# Effect of Additional Treatments Combined with Conventional Therapies in Pregnant Patients with High-Risk Antiphospholipid Syndrome: A Multicentre Study

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**Abstract**

The effect of additional treatments combined with conventional therapy on pregnancy outcomes was examined in high-risk primary antiphospholipid syndrome (PAPS) patients to identify the most effective treatment strategy. The study's inclusion criteria were (1) positivity to lupus anticoagulant alone or associated with anticardiolipin and/or anti-β2 glycoprotein I antibodies; (2) a history of severe maternal–foetal complications (Group I) or a history of one or more pregnancies refractory to conventional therapy leading to unexplained foetal deaths not associated with severe maternal–foetal complications (Group II). Two different additional treatments were considered: oral—low-dose steroids (10–20 mg prednisone daily) and/or 200 to 400 mg daily doses of hydroxychloroquine and parenteral—intravenous immunoglobulins at 2 g/kg per month and/or plasma exchange. The study's primary outcomes were live birth rates and pregnancy complications. A total of 194 pregnant PAPS patients attending 20 tertiary centres were retrospectively enrolled. Hydroxychloroquine was found to be linked to a significantly higher live birth rate with respect to the other oral treatments in the Group II patients. The high (400 mg) versus low (200 mg) doses of hydroxychloroquine ($p = 0.036$) and its administration before versus during pregnancy ($p = 0.021$) were associated with a significantly higher live birth rate. Hydroxychloroquine therapy appeared particularly efficacious in the PAPS patients without previous thrombosis. Parenteral treatments were associated with a significantly higher live birth rate with respect to the oral ones ($p = 0.037$), particularly in the Group I patients. In conclusion, some additional treatments were found to be safe and efficacious in high-risk PAPS pregnant women.

**Keywords**

- antiphospholipid syndrome
- hydroxychloroquine
- low-dose steroids
- intravenous immunoglobulins
- plasma exchange

## Introduction

A heparin–aspirin combination constitutes the conventional treatment protocol for pregnant women affected with antiphospholipid syndrome (APS). As these strategies fail in approximately 20 to 30% of cases,[1] uncovering other options for women refractory to conventional treatment or at high risk of pregnancy complications has become an urgent undertaking. High-risk antiphospholipid antibody (aPL) profiles seem to be linked to specific serological markers such as multiple aPL positivity[2–4] and, in particular, to contemporaneous positivity to all three aPL assays,[5–8] to lupus anticoagulant (LAC) activity[9] or to high aPL titers.[10,11] Moreover, some well-defined clinical features such as a history of thromboembolism[3,5,7,12–14] and/or the presence of a systemic autoimmune disease[7,9,15,16] have been found to be associated with severe maternal–foetal complications in pregnant APS women receiving conventional therapy. Several experts are convinced that in association with conventional therapy, these high-risk APS patients should also be prescribed additional treatments before/during pregnancy in the effort to improve live birth rates and/or reduce pregnancy complications which often occur despite conventional treatment.[14] Treatments prescribed in addition to conventional therapy, which currently include intravenous immunoglobulins (IVIGs), low-dose steroids, plasma exchange or hydroxychloroquine (HCQ), have produced variable results.[17,18]

A retrospective, multicentre study recently reported that pregnant APS patients with previous thrombosis and triple aPL positivity treated with additional therapy had significantly higher live birth rates with respect to those receiving conventional therapy alone.[18] A variety of additional therapies including IVIG infusions, plasma exchange and low-dose steroids, alone or combined, were evaluated in that study, but it was impossible to analyse each therapy singularly, as the number of patients studied was insufficient to draw any significant conclusions.[18] The current, large, multicentre, observational, retrospective study set out in that study's footsteps to investigate the effect of various additional treatments on pregnancy outcomes in primary APS (PAPS) women refractory to conventional therapy and/or with risk factors for pregnancy complications to identify the most efficacious ones.

## Materials and Methods

### Study Population

Only patients who fulfilled—at the time they were diagnosed with PAPS—the clinical and laboratory classification criteria established by the International Consensus in 2004[19] were retrospectively enrolled in the study.

