Review Article

Current Opinion in Gynecology and Obstetrics Hydroxychloroquine and the Prevention of Pregnancy Losses

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Abstract

Pregnancy loss is a common and devastating pregnancy complication. Recurrent early miscarriage (REM) is defined as two or more consecutive pregnancy losses during the first trimester of pregnancy. It is a distinct entity and in approximately 50% of these patients, the underlying cause is never established. REM can be idiopathic, i.e. of unknown cause, be related to infections, anatomical or chromosomal abnormalities and can also be related to the presence of autoimmune connective tissue diseases or antiphospholipid antibodies (aPL). Hydroxychloroquine (HCQ) is an antimalarial immunomodulator and is currently being investigated for its role in the prevention of idiopathic REM and REM related to antiphospholipid antibodies (aPL). In this article we review the evidence that exists to date regarding the use of HCQ in the setting of unexplained REM and REM in relation to connective tissue diseases and aPL and antiphospholipid syndrome (APS).

Keywords: Recurrent miscarriages, Mixed connective tissue disease, Antiphospholipid antibodies, Pregnancy, Pregnancy complications, Hydroxychloroquine, HCQ

Introduction

Asporadic 1st trimester miscarriage is clinically detected in approximately 10%–15% of pregnancies and is the most common complication in pregnancies. Recurrent early miscarriage (REM) is defined as two or three consecutive pregnancy losses during the first trimester of pregnancy. It is a distinct entity and has an estimated incidence of 1%–3%, and in approximately 50% of those, an etiology is never established. REM can be idiopathic, i.e., of unknown cause, be related to infections, anatomical or chromosomal abnormalities and can also be related to

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the presence of autoimmune connective tissue diseases or antiphospholipid antibodies (aPL).

One of the drugs currently investigated for its role in the prevention of idiopathic REM and REM related to antiphospholipid antibodies (aPL) and antiphospholipid syndrome (APS) is hydroxychloroquine (HCQ). HCQ is an antimalarial immunomodulator and is currently licensed for the treatment of rheumatoid arthritis (RA), discoid and systemic lupus erythematosus (SLE) and for the treatment of juvenile idiopathic arthritis [1]. Further,

HCQ has in 2018 gained orphan designation for the treatment of patients with antiphospholipid syndrome (APS) (EU/3/16/1820).

The aim of this article is to review evidence that exists to date regarding the use of HCQ in the setting of unexplained REM and REM in relation to connective tissue diseases and aPL and APS.

HCQ – its history and treatment indications

Antimalarial agents have been used medicinally for several decades. The isolation of quinine from the bark of the *Cinchona* genus was reported in 1820 by the French pharmacists Caventou and Pelletier, when it was already being used by indigenous groups in the Amazon for the treatment of fever [2]. It was at the end of the 19th Century that evidence-based reports arose for the first time on its use in cutaneous lupus. Chloroquine and HCQ were first synthesized in the middle of the 20th Century, from which point on their efficacy and role in the treatment of rheumatic disease has continued to be investigated [3]. In 1955 HCQ was FDA approved for the treatment of SLE.

Chloroquine and HCQ are weakly basic 4-aminoquinolone compounds, HCQ differing by a hydroxyl group attached to a side chain. They both possess good bioavailability after oral administration and are distributed extensively in tissues. Primary metabolism is hepatic, by cytochrome P450 enzymes, with the enantiomer of HCQ achieving lower blood levels than chloroquine. Excretion is predominantly renal, with the remainder lost through faeces, skin and breast milk, and they have a long elimination half-life of approximately 40 days, but can be detected in tissues for prolonged periods of up to several years [2].

HCQ's mechanism of action

HCQ displays pleiotropic activity within the body via multiple pathways, many of which are implicated in rheumatic disease. HCQ is a weak base, creating an affinity towards lysosomes and interfering with their acidification. This impairs protein degradation and antigen presentation which requires an acidic environment, and therefore diminishes the formation of MHC class II complexes with antigenic peptides which are responsible for stimulating CD4 T-cells. The overall effect of this is a down-regulation of the immune response to auto-antigenic peptides, and inhibition of cytokine production [4]. This was demonstrated by recording cytokine levels in SLE patients before and after 3 months treatment with chloroquine, finding that mean levels of IL-6, IL-18 and

TNF- α decreased significantly [5].

