The efficacy of hydroxychloroquine in altering pregnancy outcome in women with antiphospholipid antibodies

Evidence and clinical judgment

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Summary

The use of low-dose aspirin and heparinoids has improved the pregnancy outcome in obstetric antiphospholipid syndrome (APS). However, current treatment fails in 20–30 % of APS pregnancies, raising the need to explore other treatments to improve obstetrical outcome. Hydroxychloroquine (HCQ) is widely used in patients with autoimmune diseases, mainly systemic lupus erythematous (SLE), due to its anti-inflammatory, anti-aggregant and immune-regulatory properties. Evidence from in vitro and animal models suggests a potential protective effect of HCQ in obstetric APS. Pending the availability of prospective trials, we aimed to systematically review the available evidence and to assess the clinical judgment of a panel of experts regarding the use of HCQ in improving pregnancy outcome in women with antiphospholipid antibodies (aPL). Clinical data on the ability of HCQ to improve pregnancy outcome in women with aPL are very limited in the available literature. Only one cohort study evaluating maternal and fetal outcome of pregnancy in patients with SLE who were exposed to HCQ was identified. Four of 14 (29 %) treated with HCQ patients had pregnancy failure, compared with six of 24 (25 %) of patients not treated with HCQ. However, the effect of HCQ was not adjusted for the use of other medications such as aspirin, heparins or steroids. Selected experts were contacted by e-mail and asked to review the summary of the evidence provided by the working group and to briefly answer each of the proposed questions. Overall, the panel of experts agreed that adding HCQ could be considered in selected cases or after failure of standard treatment with aspirin and a heparin agent. Specifically, the majority of experts considered adding HCQ in specific scenarios, such as women with previous thrombosis (either arterial and/or venous), and/or with previous ischaemic placenta-mediated complications. Prospective studies are necessary before the use of HCQ during pregnancy in women with aPL should be routinely recommended for clinical practice.

Keywords

Antiphospholipid antibodies, antiphospholipid syndrome, pregnancy

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Introduction

Antiphospholipid syndrome (APS) is defined by the combination of thrombotic events and/or obstetrical morbidity in patients who have persistently positive antiphospholipid antibodies (aPL). Laboratory tests to identify aPL includes solid-phase immunoassays (ELISA) to detect anticardiolipin (aCL) and anti-β2 glycoprotein I (aβ2GPI) antibodies and functional coagulation assays for lupus anticoagulants (LAC). The presence of aPL has to be confirmed at least in two occasions more than 12 weeks apart (1).

The clinical features of obstetric APS include any of the following adverse pregnancy outcomes: 1) otherwise unexplained recurrent pregnancy loss before the 10th week of gestation, 2) otherwise unexplained fetal death ≥10 weeks of gestation, or 3) preterm birth before 34 weeks of gestation due to preeclampsia or placental insufficiency (1).

The prevention of obstetric complications is based on the use of low-dose aspirin and/or subcutaneous injections of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) (2). Women with APS who have had a previous thrombotic event are

typically treated with low-dose aspirin and intermediate or full anticoagulation doses of a heparin agent (2).

With sound medical and obstetric management, around 70 % of pregnant women with APS will deliver a viable live infant (3). However, in 20–30 % of APS pregnancies current treatment fails.

Anecdotal reports suggest that hydroxychloroquine (HCQ) may improve pregnancy outcome in APS (4, 5). HCQ is traditionally an antimalarial drug, which has been widely used in the treatment of patients with autoimmune conditions, mainly SLE where it prevents flares and improves survival (6–8). Evidence supporting the protective effects of HCQ in APS is sparse and comes mainly from animal models and *in vitro* findings. HCQ may decrease the risk of thrombotic events via inhibition of platelet aggregation and release of arachidonic acid from stimulated platelets (9, 10). In aPL animal models, HCQ decreases thrombus size after experimentally induced vascular injury (10). More recently, HCQ has been shown to reverse the binding of aPL-β2GP1 complexes to phospholipid bilayers and restore the aPL-disrupted annexin V shield on cell surfaces, a possible pathogenic mechanism in the development of pregnancy loss and thrombosis in APS (11). Taken together, these findings support HCQ treatment as a potential candidate to improve pregnancy outcome in women with aPL. However, high level evidence supporting the use of HCQ in pregnant women with aPL without SLE are sparse and inconclusive.