Patients fulfilling both the laboratory and clinical criteria were enrolled: (1) Laboratory criteria referred to laboratory risk factors, that is a positivity to LAC alone or associated with IgG/IgM anticardiolipin (aCL) and/or with IgG/IgM anti-$\beta_2$-glycoprotein I (anti-β2GPI) antibodies. In accordance with data in the literature, the following types of aPL profiles were considered laboratory risk factors: triple aPL positivity[5–8] and double/single aPL positivity always including the presence of LAC.[9] At least two consecutive positive antibody results more than 12 weeks apart were needed to meet this

requirement. (2) Clinical criteria referred to one or more of the following: a history of maternal thrombosis and/or previous severe pregnancy complications including eclampsia, severe preeclampsia (arterial pressure $\geq$160/110 and proteinuria $\geq$5 g in a 24-hour urine sample), haemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, intrauterine growth restriction (IUGR—a postnatal birth weight less than the 10th percentile for the gestational age) and/or a previous pregnancy refractory to conventional therapy leading to an unexplained foetal death at or beyond the 10th week of gestation not associated with severe pregnancy complications.

Patients with any of the following criteria were excluded: (1) a previous conventionally treated pregnancy that led to a live birth; (2) the presence of a well-defined associated autoimmune systemic disease including systemic lupus erythematosus; (3) age $\geq$ 45 years; (4) single or multiple organ failure; (5) severe pulmonary hypertension; (6) other known causes of pregnancy failure.

In addition to conventional therapy (prophylactic or therapeutic doses of heparin + low-dose aspirin), the following treatments were administered: oral treatments such as low-dose steroids (10–20 mg prednisone daily) and/or a 200 to 400 mg dose of HCQ daily or parenteral treatments such as IVIG (2 g/kg per month) and/or plasma exchange administered following a defined timetable. As no controlled clinical trials have as yet confirmed the efficacy of any additional therapy, treatment decisions tended to be based on the opinion and personal experience of the attending physician, and the patient's clinical history in this context could seem more important than a particular aPL profile.

To facilitate statistical analysis, the patients studied were arbitrarily classified into two groups depending exclusively on their clinical features: 154 patients (79.4%) who presented more severe clinical features such as a history of thrombosis and/or severe pregnancy complications including eclampsia, severe preeclampsia, HELLP syndrome and IUGR were assigned to Group 1; 40 patients (20.6%) who presented less severe clinical features such as a history of one or more pregnancies refractory to conventional treatment leading to unexplained foetal deaths not associated with severe pregnancy complications were assigned to Group II.

The study's primary outcomes were the live birth rate (i.e., the number of live newborns surviving the first 27 days after birth) and severe pregnancy complications. The mean week of gestation at delivery, the mean birth weight in percentiles and the number of neonatal complications were the secondary outcomes.

The Institutional Review Board for Observational Studies and the Audit Committee of the University of Padua's Medical Centre approved the study design. Patients who fulfilled the inclusion requirements were contacted and asked to sign informed consent forms. Their medical records were then retrieved and reviewed.

### Antibody Detection

Five of the participating centres used a home-made enzyme-linked immunosorbent assay (ELISA) in accordance with the minimal requirements proposed by the European Forum on Antiphospholipid Antibodies to determine aCL and anti-$\beta_2$GPI antibodies of IgG and IgM isotypes.[20,21] The other 15 centres that determined IgG/IgM aCL and anti-$\beta_2$GPI antibodies using commercial kits were recommended to follow the manufacturers' directions in particular with regard to the less than 10% inter- and intra-run coefficient of variability. LAC was assessed by multiple coagulation tests using platelet-poor plasma samples, following internationally accepted guidelines.[22,23]

