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Review

The efficacy of hydroxychloroquine for obstetrical outcome in anti-phospholipid syndrome: Data from a European multicenter retrospective study ☆

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ABSTRACT

In European multicenter study, we aimed to describe the real-life hydroxychloroquine use in APS patients during pregnancy and determine its benefit in refractory obstetrical APS.
We analyzed the outcome of pregnancies treated by hydroxychloroquine in patients with APS or asymptomatic antiphospholipid (aPL) antibodies carriers.
Thirty patients with APS with 35 pregnancies treated by hydroxychloroquine were analyzed. Comparing the outcome of pregnancies treated by the addition of hydroxychloroquine to previous pregnancies under the conventional treatment, pregnancy losses decreased from 81% to 19% ($p < 0.05$), without differences in the associated treatments. The univariate analysis showed that the previous intrauterine deaths and higher hydroxychloroquine amount (400 mg per day) were the factors associated with pregnancy outcome. Considering 14 patients with previous refractory obstetrical APS ($n = 5$ with obstetrical and thrombotic primary APS and $n = 9$ with purely obstetrical APS), all with previous pregnancy losses under treatment (aspirin with LMWH in 11 cases and LMWH in 3 cases), the addition of hydroxychloroquine resulted in live born babies in 11/14 (78%) cases ($p < 0.05$).
Our study shows the benefit of hydroxychloroquine addition in patients with refractory obstetrical APS and raises the need of prospective studies to confirm our preliminary study.

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Contents

1. Introduction

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by obstetrical complications and thrombotic events associated to antiphospholipid (aPL) antibodies [1–3]. The pregnancy outcome dramatically improved using the combination of aspirin and low-molecular weighted heparin (LMWH) [4,5]. Despite this regimen, 10–15% of APS experiences pregnancy losses and constitutes the refractory obstetrical APS [6–8]. Recently Ruffatti et al. showed that addition of other drugs to conventional APS treatment could ameliorate the APS obstetrical outcome, but the best regimen remains to be determined [9]. In thrombotic APS, one study recently showed that the addition of hydroxychloroquine to oral anticoagulants could prevent the thrombotic recurrences [10]. The studies the addition of hydroxychloroquine reduce the aPL bindings to syncytiotrophoblasts and restore the placental annexin A5 expression [11]. Nevertheless, no clinical data are actually available to demonstrate the interest of hydroxychloroquine to improve obstetrical outcome in APS. In this European multicenter study, we aimed to (1) describe the hydroxychloroquine use in APS patients during pregnancy in real-life practice; and (2) determine the benefit of hydroxychloroquine addition to conventional APS treatment to improve the obstetrical outcome.

2. Patients and methods

2.1. Patients

We retrospectively analyzed the outcome of pregnancies treated by hydroxychloroquine in patients with APS (Sydney criteria) or asymptomatic aPL carriers [1]. All members of European Forum on Antiphospholipid antibodies and Société Nationale Francaise de Médecine Interne (SNFMI) were asked to fulfill a standardized form. The inclusion criteria were: (1) confirmed APS (Sydney criteria) or asymptomatic aPL carriers; and (2) at least one pregnancy under hydroxychloroquine. The exclusion criteria included: (1) patients with Systemic Lupus Erythematosus (ACR criteria). Hydroxychloroquine was introduced to improve the pregnancy outcome in refractory obstetrical APS ($n = 14$), in patients with previous non-treated or non-refractory APS ($n = 7$), in aPL carriers or thrombotic APS without previous pregnancies ($n = 9$). A control group consisted in patients with confirmed APS with pregnancies treated by conventional APS treatment (aspirin and low-molecular weighted heparin) without hydroxychloroquine. These patients were matched by aPL profile (type and number of positive aPL) to the group of patients with APS pregnancies treated by hydroxychloroquine.

For each patient, data were collected as follows: APS characteristics, early embryonic loss, mothers' complications (thrombosis, preeclampsia, HELLP syndrome, diabetes, gestational hypertension), fetal complications (intrauterine deaths, fetal growth retardation, uterine Doppler abnormalities), date of beginning and characteristics of treatments, delivery, birth weight, Apgar, and neonatal complications. For each pregnancy treated by hydroxychloroquine, the last pregnancy with complete available data was also considered for each patient.

Anti-cardiolipin (ACL) antibodies and anti-β2-glycoprotein I (β2GPI) antibodies were determined using commercial enzyme-linked immunosorbent assays (Instrumentation Laboratory and ThermoFisher Scientific respectively). Lupus anticoagulant (LA) was detected using dilute Russell's viper venom and dilute activated partial thromboplastin time as screening tests. Cut-off values for medium titer (99th percentile) were 20 UGPL for IgG and 20 UMPL for IgM ACL, and 15 U/ml for IgG and IgM anti-β_2GPI antibodies for French centers, respectively. aPL positivity was considered using the thresholds of each laboratory for the other European centers.

2.2. Statistical analysis

Quantitative data are expressed as medians with ranges according to their distribution, and qualitative data as numbers with the frequencies. The Fisher's exact test or chi-square test was used to compare qualitative variables while the non-parametric Mann–Whitney test was used for quantitative variables. McNemar chi-square test was used to compare the same patients' pregnancies before/under hydroxychloroquine. To determine the factors associated with live birth in patients treated by hydroxychloroquine, a logistic univariate regression was done including the following factors: previous pregnancy complications (early embryonic loss, intrauterine death, intrauterine growth restriction, preeclampsia), pregnancy treatments (type, time of beginning, amount), auto-immune disease, antinuclear and anti-SSA antibodies, type and triple positivity of aPL. As the number of patients was limited, the multivariate analysis was not realized. Statistical analysis was performed using GraphPAd (version 9.1) and significance was defined as $p < 0.05$.

3. Results

3.1. APS patients' characteristics and pregnancies under hydroxychloroquine

Thirty patients with APS (median age 30 [19–40] years) with 35 pregnancies treated by hydroxychloroquine were analyzed (Table 1). APS was mainly primary (77%) with predominant isolated obstetrical profile (43%) and 20% of asymptomatic carriers. Associated auto-immune disease was present in 23% and consists of rheumatoid arthritis ($n = 1$), Sjogren's syndrome ($n = 1$), and undifferentiated connective tissue disease ($n = 5$).

First, we analyzed the 35 pregnancies treated by hydroxychloroquine of 30 APS patients. During these 35 pregnancies, the associated treatments were used in all patients (mostly aspirin with LMWH in 43% of cases and aspirin–LMWH–prednisone in 29% of cases), with hydroxychloroquine preconception use in 28 (80%) cases. The