Pending the availability of prospective trials, we aimed to systematically review the available evidence and to assess the clinical judgment of a panel of experts regarding the use of HCQ in improving pregnancy outcome in women with aPL.

Methods

A working group (SS, MK, and BJH) performed a systematic review of the literature as detailed below in "Literature search".

Because it was anticipated that only a very low level of evidence could be found, unanswered clinical questions were subsequently addressed to internationally recognised experts in the field in order to obtain an "evidence-based clinical judgment". This approach has been previously described (12) to address a specific and clinically relevant question in areas where best clinical practice is uncertain.

International experts were selected based on their expertise and scientific production in the field. We formulated three clinical prestructured questions with multiple choice answers on the use of HCQ in patients with aPL during pregnancy. The first question detailed eight potential scenarios in which HCQ treatment of aPL positive women without an underlying connective tissue disease during pregnancy might be considered. The second question was on the duration of therapy with HCQ and on the optimal timing for stopping after delivery. The third question was concerning potential factors to be considered when prescribing HCQ in pregnancy.

Selected experts were contacted by email and asked to review the summary of the evidences provided by the working group and to briefly answer each of the proposed questions. Experts were blinded to the answers provided by their peers. Based on the clinical judgment provided by the experts, we formulated some practical suggestions aimed to assist practicing clinicians in their daily activity. No formal method for the grading of recommendations was applied.

Literature search

A detailed literature search strategy was developed *a priori*. Keywords and subject terms used in the search included: „pregnancy" [MeSH Terms] OR pregnancy [Text Word], AND („hydroxychloroquine"[MeSH Terms] OR „hydroxychloroquine"[All Fields])", AND "antibodies, anticardiolipin"[MeSH Terms] OR („antibodies"[All Fields] AND „anticardiolipin"[All Fields]) OR „anticardiolipin antibodies"[All Fields] OR („anticardiolipin"[All Fields] AND „antibodies"[All Fields]);" and "antibodies, antiphospholipid"[MeSH Terms] OR („antibodies"[All Fields] AND „antiphospholipid"[All Fields]) OR „antiphospholipid antibodies"[All Fields] OR („antiphospholipid"[All Fields] AND „antibodies"[All Fields])", „lupus coagulation inhibitor"[MeSH Terms] OR („lupus"[All Fields] AND „coagulation"[All Fields] AND „inhibitor"[All Fields]) OR „lupus coagulation inhibitor"[All Fields] OR („lupus"[All Fields] AND „anticoagulant"[All Fields]) OR „lupus anticoagulant"[All Fields]", anti-beta[All Fields] AND 2[All Fields] AND („glycoproteins"[MeSH Terms] OR „glycoproteins"[All Fields] OR „glycoprotein"[All Fields]) AND 1[All Fields]

The search strategy was applied to Ovid MEDLINE (R) In Process & other non-indexed citations and Ovid MEDLINE (R) 1970 to December 2014.

The grey literature was searched by applying a similar strategy into Google Scholar, PubMed and the Proquest Dissertation & Theses databases.

Additional references were identified from manual review of the reference lists of included articles.

Study selection

Potential studies identified with the above search strategy were exported to an electronic reference management software program (RefWorks v.2.0). Duplicate studies were identified and removed using the filter functions "exact duplicates" and "close duplicates."

Two independent reviewers (SS and BJH) reviewed all potential studies. Eligibility was first determined by review of the title and abstract and then by full article review. Disagreements were resolved by consensus; if consensus was not achieved, a third party (MK) provided an assessment of eligibility.

As the data on eligibility was dichotomous (eligible: yes / no), inter-rater agreement at both the title and abstract review and the full article review stages were determined by calculation of Cohen's kappa coefficient (13).