### Statistical Analysis

The effects of each additional treatment were analysed separately in the two groups. The associations between the treatments and the primary outcomes were analysed using Pearson's chi square test and Fisher's exact test. The Kruskal–Wallis test with multiple pairwise comparisons was used to analyse the continuous secondary outcomes. The Bonferroni correction was used in all the multiple comparisons in which the contingency table was larger than 2 rows $\times$ 2 columns. Multiple comparisons of the primary and secondary outcomes in relation to the additional treatments were performed correcting the *p*-value using the Bonferroni adjustment. Backward conditional logistic regression analysis that was adjusted for confounding factors including disease duration, maternal age $\geq$ 35 years, congenital risk factors (factor V Leiden, prothrombin G20210A mutation, decrease in C and S protein antigens and activities, antithrombin III deficiency and increased activated protein C resistance), hypertension (blood pressure >140/90 mm Hg or use of antihypertensive drugs), body mass index $\geq$30 kg/m$^2$, aCL, anti-$\beta_2$GPI and other autoantibodies was performed to evaluate the independent role of the additional treatments on the primary outcomes. A *p*-value <0.05 was considered significant. Statistical analysis was performed using the SPSS Statistics version 24 software.

## Results

Between 1999 and 2016, a total of 194 pregnant PAPS patients (mean age = 32.05 years $\pm$ 5.02 SD, range = 17–44, mean disease duration = 5.01 years $\pm$ 4.5 SD, range = 0–16) attending 20 international centres belonging to the European Forum on Antiphospholipid Antibodies network were retrospectively assessed. For 44 of the women (22.7%), it was the first pregnancy. One hundred fifty (77.3%) had a history of pregnancy morbidity; in 81 cases (54%), the pregnancy ended in foetal death, 45 (30%) premature birth and 14 (9.3%) early miscarriage, and for 10 (6.6%) in a combination of these. The precedent pregnancy had been untreated in 18 cases (12%), and it was refractory to conventional therapy in 132 cases (88%).

One hundred twenty-seven of the PAPS patients (65.5%) had triple aPL positivity (IgG/IgM aCL plus IgG/IgM anti-$\beta_2$GPI antibodies plus LAC) and 67 (34.5%) had LAC alone or associated with IgG/IgM aCL or IgG/IgM anti-β2GPI antibodies. Group I comprised 154 patients (79.4%): 76 (49.3%) had a history of thrombosis, 44 (28.6%) had previous severe pregnancy complications and 34 (22.1%) suffered from

both complications. Group II comprised 40 patients (20.6%): all had a previous foetal death refractory to conventional therapy not associated with severe obstetrical complications.

All 194 pregnant PAPS patients were administered other treatments in addition to conventional therapy. One hundred forty-nine (76.8%) received oral additional treatments: 94 HCQ (63.1%), 36 low-dose steroids (24.2%) and 19 both (12.7%). Forty-five (23.2%) were prescribed parenteral treatments: 16 IVIG (35.5%), 8 plasma exchange (17.7%), and 21 both (46.6%). Additional treatments were initiated before pregnancy in 112 cases (57.7%) and during pregnancy in 82 (42.3%). Although no major side-effects were registered in association with the various types of treatments, one patient discontinued HCQ at the 12th week of gestation due to diffuse dermatitis.

One hundred sixty-three pregnancies (84%) ended favourably producing 164 live infants including one set of twins, all born between the 24 and 41 weeks of gestation (mean 35.7 ± 3.3 SD). There were 115 (70.5%) caesarean deliveries and 48 (29.4%) vaginal ones. Thirty-five infants (21.3%) were born in less than 34 weeks of gestation and 91 (55.5%) infants were born in ≥ 37weeks of gestation. The infants (84 males and 80 females) had a mean birth weight of 2,638.2 g ± 733.9 SD (range: 600–3,950) and a mean of 42.2 percentiles ± 28.1 SD (range: 2–99). The infants' mean Apgar score at 5 minutes was 8.8 ± 1.2 SD (range: 3–10). Thirty-one (15.9%) of the pregnancies had negative outcomes: 19 foetal deaths (61.3%), 7 early miscarriages (22.6%) and 5 premature neonates (16.1%) who died during the perinatal period.

