Hydroxychloroquine and antiphospholipid antibody-related pregnancy morbidity: a systematic review and meta-analysis

Hydroxychloroquine and antiphospholipid antibody related pregnancy morbidity –A Systematic Review and meta-analysis

Frishman M.[1], Radin M.[2], Schreiber K.[3,4,5]

1 Department of Obstetrics and Gynaecology, Guy's and St Thomas' NHS Foundation Trust, London, UK

2 Center of Research of Immunopathology and Rare Diseases- Coordinating Center of Piemonte and Valle d'Aosta Network for Rare Diseases, Department of Clinical and Biological Sciences, and SCDU Nephrology and Dialysis, S. Giovanni Bosco Hospital, Turin, Italy.

3 Department of Thrombosis and Haemophilia, Guy's and St Thomas' Hospital, London, United Kingdom.

4 Copenhagen Lupus and Vasculitis Clinic, Center for Rheumatology and Spine Diseases, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark.

5 Danish Institute of Regional Health Research, University of Southern Denmark

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Corresponding author:

Dr Karen Schreiber

Guy's and St Thomas' NHS Foundation Trust, London

Email: Karen.schreiber@gstt.nhs.uk

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Abstract

Antiphospholipid syndrome (APS) is an acquired autoimmune disease defined as the association of thrombosis and/or obstetric morbidity in patients who are persistently positive for antiphospholipid antibodies (aPL). Pregnancy morbidity includes recurrent early pregnancy loss (<10 weeks gestation), late fetal loss (>10 weeks gestation), delivery at less than 34 weeks gestation due to ischemic placental insufficiency, and other manifestations of placental insufficiency including fetal growth restriction, pre-eclampsia, eclampsia, placental abruption. The current treatment to prevent obstetric aPL-mediated morbidity is largely based on low dose aspirin (LDA) and low molecular weight heparin (LMWH).

Alternative treatment regimens to prevent obstetric aPL related morbidity include the antimalarial hydroxychloroquine (HCQ). Although promising, the evidence on the efficacy of HCQ to prevent aPL related pregnancy morbidity remains to be determined.

The aim of this systematic review is to identify the currently available evidence on the efficacy of HCQ to prevent aPL related obstetric morbidity.

After screening the available literature applying a a priori defined protocol, we identified 4 retrospective observational studies. No definite signal of harm was identified as none of the studies reported AE.

When comparing a total of 214 aPL positive women with a total of 250 HCQ exposed aPL positive pregnancies and 521 pregnancies not exposed to HCQ, we found that …..

While our

Introduction:

Antiphospholipid syndrome (APS) is an acquired autoimmune disease defined as the association of thrombotic events and/or obstetric morbidity in patients who are persistently positive for antiphospholipid antibodies (aPL)[1]. This includes recurrent early pregnancy loss (<10 weeks gestation), late fetal loss (>10 weeks gestation), delivery at less than 34 weeks gestation due to ischemic placental insufficiency, and other manifestations of placental insufficiency including fetal growth restriction, pre-eclampsia, eclampsia, placental abruption and HELLP syndrome[1]. The antibodies currently included in the classification of APS are antibodies to cardiolipin, to β2-glycoprotein 1 and lupus anticoagulant.

aPL have been found to be present in 15-20% of women with recurrent first trimester miscarriage[2,] in 12% of women with severe pre-eclampsia (PET)[2] and in 11% of women following a stillbirth[3].

The current standard practice for first-line treatment of obstetric APS is a based on low-dose aspirin (LDA) and low molecular weight heparin (LMWH), sometimes in combination[4,5]. When treatment with this fails, or based on background and risk factors, additional agents to prevent pregnancy morbidity have been suggested. These agents include low dose steroids, azathioprine, IVIG, and hydroxychloroquine (HCQ)[6].Pravastatin has been shown to have some potential to reverse aPL-mediated effects of placental insufficiency, however, pravastatinis contraindicated in pregnancy and clinical data on its use are scarce[7]. Current treatment protocols are based on limited evidence due to a lack of randomized controlled trials (RCT)to date[6].