Inclusion and exclusion criteria

A study was included if it 1) reported on the laboratory investigation of any aPL, 2) reported on pregnancy outcomes, 3) reported on therapy with HCQ, and 4) included a control group.

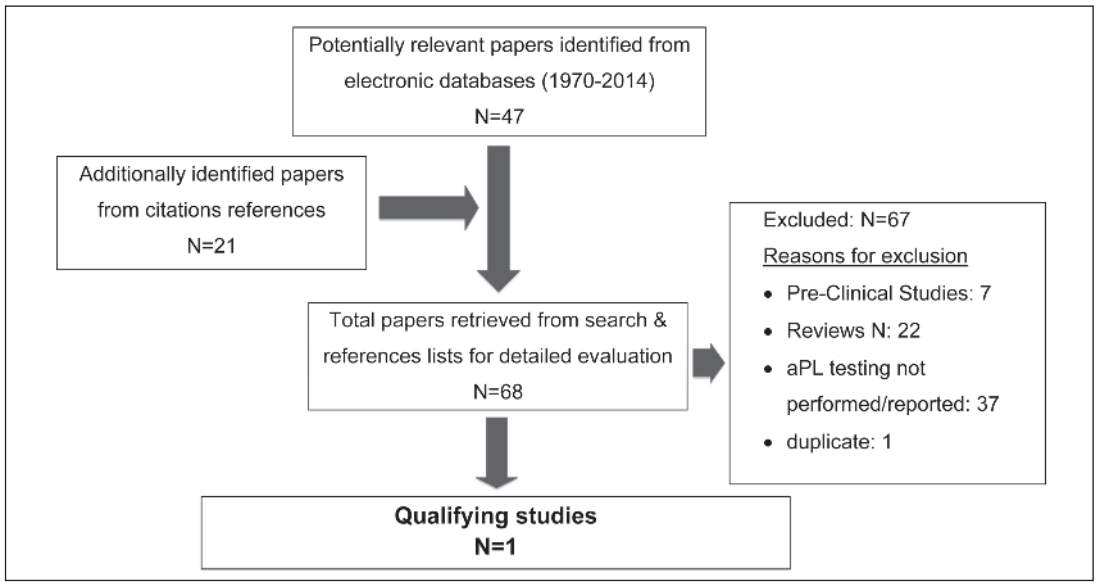

Figure 1: Literature search strategy on the association between hydroxycloroquine and pregnancy morbidity in women with anti-phospholipid antibodies.

Studies enrolling patients with underlying autoimmune disorders (e.g. Systemic Lupus Erythematosus, SLE) were also included when meeting the above criteria.

Review articles, case report, and case series without a control group were excluded from the analysis.

Data extraction

All the papers were scrutinised for the following: 1) study design (retrospective cohort, prospective cohort, case–control, cross-sectional, and case series); 2) number of patients; 3) type of outcome; 4) number and type of aPL tests used; 5) definition of "positive criteria aPL" (low, medium or high titer, or other, when available) as per the study's definition ; 6) confirmation of criteria aPL, at least six weeks (1) or 12 weeks (14) apart; 7) presence of control group; and 8) use of HCQ during pregnancy.

Results of the literature review

►Figure 1 summarises results from the literature research. Only one study was included (15). Value of kappa coefficient among Authors was 0.76, reflecting excellent agreement.

Buchanan et al. studied maternal and fetal outcome of pregnancy in patients with SLE positive for aPL who were exposed to HCQ. In their cohort, four of 14 (29%) HCQ patients positive for aPL had pregnancy failure, compared with six of 24 (25%) patients who were not exposed to HCQ. There was no difference in incidence of maternal thrombosis between the HCQ and control patients. However, it worth noting that the study was not designed to specifically address the question about the use of HCQ in women with aPL during pregnancy . Besides, the effect of HCQ was not adjusted for the use of other medications such as aspirin, heparins or steroids.

Expert questionnaire results

►Table 1 summarises the answers for each question. Additional comments provided by the experts were also taken into account when interpreting the results.

Question 1: Is there a role for HCQ treatment of aPL positive women without an underlying connective tissue disease during pregnancy, and if so, when would you consider using it?