There were 59 cases (30.4%) of severe pregnancy complications: 16 (27.1%) had eclampsia or severe preeclampsia, 16 (27.1%) had IUGR, 6 (10.2%) had HELLP syndrome, 3 (5.1%) had vascular thrombosis and 2 (3.4%) had catastrophic APS during puerperium. There were multiple complications in 16 cases (27.1%). There were 43 out of 149 (28.9%) pregnancy complications during oral treatment and 16 out of 45 (35.5%) during parenteral treatment; the difference was not significant ($p = 0.502$). There was also no significant difference in the two patient groups in the frequency of each type of pregnancy complication.

Neonatal complications were recorded in 19 cases (11.6%): 12 had respiratory distress (63.2%), 4 had infections (21.0%), 1 had West's syndrome (5.3%; in this case, the mother had received low-dose steroid), 1 had multiple malformations (5.3%; in this case, the mother had received low-dose steroid) and 1 had intra-lobar pulmonary sequestration (5.3%), which was excised without complications 9 months after birth (in this case, the mother had been prescribed plasma exchange and IVIG).

### The Effect of the Different Additional Treatments

The live birth rate and severe pregnancy complications (the primary outcomes) were first analysed in relation to the oral and parenteral treatments (►**Table 1**). Parenteral therapies produced a significantly higher live birth rate with respect to oral treatments ($p = 0.037$), but only when the patients were considered together. The level of significance was higher in the group I patients (Group I: $p = 0.083$ vs. Group II: $p = 0.596$).

As far as the primary outcomes linked to the different oral treatments (►**Table 2**) were concerned, HCQ therapy administered alone was associated with a significantly higher live birth rate with respect to both low-dose steroid alone and HCQ + low-dose steroid treatments in all the patients considered together ($p = 0.027$) as well as in the Group II patients considered separately ($p = 0.017$). Severe pregnancy complications were significantly less frequent in the HCQ-treated patients ($p = 0.008$) with respect to the other oral therapies-treated patients. This latter HCQ's effect was more evident in the Group II ($p = 0.008$) than in the Group I ($p = 0.042$) patients. Four hundred milligram daily doses of HCQ versus 200 mg doses ($p = 0.036$) and its administration before versus during pregnancy ($p = 0.021$) were associated with a significant increase in the live birth rate (►**Table 3**). When drug dosage was not considered, no statistically significant differences were found in the live birth rate between the patients who started HCQ before or during pregnancy

**Table 1** Live birth rate and pregnancy complications in PAPS patients receiving additional oral and parenteral treatments

| Pregnant PAPS patients | Oral treatments | | Parenteral treatments | | *p* |
|---|---|---|---|---|---|
| | No. | % | No. | % | |
| | **Live birth rate** | | | | |
| All patients: 194 | 121/149 | 81.2 | 42/45 | 93.3 | 0.037[a] |
| Group I: 154 | 92/111 | 82.9 | 40/43 | 93.0 | 0.083 |
| Group II: 40 | 29/38 | 76.3 | 2/2 | 100 | 0.596 |
| | **Pregnancy complications** | | | | |
| All patients: 194 | 45/149 | 30.2 | 14/45 | 31.1 | 0.522 |
| Group I: 154 | 37/111 | 33.3 | 12/43 | 27.9 | 0.327 |
| Group II: 40 | 8/38 | 21.1 | 2/2 | 100 | 0.058 |

Abbreviation: PAPS, primary antiphospholipid syndrome.
Notes: Group I, PAPS patients with a history of thrombosis and/or severe pregnancy complications. Group II, PAPS patients with a history of refractory to conventional treatment foetal death occurring without any severe pregnancy complication.
[a]Statistical significance.

