Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 29s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Hydroxychloroquine Therapy in Women with Recurrent Pregnancy Loss due to Anti-phospholipid Antibody Syndrome Refractory to Low Dose Aspirin and Heparin

Salwa Mahmoud Ali[1], Mohamed Nagi Mohesen[1], Ahmed Kamal Abd-Elsamee Elgarf[*2], Mohamed AHussien[1]

[1]Obstetrics and Gynecology department, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt

[2] Obstetrics and Gynecology department, Wadi El Neel Hospital, Cairo,

***Corresponding author:**

Ahmed Kamal Abd-Elsamee Elgarf

Consultant at Obstetrics and Gynecology department, Wadi El Neel Hospital, Cairo,

Email ID: Midoelgarf126@gmail.com

Cite this paper as: Salwa Mahmoud Ali, Mohamed Nagi Mohesen, Ahmed Kamal, Abd-Elsamee Elgarf, Mohamed AHussien, (2025) Hydroxychloroquine Therapy in Women with Recurrent Pregnancy Loss due to Anti-phospholipid Antibody Syndrome Refractory to Low Dose Aspirin and Heparin. *Journal of Neonatal Surgery*, 14 (29s), 506-514.

ABSTRACT

Introduction: Antiphospholipid antibody syndrome (APS) is the primary treatable etiology of recurrent pregnancy loss (RPL). Hydroxychloroquine (HCQ) is extensively used in the treatment of individuals with autoimmune disorders; HCQ facilitates the restoration of trophoblast fusion impaired by autoantibodies.This study was to evaluate the effectiveness of adjuvant HCQ therapy on pregnancy outcomes in pregnant women experiencing RPL due to anti-phospholipid antibody syndrome that is resistant to standard treatment with low-dose aspirin (LDA) and prophylactic low-molecular-weight heparin (LMWH).

Methodology: This randomized controlled clinical trial involved 100 pregnant women, who were evenly allocated into two groups. The HCQ group received adjuvant HCQ 200 mg tablets twice daily until the conclusion of pregnancy, along with LDA until the 35th week of gestation, and LMWH during pregnancy and for 3–6 weeks postpartum. The control group was administered only low-dose aspirin and LMWH. Subsequent appointments were arranged in accordance with established norms.

Results: Gestational age at delivery was statistically significant higher among HCQ group 33.1±5.5 vs. 24.8±7.5 weeks with higher live birth rate and lower percent of fetal loss; 34.0±3.1 vs. 32.5±4.0 and 22.8±2.3 vs. 24.2±5.4 respectively. Bleeding or thrombotic events were statistically significant lower among HCQ group 4 (8%) vs. 10 (20.0%) respectively. During pregnancy and postpartum maternal thrombotic events were 3 (6.0%) vs. 5 (10.0%) and 1 (2.0%) vs. 7 (14.0%) respectively. Neonatal birth weight and Apgar score ≥ 7.0 were statistically significant higher among HCQ group; 2.600±0.611 vs. 2.125±0.215 gram and 27(54.0%) vs. 10(20.0%) respectively. The need for NICU admission was lower among HCQ group; 3(6.0%) vs. 16(32.0%). Postnatal maternal mortality rates were lower among HCQ group; 20(40%) vs. 34(68%).

Discussion: The use of HCQ for obstetrical APS is a potential treatment option to improve maternal and neonatal outcomes.

Keywords: *Hydroxychloroquine, Recurrent Pregnancy Loss, Anti-phospholipid Antibody Syndrome, Aspirin, Heparin*

1. INTRODUCTION

Recurrent pregnancy loss (RPL) is two or more failed clinical pregnancies, as evidenced by ultrasonography or histology. Globally, it involves three or more early pregnancy losses **[1]**. Around 2% of pregnant women lose two pregnancies. RPL has no known etiology in up to 50% of cases **[2]**. RPL is a complex reproductive medicine condition that frustrates patients, families, and doctors **[3]**. The unknown cause of RPL may cause patients anxiety **[4]**. Primary RPL is pregnancy loss in women who have never given birth. Secondary RPL occurs in women who have delivered a live birth **[5]**. Genetic, anatomical, endocrine, APS, immunological, and environmental factors can cause RPL **[6]**. APS is an acquired autoimmune illness that causes thrombosis and obstetric issues due to prolonged aPL **[7]**. Obstetric morbidities in APS include RPL, aPL-associated ischemic placental dysfunction, preeclampsia, eclampsia, and HELLP syndrome (hemolysis, elevated liver enzyme levels, and low platelet counts), IUGR, premature delivery, and intrauterine fetal death. APS is divided into groups