Antimalarial agents have been used medicinally for several decades, providing us with copious evidence for their promising safety profile, including for women of childbearing age

and throughout pregnancy. HCQ was FDA approved for the treatment of SLE in 1955, and has been found to act via multiple pathways implicated in rheumatic disease. The European Medicines Agency (EMA) has granted an Orphan license for HCQ and the treatment of APS[8]. The current British Society of Rheumatology (BSR) guidelines published in 2016 and the European League Against Rheumatism (EULAR) recommendations for women's health from 2017 both advise that, with the current available evidence, HCQ is compatible with all phases of pregnancy and breastfeeding, and that it is beneficial during pregnancy to reduce the risk of SLE flares and of poor obstetrical outcomes[9,10]. To the best of our knowledge there are no published data from RCTs on the role of HCQ for the prevention of aPL related pregnancy morbidity.

The aim of this systematic review is to assess and evaluate the current evidence available on the effect of HCQ treatment on aPL-related pregnancy morbidity.

Methods:

Study selection criteria

Inclusion criteria were as follows; Studies which reported i) a population of aPL positive women of at least 30 and ii) Pregnancies exposed to HCQ with reported pregnancy outcomes. Studies were excluded if the majority of the cohort were not aPL positive, or if pregnancy outcomes for those treated with HCQ were not clearly separated from those who had not been exposed. Studies on animals, review articles, non-English articles and commentaries, conference abstracts or statements, and expert opinion statements were excluded. Narrative review articles and existing guidelines were checked for references.

Search strategy

The evidence used to compile this systematic review was identified by searches using the National Institute for Health and Care Excellence Healthcare Database Advanced Search. Search terms comprised of 'hydroxychloroquine', 'pregnancy' and 'antiphospholipid', using truncation to capture all relevant material. These search terms were combined using the Boolean operator 'AND'. The same search was run across PubMed, EMBASE and Medline. The full search strategy is shown in appendix 1.

Study selection

Two reviewers independently screened titles and abstracts of retrieved references for relevant studies based on population and intervention. Relevant articles were identified based on the title and abstract. Eligible articles for full text review were identified and a data a data extraction sheet was developed to capture the relevant data from each individual article and allow comparison between the findings.

Outcome of interest

1) *Safety: we used a hypothesis generating/scoping approach to capture any new or unexpected serious adverse events (AE) that may have been reported*
2) *Efficacy in reducing pregnancy morbidity:* We examined the effect of HCQ in addition to conventional treatment in aPL positive women with the outcome of interest as follows: i) live birth ii) any aPL-related pregnancy complications defined as 1) recurrent miscarriage at < 10 weeks gestation and 2) late fetal loss (>10 weeks gestation), delivery at less than 34 weeks gestation due to ischemic placental insufficiency, and other manifestations of placental insufficiency including fetal growth restriction, pre-eclampsia, eclampsia, placental abruption and HELLP syndrome as per Miyakis criteria[1].

Data extraction

Two reviewers (M.F. and K.S.) independently extracted data from all included studies onto our data extraction sheet. To avoid a bias towards the null that could arise from attempting to evaluate AE in patients who had never received the intervention, participant numbers were extracted based on the study population that had received HCQ and where outcomes had been measured.

Assessment of study quality

Three reviewers (M.F., A.A. and K.S) were involved in the independent assessment of the quality of included studies using the Cochrane Collaboration tools

(https://training.cochrane.org/handbook). We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (https://training.cochrane.org/handbook/current/chapter-14#section-14-1). The ROBINS-I risk of bias tool was used to assess the non-randomized studies of interventions included in this study (https://methods.cochrane.org/methods-cochrane/robins-i-tool).

Statistical analysis

We focused our analysis on the measure of relative effect measure between intervention and control.

Meta-analyses were conducted using Review Manager v 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark) if there were quantitative data of sufficient quantity and similarity between the studies. Depending on the reported effect measures and extent of statistical heterogeneity (assessed using the I^2 statistic), we planned to pool odds ratios (OR) or mean differences with a fixed effects model if there was an absence of heterogeneity and random effects models when substantial heterogeneity (50% or above) was detected. If the data were sparse or clinically heterogeneous, our aim was to report a narrative synthesis.