**Table 2** Live birth rate and pregnancy complications linked to the three types of oral additional treatments

| Pregnant PAPS patients | HCQ | | LDS | | HCQ + LDS | | *p* |
|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | |
| | **Live birth rate** | | | | | | |
| All patients: 149 | 82/94 | 87.2 | 27/36 | 75.0 | 12/19 | 63.1 | 0.027[a] |
| Group I: 111 | 63/74 | 85.1 | 22/27 | 81.5 | 7/10 | 70.0 | 0.479 |
| Group II: 38 | 19/20 | 95.0 | 5/9 | 55.5 | 5/9 | 55.5 | 0.017[a] |
| | **Pregnancy complications** | | | | | | |
| All patients: 149 | 19/94 | 20.2 | 16/36 | 44.4 | 9/19 | 47.4 | 0.008[a] |
| Group I: 111 | 19/74 | 25.7 | 14/27 | 51.8 | 4/10 | 40.0 | 0.042[a] |
| Group II: 38 | 1/20 | 5 | 2/9 | 22.2 | 5/9 | 55.5 | 0.008[a] |

Abbreviations: HCQ, hydroxychloroquine; HCQ + LDS, hydroxychloroquine plus low-dose steroid; LDS, low-dose steroid; PAPS, primary antiphospholipid syndrome.
Notes: Group I, PAPS patients with a history of thrombosis and/or severe pregnancy complications. Group II, PAPS patients with a history of refractory to conventional treatment foetal death occurring without any severe pregnancy complication.
[a]Statistical significance.

($p = 0.462$). It should be noted that HCQ taken before pregnancy, which was administered at the time the pregnancy was being planned, led to a mean pregnancy duration of 37.1 weeks ± 2.4 SD; HCQ taken during pregnancy, which was administered at a mean gestational age of 9.5 weeks ± 7.3 SD, was linked to a mean pregnancy duration of 35.2 weeks ± 3.3 SD.

Unsuccessful pregnancies during HCQ treatment were significantly associated with previous thrombosis ($p = 0.025$). In fact, 10 out of the 12 women (83.3%) receiving HCQ and suffering from a pregnancy failure had a history of thrombosis. Pregnancy losses in the other additional treatment patients were not, instead, significantly associated with a history of thrombosis. Six out of the 12 pregnancy losses (50%) occurring in the HCQ-treated women took place early in the pregnancy (before the 10th week of gestation), but only 1 out of the 19 (5.3%) pregnancy losses associated with other additional therapies occurred early. Spontaneous abortions were, thus, significantly more frequent in the women administered HCQ treatment with respect to the other additional treatment patients ($p = 0.0034$). Five out of the six women (83.3%) suffering from early pregnancy loss during HCQ therapy were taking 200 mg daily doses.

When the primary outcomes in the different parenteral treatment groups were compared (►**Table 4**), no significant differences were found in the live birth rates. Severe pregnancy complications were significantly less frequent in the patients treated with plasma exchange plus IVIG with respect to those treated with the other parenteral therapies both when the patients were considered together ($p = 0.034$) as well as in the Group I ($p = 0.035$) women analysed separately.

The findings regarding the secondary outcomes in the different additional therapies–treated patients are outlined in ►**Table 5**. According to the Kruskal–Wallis test, the patients receiving HCQ had significantly later mean weeks of pregnancy, while those treated with plasma exchange alone had earlier ones ($p < 0.001$).

According to logistic regression analysis, IVIG administered alone (odds ratio [OR] = 0.123, 95% confidence interval [CI] = 0.038–0.403, $p = 0.001$), IVIG plus plasma exchange (OR = 0.135, 95% CI = 0.033–0.550, $p = 0.005$) and HCQ (OR = 0.450, 95% CI = 0.207–0.978, $p = 0.044$) alone had protective effects on severe pregnancy complications in the Group I patients. Moreover, congenital risk factors ($p = 0.004$) and body mass index ≥30 kg/m$^2$ ($p = 0.019$) were found to be independent risk factors for pregnancy complications in the Group II patients.

No statistical differences were found between the patients with triple aPL positivity and those with LAC alone or associated with IgG/IgM aCL or IgG/IgM anti-$\beta_2$GPI antibodies.