Another aspect of the immune response targeted by HCQ, is the Toll-like receptor (TLR) mediated response (Figure 1). TLRs are transmembrane receptors expressed on antigen presenting cells, which serve to recognize molecules derived from foreign organisms, and ultimately trigger the cascade of events resulting in the release of proinflammatory cytokines. TLRs also require an acidic environment to function and are inhibited by HCQ in this way, as well as HCQ binding directly to nucleic acids, affecting their conformation and ability to bind TLRs, and therefore inhibiting the downstream effects of cytokine release [6].

Several mechanisms contribute to the antithrombotic effects of HCQ, which may be the most relevant to improving pregnancy morbidity, particularly in the presence of prothrombotic antiphospholipid antibodies (aPL). HCQ has been found to inhibit the increased expression of GPIIb/IIIa on platelets caused by aPL, which results in excess platelet aggregation [7]. HCQ also serves to restore Annexin A5, a natural anticoagulant shield which is disrupted by aPL, leading to exposure of procoagulant substances and increased risk of thrombosis [8]. This is not an inclusive list of all mechanisms of action of HCQ, and many more are known or being investigated in order to better understand the drug and its potential uses.

Side-effects of HCQ

HCQ has a desirable side-effect profile, and is considered relatively safe and non-toxic when compared with other disease-modifying drugs (DMARDs) such as azathioprine, mycophenolate mofetil or methotrexate. The most common side-effects of HCQ are of gastrointestinal nature and often subside after a few days of treatment. The most significant long-term concern with HCQ is retinal toxicity, as it has been associated with retinopathy in approximately 10% of patients receiving chloroquine and 1% of those receiving HCQ after 7 years [9].

The exact mechanism of retinal toxicity is not known, however it is thought that the changes are almost always reversible if monitoring is performed accordingly. The American Academy of Ophthalmology published revised guidelines in 2016 advising baseline examination when commencing HCQ or chloroquine, followed by annual screening beginning after 5 years [10]. In response to the American guidelines, the British Royal College of Ophthalmologists published their updated guidelines in February 2018 [11].

Figure 1: Hydroxychloroquine's mechanism of action on B cell activation

The blue cell illustrates a B cell with its nucleus (purple). Hydroxychloroquine is an immunomodulator with actions on B cell activation via several pathways including TLR-7, TLR-9 and BAFF. As a result hydroxychloroquine suppresses the TLR9-mediated human B cell functions which are required during inflammatory processes.

Key: BAFF - B cell activating factor of the TNF family; BCMA - B cell maturation antigen; BCR-RNA - B cell receptor RNA; HCQ - hydroxychloroquine; TACI - transmembrane activator and calcium-modulator; TLR - Toll like receptor

Use of HCQ in pregnancy

Thanks to the long-standing use of HCQ both as an antimalarial, and in the treatment of rheumatic disease such as SLE, its safety profile has been extensively reviewed and recorded. Autoimmune diseases have a high prevalence in women of child-bearing age, so it is unsurprising that the question of whether it is safe in the periods of preconception, pregnancy and lactation has been addressed in several studies [12,13].

Early work done by Parke et al. looking at SLE patients receiving HCQ revealed no association of its use with abnormalities in their offspring. They also highlighted that disease activity may be a major contributing factor to fetal loss in patients with SLE, and the importance of continuing HCQ during pregnancy in order to minimize disease flares [14,15]. Buchanan et al. looked at a cohort of 36 pregnancies in 33 women, and also found no signs of teratogenicity when compared to their 53 control patients [16]. Larger literature surveys in more recent years have also concluded that antimalarials can be

regarded as safe for the fetus, with HCQ preferred over chloroquine as there have been a higher number of pregnancies in which its effects have been studied [17].

An important safety consideration for drugs used during pregnancy, is whether they are safe in breast feeding. HCQ is present in breast milk of women who are treated with HCQ, however the level ingested by breastfed infants is less than 0.2mg/kg/day which is a small fraction of the adult therapeutic dose of 6.5mg/kg/day, and therefore unlikely to cause any toxic effects [18].

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 [19,20].