based on aPL, which include lupus anticoagulant (LA), IgG and IgM anticardiolipin antibodies (aCL), and anti-β2-glycoprotein-I (aβ2GPI) antibodies **[8]**. It is possible to diagnose chronic aPL if there is a history of thrombosis or bad obstetrical outcomes, such as three losses before 10 weeks of pregnancy, one loss after 10 weeks, or early delivery due to preeclampsia or placental insufficiency **[9]**. APS patients use LDA and LMWH throughout pregnancy to prevent aPL-related obstetric issues **[10]**. Although this regimen improves obstetrical outcomes, 20–30% of women with APS still have RPL, known as refractory APS. Poor prevention of APL-related obstetric issues necessitates greater research into adjuvant treatment **[11]**. Standard care medicine has tested corticosteroids and intravenous immunoglobulins (IVIG). Prednisolone increased live birth rates by 61%, while IVIG had no effect **[12]**. HCQ is also showing promise in treating refractory obstetrical APS **[13]**. SLE patients utilize HCQ, an anti-thrombotic, anti-inflammatory, and immunomodulatory medication **[14]**. Few studies have shown that HCQ prevents obstetrical APS, although in vitro and in vivo studies have shown its therapeutic benefits; In vitro, HCQ reverses aPL-β2GPI complex binding to cell membranes and lowers the risk of thrombosis by stopping platelets from clumping together. It also restores annexin A5, a placental anticoagulant protein. aPL-mediated inhibition of IL-6 can be reversed by HCQ, which lets trophoblast cells migrate during the first trimester **[15]**. In vivo animal studies suggest HCQ may reduce aPL-induced thrombus size and duration. HCQ, together with regular prophylaxis, may improve obstetrical outcomes in APS patients **[16]**. There isn't a lot of strong evidence that HCQ can help with refractory obstetrical APS, but we wanted to look at all the clinical data on what happened to the babies whose mothers took HCQ while they were pregnant **[17]**. The study looked at what happens to pregnant women who keep losing their babies because of anti-phospholipid antibody syndrome and who did not respond to LDA or prophylactic LMWH. It also looked at the effects of adding HCQ to their treatment.

2. PATIENTS AND METHODS:

This randomized controlled clinical trial was conducted at antenatal care clinic - Obstetrics and Gynecology Department, Faculty of Medicine, Beni-Suef University Hospital from July 2022 until January 2024.

I. Study population:

Pregnant women attended our hospital with the following criteria:

- **Inclusion criteria:**
  1) 1sttrimesteric pregnant women
  2) With RPL, secondary to APS; defined as the presence of at least one clinical and one lab-based criterion **[18]**:
  3) Refractoriness to standard APS treatment, defined as previous fetal demise despite treatment with LDA and prophylactic dose LMWH throughout pregnancy.
- **Exclusion criteria:**
  1) Abnormal uterine anomalies at 3D ultrasonography
  2) Karyotyping abnormalities within the couple
  3) Other medical morbidity affecting fetal outcome e.g DM and hypertension.
  4) Allergy or adverse event to hydroxychloroquine.
  5) History of retinopathy
  6) Psoriasis
  7) Uncontrolled epilepsy
  8) History of active cardiac condition
  9) Current treatment with hydroxychloroquine.
  10) Previous pregnancy failure on hydroxychloroquine

II. Sampling Method "randomization":

Systematic random selection was employed, and women who met the inclusion criteria were randomly assigned to one of the groups. One hundred envelopes were numbered sequentially, and each envelope contained the corresponding letter that indicated the assigned group, as determined by a randomization table. All envelopes were subsequently sealed and placed in a single box. Randomization was performed using a computer-generated randomization sheet through MedCalc ® version 13.

Sample size:

A total of 100 pregnant women were enrolled, after consenting each of them and divided into two equal groups:

1) **HCQ group:** In this group, adjuvant HCQ was used, in addition to low dose aspirin and LMWH during pregnancy.
2) **Control Group:** In this group, only the standard treatment of low dose aspirin and LMWH was used during pregnancy

III. Sample size justification:

Setting the power= 0.80 and α=0.05 with using PASS 11th release, a minimal sample size of 50 cases in each group are required to get statistical significance between assumed difference of 25.0% and assumed incidence of live birth in control of 57.0% **[19]**.