**Table 3** Effect on live birth rate linked to two dosages of HCQ (200 or 400 mg) and the timing of its administration (before or during)

| Live birth rate | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HCQ dose | | | | | Before pregnancy | | | | | During pregnancy | | | | |
| 400 mg | | 200 mg | | *p* | 400 mg | | 200 mg | | *p* | 400 mg | | 200 mg | | *p* |
| No. | % | No. | % | | No. | % | No. | % | | No. | % | No. | % | |
| 47 | 94 | 35 | 79.5 | 0.036[a] | 34 | 97.1 | 31 | 79.5 | 0.021[a] | 13 | 86.7 | 3 | 75 | 0.530 |

Abbreviation: HCQ, hydroxychloroquine.
[a]Statistical significance.

**Table 4** Live birth rate and pregnancy complications related to the three parenteral additional treatments

| Pregnant PAPS patients | PE | | IVIG | | PE + IVIG | | *p* |
|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | |
| | **Live birth rate** | | | | | | |
| All patients: 45 | 7/8 | 87.5 | 15/16 | 93.7 | 20/21 | 95.2 | 0.754 |
| Group I: 43 | 7/8 | 87.5 | 13/14 | 92.8 | 20/21 | 95.2 | 0.765 |
| Group II: 2 | – | | 2/2 | 100 | – | | n.a. |
| | **Pregnancy complications** | | | | | | |
| All patients: 45 | 5/8 | 62.5 | 6/16 | 37.5 | 3/21 | 14.3 | 0.034[a] |
| Group I: 43 | 5/8 | 62.5 | 4/14 | 28.6 | 3/21 | 14.3 | 0.035[a] |
| Group II: 2 | – | | 2/2 | 100 | – | | n.a. |

Abbreviations: IVIG, intravenous immunoglobulins; n.a., not applicable; PAPS, primary antiphospholipid syndrome; PE, plasma exchange; PE + IVIG, plasma exchange plus intravenous immunoglobulins.
Notes: Group I, PAPS patients with a history of thrombosis and/or severe pregnancy complications. Group II, PAPS patients with a history of refractory to conventional treatment foetal death occurring without any severe pregnancy complication.
[a]Statistical significance.

## Discussion

This is the first study comparing the effect of different treatments administered in addition to conventional therapy to a large cohort of pregnant PAPS patients refractory to conventional therapy and/or at high risk of pregnancy complications. The patients studied were considered at high risk of pregnancy-related complications on the basis of a clinical history of maternal–foetal complications and an aPL profile characterized by the presence of LAC alone or associated with aCL and/or anti-$\beta_2$GPI antibodies. The study's most interesting findings concerned HCQ therapy which produced, mainly in the Group II patients, a significantly higher birth rate and significantly fewer severe pregnancy complications with respect to the other oral additional treatments. HCQ was found to be the most efficacious oral treatment used in association with conventional therapy in the PAPS patients with a previous foetal death refractory to conventional therapy.

These findings are in agreement with those reported by two clinical studies examining the effect of HCQ in pregnant APS women that reported fewer pregnancy losses in the treated than in the untreated patients.[24,25] The novelty of the current study regards the dosage and timing of HCQ treatment. In fact, the 400 mg dose of HCQ versus the 200 mg and its administration before but not during pregnancy were the two features that were associated with a significant increase in the live birth rate. HCQ therapy appeared particularly beneficial in the PAPS patients without previous thrombosis. In fact, the 10 out of the 12 unsuccessful pregnancies receiving HCQ treatment were significantly associated with a history of maternal thrombosis.

While it is true that only a few number of cases (45 cases) were treated with parenteral additional treatments, that therapy led to a significantly higher live birth rate with respect to the oral medications, but only when all of the patients were considered together. As this result was mainly due to the contribution of the Group I patients, the more severe clinical subset, it suggests that these treatments should be reserved for PAPS patients with a history of severe maternal–foetal complications and/or in those refractory to HCQ additional treatment. In addition, logistic regression analysis showed that both IVIG + plasma exchange and IVIG alone had a significant protective effect against severe pregnancy complications in the Group I patients.

