAMPSIA

It is well known that women affected by lupus have a 3 to 4 fold higher risk of developing preeclampsia than non-affected women, during pregnancy (27). Most recently, it has been noticed that many of the pathways targeted by the antimalarial

drugs, especially HCQ, are similar to those which are abnormal in preeclampsia (12,28,29). Starting from this finding, clinical studies on the treatment with hydroxychloroquine in women with autoimmune diseases, have begun to evaluate the impact of this medication in preeclampsia.

In a retrospective study published in 2016, evaluating 96 mothers with persistent antiphospholipid antibodies which obtained 170 pregnancies, Sciascia et al. (28) found that HCQ in dose of 200 to 400 mg per day reduced adverse pregnancy outcomes, especially fetal losses after 10 weeks of gestation and other placental complications, such as preeclampsia, intrauterine growth restriction or placental abruption (28,29). Moreover, the child's birth weight was higher and pregnancy duration was longer for those women treated with HCQ (28,29).

Similarly, Seo et al. published in 2019 a retrospective trial of 152 pregnancies in 122 mothers with SLE, which measured an 89% reduction in preeclampsia in the mothers treated with HCQ versus the non-treated ones (30).

The safety profile of HCQ together with the evidence of targeting similar pathophysiology mechanisms as those of preeclampsia, makes it a valid alternative to be further studied as an adjuvant therapy to preeclampsia related complication (12).

ADVERSE PREGNANCY OUTCOMES

The Canadian Hydroxychloroquine Study Group showed by using of a randomized controlled trial, that discontinuation of HCQ doubles the risk of lupus flare during the following 6 months in non-pregnant patients (31,32). As a result, withdrawal of HCQ early on pregnancy, together with increased disease activity per se in pregnant patients with lupus, may be followed by exacerbation of the disease which could have adverse outcomes both to the mother and fetus (7,31,32). In spite of that, there are many concerns about its safety in pregnancy given that HCQ passes the placental barrier and studies on the risks of perinatal defects associated with hydroxychloroquine administration are sparse due to ethical considerations (5).

Interest in HCQ has recently increased during the Coronavirus pandemic because it has been proposed as potential therapy and prophylaxis for SARS-CoV-2 infections, although data do not show their efficacy to treat COVID-19 (33-36).

Huybrechts et al. published in 2020, a population-based cohort study including 1,867 HCQ exposed pregnancies during the first trimester and 19,080 unexposed pregnancies (after restriction and matching) and showed a 26% increase in the risk of major congenital malformations among exposed, with daily doses of HCQ ≥ 400 mg (37). The structural birth defects are variants of oral clefts, gastrointestinal, respiratory, cardiac, urinary, genital, musculoskeletal, and limb defects, but no specific pattern of malformations was described (37).

Another study of Andersson et al., published by Oxford University Press on behalf of the British Society for Rheumatology in 2021, was performed to investigate the associated risks of major birth defects, small size for gestational age fetus and preterm birth, of chloroquine and HCQ exposed pregnancies, from a Danish cohort of 1240875 pregnancies (38). It concluded that exposure to chloroquine and HCQ in pregnancy was not associated with an increased risk of major birth defects, small size for gestational age fetus, preterm birth, compared with unexposed pregnancies (38).

Moreover, Bérard et al, using of a population-based prospective study conducted within the Quebec Pregnancy Cohort, did not observe a clear increased risk of prematurity, low birth weight and major congenital malformations, in women exposed to chloroquine and HCQ in pregnancy, although the number of exposed cases remained low (39).

At the same time, a lot of concerns remains about the toxicity of HCQ, due to previous described animal observations and rare, but severe, ocular adverse effects such as retinal damage of both chloroquine and HCQ in treated patients, after several years of exposure (32,40).

It is worth mentioning 2 reviews of 9 and 12 studies (40,41,42) including 246 and respectively 588 children, which did not find an increased risk of eye abnormalities in children exposed in pregnancy to chloroquine and HCQ, but the authors of the reviews underlined the presence of numerous biases, the insufficiency of data, and the need to follow up the exposed children over a longer period (40,41,42).

These data are similar with those reported by Klinger et al. (43), who showed that results of ophthalmologic tests were normal in 14 children prenatally exposed to hydroxychloroquine (32,43).

Last but not the least, Costedoat-Chalumeau et al. performed electrocardiograms (EKG) in some of the children enrolled in their study (5), because cardiac abnormalities of conduction have been reported in adults who received long-term treatment with HCQ (44), but the EKG findings were considered normal for age (32,5).

CONCLUSIONS

Currently available data of HCQ in pregnant women are rather reassuring when it is used in the indications of their marketing authorization.

Teratogenic medication typically produce a specific pattern of birth defects, while the observed defects among the women exposed to HCQ did not present a clear pattern, suggesting no strong evidence for the risk of specific birth defects, but fur-

ther studies are needed to confirm and standardize the safety profile of this drug.

The excellent safety profile with minimal side effects together with the evidence of targeting similar pathophysiology pathway as in preeclampsia, makes it an interesting option to be explored further as an adjuvant therapy to treat preeclampsia and its related complications.

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