Results

We identified 15 full text articles and subsequently excluded eleven studies, as specific aPL related HCQ exposed outcomes were not reported (Figure 1). Four studies were included for full text analysis[11-14]. Table 1 shows the characteristics of the studies included. No RCTs were identified.

Observational studies

All four studies medium quality studies were of retrospective observational character comprising a total of 214 aPL positive women with a total of 250 HCQ exposed aPL positive pregnancies and 521 pregnancies not exposed to HCQ[11-14]. All studies used 200-400 mg HCQ, which was specified in two of the four studies [12,13]. In all studies some, but not all,

patients received additional treatment including Prednisolone, azathioprine, intravenous immunoglobulins (IVIG). Table 1 outlines the characteristics of the studies included.

The first study by Zou et al. (REF) is a retrospective observational cohort conducted in a single centre in China with the main aim to analyse the data of patients with OAPS from 2000 – 2017.

Zou et al. included 180 patients with obstetric APS (OAPS) with a total of 450 pregnancies in their cohort, of which 66 were exposed to HCQ and 26 were not exposed to HCQ. Pregnancy outcomes were reported for 40 of the HCQ exposed pregnancies, but the HCQ dose used was not mentioned and it was not clear if the addition of HCQ was protocolized. It was however mentioned, that medications including low dose aspirin (ASA), low molecular weight heparin (LMWH), glucocorticoids(GC), intravenous immunoglobulins (IVIG), azathioprine(AZA) and corticosteroids(CS) were used in their population. Of the 66 patients exposed to HCQ, 35 had a live birth, and seven patients had a $2^{nd}/3^{rd}$ trimester pregnancy loss or features of placental insufficiency. In those pregnancies not exposed to HCQ (n = 40), twenty had a live birth but the number of pregnancies not exposed to HCQ who experienced a $2^{nd}/3^{rd}$ trimester pregnancy loss or features of placental insufficiency could not be extrapolated, however five patients in the exposed and four in the non-exposed group developed *any* pregnancy complication. No adverse events following HCQ exposure were reported [11].

The second included study is a retrospective observational European multicentre cohort published by Ruffatti et al., who included 194 patients between 1999 and 2006 from 20 centres belonging to the European Forum of Antiphospholipid Antibodies network[12]. Of the 194 patients, 94 (63%) were also exposed to HCQ. Of these 94, 69 (x%) had a live birth, six (x%) of the HCQ exposed had a miscarriage at < 10 weeks gestation (5 on 200mg, 1 on 400mg) and 6 (x%) had a $2^{nd}/3^{rd}$ trimester pregnancy loss, whilst the number of HCQ who developed features of placental insufficiency was not specified. Forty patients (x%) in the HCQ exposed group developed any pregnancy complication, whereas 31 (x%) in the non-HCQ exposed group developed any pregnancy complication [12].

The third study reports the results from a single centre retrospective observational cohort in the United Kingdom with the aim to assess pregnancy outcomes in aPL positive women treated with HCQ[13]. A total of 170 pregnancies were included, of which 51 were exposed to HCQ and 119 were control pregnancies. Thirty-four (x%) pregnancies of the HCQ exposed pregnancies versus 60 (x%) of the not exposed ended in a live birth. In this cohort, twenty (x%) patients of the HCQ exposed versus 75 (x%) of the non-exposed developed any pregnancy complication[13].

Lastly, Mekinian also reports the results of a retrospective single centre cohort study from France with the aim to analyse the pregnancy outcome of patients treated with HCQ in women with aPL or APS and included a cohort of 30 women. Twenty pregnancies were exposed to HCQ, and 25 were not exposed to HCQ. Of the HCQ exposed pregnancies, sixteen had a live birth (x%), whereas 23 of the non-exposed resulted in a live birth (x%). Data on specific pregnancy outcomes were difficult to extract [14].

