

# Would Hydroxychloroquine Be A New Promising Drug in Managing Antiphospholipid Syndrome?

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## Abstract

Once Antiphospholipid syndrome (APS) is diagnosed, risk profile of the patient will impact its management whether there was a previous thrombotic event or not, association with other autoimmune disorders, presence of other obstetrical complications as well as being currently pregnant. The current recommended regimen for preventing obstetrical complications. The current recommended regimen for preventing obstetrical complications includes low molecular weight Heparin and low dose aspirin. This regimen decreases the risk of miscarriage by only 54%. Here, we will review the studies that evaluated adding Hydroxychloroquine (HCQ) to the treatment of APS and how effective it would be.

**Keywords:** Antiphospholipid syndrome; Hydroxychloroquine; Miscarriage

## Introduction

Antiphospholipid syndrome is an autoimmune disorder defined by the presence of either vascular thrombosis or characteristic obstetrical morbidities along with positive laboratory tests of circulating antibodies. Women with APS would present with pregnancy morbidities including three recurrent miscarriages before 10th week or unexplained stillbirth [1]. Once diagnosis is confirmed, management of APS is warranted to prevent obstetrical morbidities and risk of thrombosis which would reach 25% during pregnancy and the postpartum period. Long term follow-up revealed that 50% of women with APS but without thrombotic events would develop vascular thrombosis during 3-10 years and 10% would develop systematic lupus erythematosus (SLE) [2]. Different guidelines recommend prophylactic heparin during pregnancy and the postpartum period to prevent risk of thrombosis and increase the rate of live births [1, 3]. In a Cochrane review of randomized trials, combination of low dose aspirin and heparin decreases the risk of miscarriage by 54% [4]. Without any pharmacologic treatment, the live birth rate would reach only 10% in women suffering from APS with recurrent miscarriage [5].

Looking for other medications that would decrease risk of thrombosis, Hydroxychloroquine (HCQ) was historically evaluated to play this role. HCQ is an anti-malarial medication which is used to treat autoimmune rheumatic conditions gaining benefit from its

ability to boost immune system against self-antigens [6]. In 1970s, placebo controlled randomized trials examined HCQ as a promising agent to prevent postoperative venous thrombosis in fields of general and orthopedic surgeries, but it failed [7,8]. Later, in a nested case control study of SLE patients with thrombosis matched with SLE controls without thrombosis, HCQ was associated with 68% decrease in risk of thrombosis [9]. This reduction was only borderline ( $P=0.05$ ) in a case control study of SLE patients with positive APS but without previous thrombosis matched with SLE controls without APS [10]. In a small prospective cohort study of primary APS with previous venous thrombosis, HCQ was added to the oral anticoagulant (OA) in 20 patients while the other 20 patients were treated with OA alone. Six cases of recurrences were documented in the group treated with OA alone versus no recurrence in the group treated with HCQ with OA. However, evidence from this study is limited due to small size of the cohort and selection bias where risk of relapses (30%) is also high in the group receiving OA [11].

Mekinian et al. [12] addressed the role of HCQ in pregnant women with APS without baseline SLE in a retrospective cohort study, where both cases and controls received combination treatment of low molecular weight heparin (LMWH) and aspirin with the addition of HCQ to the cases. Pregnancy loss was

significantly decreased from 81% to 19% [12]. This study was a multicenter study with a small sample size and more autoimmune diseases reported in the cases where prednisone was added also to their treatment regimen contributing to selection bias. The used LMWH was not clearly identified if it was the same among centers or different LMWH was used where pregnancy loss was very high in the control group although being treated with the recommended conventional regimen. Another retrospective study examined the role of adding HCQ to patients with APS during their pregnancy. In this study, HCQ was given to the group of patients with SLE while in the control group only 5 patients diagnosed with SLE and APS who refused HCQ during pregnancy. Results confirmed the safety profile of HCQ with higher rate of live birth (66.7% versus 57.1%,  $P=0.05$ ) and lower rate of pregnancy complications (47% versus 63%,  $P=0.004$ ) in the HCQ group. However, the group who received conventional treatment without HCQ had significantly higher previous pregnancy morbidities ( $P=0.004$ ). Also, different baseline regimens of aspirin +/- prophylactic or therapeutic LMWH were given with or without HCQ [13]. Adding to the fact that HCQ was given to the group diagnosed with both SLE plus APS, selection bias is profound. So, results should be taken cautiously.

A recent small retrospective cohort study of patients diagnosed with APS without any related connective tissue disease evaluated the role of adding HCQ to the conventional treatment of LMWH. HCQ was started six months prior to gestation and continued all over the pregnancy. Patients received HCQ have higher birth rate than the control group ( $P=0.05$ ) [14]. The PREGNANTS study determined the severity of APS depending on the underlying positive antiphospholipid antibody. Being treated with combination of prophylactic LMWH and low dose aspirin, the rate of live birth was 79.6% if only lupus anticoagulant is positive, 56.3% if only anticardiolipin is positive, 47.7% if anti- $\beta_2$  glycoprotein-I only is positive, 43.3% if double positive and lupus anticoagulant is negative and 30% if triple positive [15]. In case of severe APS with previous pregnancy morbidities, adding HCQ to the combination treatment would be a credit waiting the evidence expected from "HYPATIA" randomized controlled trial [16] which is planned to evaluate the pregnancy outcomes after adding HCQ to the standard treatment. In conclusion, management of APS should be considered in light of previous thrombotic event, the risk associated with the underlying positive antiphospholipid antibodies and adverse obstetrical events. Adding Hydroxychloroquine to the standard regimen of LMWH and low dose aspirin would be highly promising in severe APS cases waiting further evidence from HYPATIA study.

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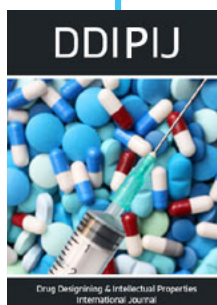
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