Most of the experts (5 out of 7) would not consider the use HCQ in an aPL positive primigravida without any history of thrombosis/pregnancy morbidity in addition to aspirin. None of them would consider using HCQ in aPL positive woman without any history of thrombosis/pregnancy morbidity as an alternative to aspirin.

The majority of experts (5 out of 7) stated they would consider a role for HCQ in addition to aspirin and/or LMWH in women with previous aPL related complications, even though this is not part of their current practice.

No agreement was achieved in regards to the use of HCQ in patients with previous late pregnancy complications, such as late fetal loss beyond 10 weeks of gestation or placenta-mediated complications, even though most of them use/would consider HCQ as additional option to aspirin and LMWH in these settings (5 out of 7 and 4 out of 7, respectively).

Similarly, no unanimous consensus was achieved when experts were asked whether to consider HCQ in aPL-positive pregnant women with a history of previous venous or arterial thrombosis as adjuvant treatment to aspirin and LMWH (4 out of 7 use/would consider the use of HCQ).

Table 1: Summary of the questions and expert opinions.

	YES	NO	Potentially but not my current practice
Question 1: Is there a role for hydroxychloroquine treatment of aPL positive women without an underlying connective tissue disease during pregnancy, and if so, when would you consider using it?			
aPL positive primigravida without any history of thrombosis/pregnancy morbidity in addition to aspirin	2	5	0
aPL positive woman without any history of thrombosis/pregnancy morbidity as an alternative to aspirin	0	7	0
aPL positive woman with an history of 3 or more unexplained consecutive spontaneous abortions before the 10th week of gestation but no history of thrombosis i.e. proved obstetric APS, in addition to aspirin and/or LMWH	1	1	5
aPL positive woman with an history of death of a morphologically normal fetus at or beyond the 10th week in addition to Aspirin and LMWH	2	2	3
aPL positive woman with an history of eclampsia or severe preeclampsia &/or intrauterine growth restriction &/or placental abruption before 34 weeks, in addition to aspirin and LMWH	3	3	1
aPL positive woman with a history of venous thrombosis in addition to aspirin and LMWH	3	3	1
aPL positive woman with a history of arterial thrombosis in addition to aspirin and LMWH?	3	3	1
Question 2: What is the optimal duration of HCQ therapy after pregnancy, if it is used in patients without an underlying connective tissue disorder?			
duration of hydroxychloroquine treatment should follow the same principles of Aspirin prophylactic use	3	3	1
treat the patient for 6 weeks after delivery initially and then assess	2	4	1
treat most patients for 3 months after delivery	1	5	1
Question 3: Would you take into account any of the following factors when prescribing hydroxychloroquine for an aPL positive woman without an underlying connective tissue disease during pregnancy?*			
triple aPL positivity	4	3	0
ANA	4	2	1
CV risk factor	4	2	1

aPL, antiphospholipid antibodies; LMWH, low-molecular-weight heparin; ANA, anti nuclear antibodies; CV, cardio vascular. * Two of the experts made an additional comment, stating that they would consider the use of HCQ in addition to standard treatment in women with few opportunities for further pregnancies (e.g. advancing age and/or concomitant infertility).

Question 2: What is the optimal duration of HCQ therapy after pregnancy, if it is used in patients without an underlying connective tissue disorder?

No expert agreement was achieved in terms of the duration of HCQ (4 out of 7 use/would use HCQ in this setting following a similar indication as low dose aspirin). Most of the expert panel would not consider a treatment length of six weeks postpartum as adequate thromboprophylaxis. Likewise, the panel would not consider a three months postpartum prophylactic dose in this setting (5 out of 7).

Question 3: Would you take into account any of the following factors when prescribing HCQ for an aPL-positive woman without an underlying connective tissue disease during pregnancy?

Most experts would consider HCQ in aPL positive pregnant women with additional factors including triple aPL positivity, ANA positivity or cardiovascular risk factors (4 out of 7, 5 out of 7 and 5 out of 7, respectively). Two of the experts made an additional comment, stating that they would consider the use of HCQ in addition to standard treatment in women with few opportunities for further pregnancies, e.g. advancing age and/or concomitant reduced fertility.