Study quality

There is a considerable risk of bias in the retrospective cohort studies which were included. Patients who received HCQ will have had a reason to be treated with HCQ, and in three studies HCQ was most likely administered due to a concomitant mixed connective tissue disease (most often SLE). None of the studies conducted a propensity score matching to correct for confounding by treatment indication.

The results of the individual studies are outlined in table 2.

Safety

When used in pregnancy, HCQ is not associated to any definite signal of harm as none of the studies reported AE.

Outcome live birth

All studies reported on live births in HCQ-exposed and non-exposed patients, which was one of our main outcomes. Live births in the HCQ exposed groups ranged from 66-93%. Overall, HCQ exposure was not associated with an increased rate of live births (pooled OR 1.33 [95% confidence interval (CI) 0.62-2.86]). There was considerable heterogeneity in the analysis (I^2= 53%).

Outcome placental insufficiency

We were unable to perform a meta-analysis on the outcome *placental insufficiency* as the data were not extractable a sufficient number of studies.

Outcome any pregnancy complication

The outcome any pregnancy complication is a composite of those reported in the individual studies. The outcome any pregnancy complication in the HCQ exposed group ranged from 66-93%. Overall, HCQ exposure was not associated with an increased rate of live births (pooled OR0.66 [95% confidence interval (CI) 0.32-1.38]). There was considerable heterogeneity in the analysis (I^2= 59%).

Discussion

Our systematic search did not identify any published results from RCTs on the efficacy of HCQ in aPL positive pregnant women. We identified four medium quality studies of observational design. The available evidence demonstrates that HCQ exposure in pregnant women with aPL remains based on cohort studies rather than interventional studies.

In the studies included into our systematic review, data on the outcome *live birth* were extractable and a meta-analysis showed a non-significant effect on live births (OR 1.33, [95% CI 0.62 – 2.85]) although these findings were only backed by a medium quality of evidence (GRADE, Table 1). Assessing the outcome *any aPL related pregnancy complication* three of the four studies were included in our meta-analysis and showed no significant difference

between the intervention or control groups (OR 0.66, [95% CI 0.32 – 1.38]) based on three medium quality retrospective observational cohorts studies.

These retrospective observational studies, albeit relatively small and heterogenous in their design, have still highlighted promising outcomes for the treatment of aPL pregnancies with HCQ, particularly in women with a background of previous pregnancy losses. It is evident that the current data is limited and lacking in prospective data. This gap has been identified, and there are currently RCT underway, such as HYPATIA[15] which is looking at aPL positive women with randomization to a HCQ group or placebo for follow-up throughout preconception, pregnancy and delivery with an endpoint of the outcome of that pregnancy, including any complications encountered. Trials such as this will hopefully provide much needed robust evidence on the use of HCQ in this setting.

Limitations

All included studies [11-14] were of retrospective design and carry a potential risk of confounding by treatment indication, and in none of the studies were attempts to correct this with a propensity score matching. It was also not clear if patients included in the single centre and multicentre were treated following the same protocol, or whether treatment decisions were made on an individual basis

Retrospective cohorts as were the only type of studies identified for inclusion. There are obvious limitations to such data, particularly where HCQ exposure versus non exposure was not the primary focus of the study which means they may not have been reliably and sufficiently reported. Further, AE of HCQ treatment was not a primary outcome for any of the studies and may therefore not have been captured.

Second, the included studies were heterogenous in their design and way of reporting pregnancy outcomes. This limited the extent of comparison and analysis between them, and is something that would be overcome by conducting larger RCTs looking at pregnancy outcomes in those treated with HCQ versus standard treatment.

Conclusion

HCQ → safe

No data on PAPS Vs SAPS

We need a RTCs

Appendix 1:

Search strategies

The following search strategy was run separately on PubMed, Embase and MEDLINE.

Three separate searches were set up; “hydroxychloroquine” in fields title and abstract. “pregnan*” in fields title and abstract. “antiphospholipid” in fields title and abstract.

All three searches were then combined using the Boolean operator “AND”.

Appendix 2:

ROBINS-I risk of bias tool was used to assess the non-randomized studies of interventions included in this study

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