HCQ in recurrent early miscarriage and 'late pregnancy complications' in SLE

HCQ has been used in the treatment of SLE since 1955. HCQ has been found to have various disease-modifying effects, and be beneficial to specific outcomes, including pregnancy morbidity [21]. Several studies have noted the benefit of HCQ on SLE disease activity and flares [22,23]. This suppressive effect on lupus flares appears to hold true during pregnancy as well, as demonstrated by Clowse et al. [24] who failed to find statistically significant differences in pregnancy outcomes in women with SLE with either no HCQ exposure, continuous exposure, or cessation of HCQ, however they did find that the degree of lupus activity during pregnancy was significantly higher in those who stopped taking HCQ. This is a relevant finding, given that the incidence of SLE flare is increased during pregnancy and the postpartum period [25].

SLE has its highest incidence in women of reproductive age, and for some time has been associated with poor obstetric outcomes, including miscarriage, stillbirth, preterm labour, intrauterine growth restriction (IUGR) and pre-eclampsia [26]. HCQ, with its favourable safety profile in pregnancy and lactation, has served to significantly improve these outcomes. Retrospective cohort studies have looked at some of these outcomes, comparing groups taking HCQ throughout pregnancy to those who did not. Findings have shown that HCQ reduced the rate of late prematurity, between 34-37 weeks [27], as well as the rate of IUGR below the 10th percentile in children born to mothers with SLE [28]. A randomized controlled trial (RCT) including 17 patients by Levy et al. also supported the findings of improved gestational age with HCQ treatment, although did not reach statistical significance [29]. An important consideration when looking at pregnancy outcomes and treatments in women with SLE is whether these patients have concurrent aPL present (aPL themselves are related to pregnancy morbidity).

HCQ in recurrent early miscarriage and '2nd and 3rd trimester complications' in APS

APS is an acquired autoimmune disease defined as the association of thrombotic events and/or obstetric morbidity in patients persistently positive for aPL. Pregnancy morbidity related to aPL include recurrent early (<10 weeks gestation), late foetal loss (>10 weeks gestation) or delivery at less than 34 weeks of gestation due to ischemic placental insufficiency [30]. Placental insufficiency can also result in foetal growth restriction (FGR), pre-eclampsia, eclampsia, placental abruption,

HELLP syndrome (haemolysis, elevated liver enzymes, low platelets) and foetal death. The prevalence of aPL among patients with SLE is 46% for anticardiolipin antibodies and 26% for lupus anticoagulant. aPL also occur at a low frequency in the general population [31], and have been found to be present in 15-20% of women with recurrent first trimester miscarriage [32] and in 11% of women following a stillbirth [33].

It has been highlighted that HCQ may be an important additional treatment in APS pregnancies, alongside current regimens [34]. Retrospective studies have found significant improvements in pregnancy outcomes with the additional use of HCQ in aPL positive pregnancies. In these studies HCQ has been added as an adjunct to aspirin and/or LMWH. In a retrospective study of 170 pregnancies it was found that those women treated with HCQ had a significantly higher live birth rate, and lower prevalence of aPL-related pregnancy morbidity than those who did not receive HCQ, specifically fewer fetal losses >10 weeks gestation and preterm deliveries at <37 weeks. Interestingly, no significant difference was observed between the two groups when comparing the rate of fetal losses at <10 weeks gestation [35]. This study did not separate women who had APS only from those with APS and SLE, and therefore the prevalence of SLE was not uniform across the two groups. However a study isolating subjects with APS (without SLE) and a history of previous pregnancy complications resulted in similar findings of a higher live birth rate and fewer severe pregnancy complications in those treated with HCQ [36]. In a third retrospective study, Mekinian et al. showed that women with obstetric APS and refractory obstetric APS treated with HCQ had better pregnancy outcomes, i.e., fewer miscarriages, compared to those without HCQ [37].

Retrospective studies are revealing promising evidence for the addition of HCQ to established therapies in the management of pregnancy in aPL positive women. To date, RCTs and prospective data for the use of HCQ is lacking, and required in order to put evidence-based practices in place. There are trials on going such as HYPATIA 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 [38]. Further prospective trials, such as HYDROSAPL and HIBISCUS will inform on the use of HCQ in the treatment of both thrombotic and obstetric APS hopefully in the foreseeable future [39,40]. The evidence on the use of HCQ in this setting is urgently

needed.