Practical suggestions based on "evidence and clinical judgement"

On the basis of the available evidence and of the clinical judgments provided by the seven international experts, we tried to address questions that are clinically relevant for the practicing clinician dealing with pregnancy in aPL positive women without SLE and to provide clinicians with some practical recommendations. As it is now widely accepted that all patients with SLE should receive HCQ to reduce disease activity and damage (16), the questionnaire focused on the management of women with aPL without other underlying connective tissue disease during pregnancy.

As only one low-quality study was found, recommendations mostly rely on expert opinion.

Overall, experts agreed that adding HCQ could be considered in selected cases or after failure of standard treatment with aspirin and a heparin agent. Despite no unanimous agreement, the majority of experts would consider adding HCQ in specific scenarios, such as women with previous thrombosis (either arterial and/or venous), and/or with previous placenta mediated complications. It was also additionally mentioned that age and/concomitant reduced fertility could be considered as indications.

Only one expert would consider using HCQ in addition to aspirin and/or a heparin agent in the future management of aPL positive woman with an history of three or more unexplained consecutive spontaneous abortions before the 10th week of gestation but no history of thrombosis, i.e., proved obstetric APS.

There was full agreement and easy consensus among experts not to consider HCQ as an alternative to aspirin. This option was considered only in case of allergy/intolerance to aspirin as an alternative to clopidogrel and was pointed out by two experts as an additional note.

All of the experts, who support the additional use of HCQ, suggested that the duration of HCQ treatment should follow the same principles of low dose aspirin. One could speculate that women could start taking HCQ when actively trying to conceive. However, no further specific suggestion was proposed about the timing of starting HCQ.

Triple positivity for aPL, the presence of ANA and/or concomitant cardiovascular risk factors were factors supporting the use in addition to the standard therapy for some experts.

The heterogeneity among expert opinions probably reflects the lack of solid data from adequately designed trials to address this very question. Currently no international standardised protocols for the management of aPL pregnant women are available. Furthermore, when considering women with previous poor pregnancy outcomes despite low dose aspirin and a heparin agent, the available evidence regarding treatment is scarce, and the management is largely dependent on the expertise of the centres and the responsible physician. The different attitude towards the use of HCQ may also reflect the different clinical experience of the interviewed clinicians and the current standard of care within the different countries.

The approach proposed has been previously described by Ageno et al. (12). In their systematic review, three studies were included, being two trials enrolled in a meta-analysis. We extended our systematic review beyond randomised controlled trials (RTCs) by also including observational studies, due to the lack of available RTCs, as considered in the Updated Method Guidelines for Systematic Reviews in the Cochrane Collaboration Back Review Group (17).

In conclusion, evidence of protective effects of HCQ in APS similar to the situation in SLE arises from *in vitro* studies or anecdotal reports. Clinical data on the ability of HCQ to improve pregnancy outcome in women with aPL are virtually absent.

Until prospective studies are available, unmet clinical questions were addressed to internationally recognized experts in the field, suggesting that HCQ might be considered in addition to conventional APS treatment in selected cases (such as women with previous thrombosis, and/or with previous placenta mediated complications) or after failure of standard treatment with aspirin and a heparin agent. Prospective studies are necessary before the use of HCQ during pregnancy in women with aPL should more commonly be brought into clinical practice.

What is known about this topic?

- The use of low-dose aspirin and heparinoids has improved the pregnancy outcome in obstetric APS.
- Anecdotal reports suggest that HCQ may improve pregnancy outcome in APS.

What does this paper add?

- Clinical data on the ability of HCQ to improve pregnancy outcome in women with aPL are very limited in the available literature.
- A panel of experts agreed that adding HCQ could be considered in selected cases or after failure of standard treatment with aspirin and a heparin agent.
- Adding HCQ may be considered in specific scenarios, such as women with previous thrombosis, and/or with previous ischaemic placenta-mediated complications.

Conflicts of interest

K. Schreiber has received educational support from Daiichi Sankyo. No other conflicts declared.

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