**Table 5** Secondary outcomes related to the six additional treatments

| Secondary outcomes | HCQ | LDS | HCQ + LDS | PE | IVIG | PE + IVIG | *p* |
|---|---|---|---|---|---|---|---|
| Week at delivery, mean ± SD | 36.8 ± 2.8 | 35.7 ± 3 | 36.3 ± 2.7 | 31.1 ± 4.7 | 35.3 ± 2.5 | 33.7 ± 2.9 | < 0.001[a] |
| Weight percentiles, mean ± SD | 49.3 ± 29.7 | 36.3 ± 3 | 33.2 ± 20.5 | 32.4 ± 25.7 | 36.7 ± 20.4 | 36.7 ± 23.8 | 0.121 |
| Neonatal complication, no. (%) | 6 (7.3%) | 5 (14%) | 2 (16.7%) | 3 (43%) | 1 (6.7%) | 2 (9.5%) | 0.092 |

Abbreviations: HCQ, hydroxychloroquine; HCQ + LDS, hydroxychloroquine plus low-dose steroid; IVIG, intravenous immunoglobulins; LDS, low-dose steroid; PE, plasma exchange; PE + IVIG, plasma exchange plus intravenous immunoglobulins.
[a]Statistical significance.

There were no major side effects correlated to the various types of treatments neither in the mothers nor in the children. As far as HCQ safety is concerned, our data are in accordance with those of a systematic review and a meta-analysis[26] that recently reported that its use during pregnancy was not associated with a relevant increase in congenital malformations. In view of the fact that only a few studies have focused on HCQ treatment during PAPS pregnancies, data from future investigations examining the long-term follow-up of mothers and children will provide more precise information about its safety in these patients. It is especially important to evaluate any side effects that could be linked to high dosage (400 mg daily) and/or long-term duration (before pregnancy).

While it is true that IVIG infusions and plasma exchange are indeed costly, the current study confirmed that they are safe and lead to a high live birth rate in women who have little hope of having successful pregnancies.[27–29] As this particular patient subset is quite rare, the expense of additional parenteral treatments could be justified by the small number requiring such treatment.

One of the study's limitations is its retrospective nature, but the rarity of these types of PAPS patients complicates performing prospective studies or clinical trials on additional treatments. The fact that the study did not have a core reference laboratory could be considered another limitation of this study. LAC was nevertheless homogeneously identified by each attending centre following international guidelines.[22,23] As explained, homemade ELISA procedures and a variety of commercial kits were utilized by the various participating centres to determine aCL and anti-$\beta_2$GPI antibodies. Despite many efforts to standardize the assays for these antibodies, methodological problems continue to persist and there are significant inter-assay and interlaboratory variations in results even in connection to commercial kits.[30–32] It was thus impossible to compare all the methods used in the study in a standardized way to determine if they had any effect on the laboratory results. The strengths of the study could be its large number and the homogeneity of the study population composed only of PAPS patients refractory to conventional therapy and/or at high risk of pregnancy complications.

Our results will hopefully help point the direction of future clinical trials investigating the effect of additional treatments on refractory and high-risk PAPS patients with severe clinical history and LAC positivity. For the time being, the conclusion that can be drawn is that some additional treatments seem to be safe and efficacious in refractory/high-risk PAPS pregnant women. Four hundred milligram daily HCQ therapy begun before pregnancy may be a good option especially for PAPS patients with a previous pregnancy refractory to conventional therapy leading to a foetal death not associated with severe pregnancy complications. IVIG combined with plasma exchange or alone could be used in very high-risk pregnant PAPS women and particularly in those with a history of thrombosis and/or refractory to previous HCQ additional treatment.

## What is known about this topic?

- Since conventional therapeutic strategies fail in approximately 20 to 30% of pregnant patients affected with antiphospholipid syndrome (APS), there is an urgent need to define other therapeutic options to be used in addition to conventional treatment.
- The most efficacious additional treatment to be combined with conventional therapy for high-risk APS pregnant women has not yet been established.

## What does this paper add?

- Four hundred milligram daily hydroxychloroquine therapy begun before pregnancy may be a good option especially in APS patients with a previous, uncomplicated, refractory to conventional therapy foetal death.
- Intravenous immunoglobulins combined with plasma exchange or alone could be used in pregnant APS women with previous severe pregnancy complications.

Conflict of Interest
None.

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None.

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