HCQ in undifferentiated connective tissue disease

Undifferentiated connective tissue disease (UCTD) is the manifestation of certain characteristics of systemic autoimmune diseases that fail to meet the diagnostic criteria of one of the defined connective tissue diseases [41]. In a small cohort study of 25 pregnancies in women diagnosed with UCTD, 22 of these resulted in a live birth, and 3 in first trimester losses which is not dissimilar to the rate in the general population. The number of patients was too low to determine whether UCTD may carry an increased risk of miscarriage. Only one of the subjects received HCQ for a disease flare, and treatments were not compared [42]. A slightly larger study where 55 pregnancies in 50 women with UCTD were compared to 53 non-pregnant women with UCTD. Twenty-nine of the UCTD pregnancies received HCQ, either alone or in combination with other treatments, and overall the pregnancy outcomes recorded were good, with two first trimester miscarriages and one third trimester loss which was one twin of a twin pregnancy. Again comparisons were not made between the treatment groups. It was also observed that women with UCTD suffered more flares of their disease during pregnancy, and in some cases the disease evolved into overt CTD [41]. It is difficult to draw clear conclusions from these retrospective studies. Currently there is a lack of prospective data informing on the use of HCQ in undifferentiated mixed connective tissue disease [43].

A clinical trial is underway which will recruit women diagnosed with UCTD and a history of two or more failed pregnancies of unknown origin, and assign them to one of three arms; anticoagulation with prednisolone and HCQ, anticoagulation and HCQ, or anticoagulation alone. Outcomes will be looking at live birth rate and various pregnancy complications [44].

HCQ in unexplained recurrent early miscarriage

The majority of studies to date have focused on the use of HCQ to improve pregnancy outcomes in women with established autoimmune disorders, which are associated with pregnancy morbidity including REM. However there is little data on whether there may be a role for HCQ in those who experience recurrent early miscarriage with no apparent underlying cause. Recurrent miscarriage has an estimated incidence of 1%-3%, and in approximately 50% of those, an etiology is never established [45].

A literature review published by Mekinian et al. in 2016 found that there was currently no clinical data on the efficacy of HCQ in women with recurrent unexplained miscarriage [37]. There are two prospective clinical trials going on, both currently in phase 3, looking at HCQ treatment in women with unexplained consecutive recurrent pregnancy losses. The definition of recurrent being at least three consecutive losses in the trial by Pasquier et al. and at least four consecutive losses or three plus one second trimester loss in the Svarre Nielsen et al. trial. Exclusion criteria include features of autoimmune disease and other known causes of miscarriage such as uterine cavity abnormalities, abnormal parental karyotypes, or infections, which should isolate truly unexplained miscarriages as much as possible as the study subjects. Both trials are looking at the same two arms of HCQ treatment versus placebo [46,47]. These trials, if successful, should provide invaluable data regarding a potentially beneficial treatment to improve pregnancy outcomes in women with recurrent unexplained miscarriages.

We acknowledge some inconsistency in the retrieved studies when referring to the definitions of miscarriage rather than 'pregnancy loss'; however, such heterogeneity reflects differences among the studies used in our analysis. When definitions were not unanimously detailed, we preferred to maintain the terminology used in each study.

Summary

REM is a devastating pregnancy complication. REM has been associated to the presence of some autoimmune connective tissue diseases, including SLE and UCTD, and is related to the persistent presence of aPL. In some patients however, no causes are found for REM. HCQ is an antimalarial compatible with pregnancy and lactation. Retrospective data suggest that the addition of HCQ to standard treatment regimens in women with SLE, aPL or APS and UCTD has been found to reduce both REM and late complications such as preterm delivery and IUGR. The role of HCQ in unexplained REM has not been investigated as extensively and there is currently a lack of clinical data to suggest any benefit of HCQ in women with REM of unknown cause. Ongoing RCTs on the use of HCQ in the setting of aPL, UCTD and REM of unknown aetiology will hopefully provide the evidence in the near future.

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Conflict of interests

None of the authors have any conflict of interest.

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