Ethical considerations:

Prior to participating in the study, patients were apprised of its nature, extent, and possible consequences in a comprehensible way. The case report only recorded patient initials, while investigators secured any records containing the patient's name in a secure place. The investigators maintained a personal patient identification list including patient initials and names to identify records.
In accordance with local requirements, the protocol and associated materials received ethical and research approval from the OB/GYN department council at Beni-Suef University Hospital prior to the commencement of the study. Hydroxychloroquine may induce side effects including alopecia, nausea, weight reduction, cephalalgia, anxiety, abdominal cramps, diarrhea, rash, vertigo, and syncope.

IV. Study interventions and procedures:

1. The demographic, maternal characteristics were extracted from a questionnaire during their first antenatal health care.
2. According to inclusion and exclusion criteria; patients were subjected to:

a) Complete history taking of clinical importance including:

- **Personal history:** age, residence, occupation, marital status and special habits as smoking, alcohol, etc.
- **Present history:** Previous history of VTE or other medical morbidity affecting fetal outcomes as hypothyroidism or hyperthyroidism, DM and hypertension or history of retinopathy.
- **Menstrual history:** day of last menstrual period and regularity.
- **Obstetric history:** gravidity, parity, previous miscarriages or obstetric complications as previous history of sever pre-eclampsia or IUFD or Accidental hemorrhage.
- **Drug history:** type, duration of use before pregnancy, current medication, history of aspirin and LMWH in previous pregnancies (dose, start, duration), and outcome of theses pregnancies.
- **Medical history:** medical comorbidities with pregnancy as hepatic, renal, endocrinal, psychosocial condition, cardiovascular, diabetes, chronic hypertension.
- **Surgical history:** Previous cesarean sections and its neonatal outcomes.
- **Family history** of maternal or fetal complications with pregnancy.

b) General examination with special emphasis on:

- Assessment of vital data, cardiac and chest conditions.
- Pre-pregnancy, BMI (Pre-BMI) or 1st ANC visit BMI
- We examined upper and lower limb for any signs of venous thromboembolism.
- Abdominal examination: to exclude previous scar if present

c) Investigation:

- Pregnancy test e.g., serum qualitative beta-HCG.
- Routine investigations e.g., full blood count, random blood sugar and urine analysis.
- Kidney function tests e.g., serum creatinine, BUN, protein/creatinine ratio; and liver function tests e.g., AST, ALT and serum albumin.
- Lupus markers e.g., ANA and Anti-DNA.
- Conventional antiphospholipid (aPL) antibodies e.g., lupus anticoagulant (LA), anticardiolipin (aCL), and anti-β_2 glycoprotein I (anti-β_2GPI) antibodies; on two occasions at least 12 weeks apart. aCL was quantified by indirect ELISA, anti-β2GP1 (isotypes immunoglobulin G and M) were quantified by

indirect ELISA and LA detection was determined by dilute Russell's viper venom time and dilute activated partial thromboplastin time.

- Thyroid function tests (free T3, free T4, TSH) and antithyroid Abs as (TG Ab, TPO Ab, TSHr Ab).

d) Antenatal ultrasound examination, which included ultrasound measurements of classical fetal biometric parameters that were taken using MindrayDP-15 Digital Ultrasonic Diagnostic Imaging System and GE Logiq E9 ultrasound machine, 2–5 MHz wide band convex, curved array transducer.

e) All ultrasound examinations were done by an expert and professional medical personnel to ensure the accuracy of examination results.

3. The study was conducted on (100) pregnant women who were divided into two groups:
   - **HCQ group:** 50 pregnant women with RBL secondary to APS, that is refractory to the standard treatment of LDA and prophylactic dose of LMWH. In this group, adjuvant HCQ was used -200 mg HCQ tablets, (**Hydroquine®** 200mg which was manufactured by MinaPharm Company)- was used twice daily till the end of pregnancy, in addition to LDA and LMWH during pregnancy.
   - **Control group:** 50 pregnant women RPL secondary to APS that is refractory to low dose aspirin and prophylactic dose of LMWH. In this group, only the standard treatment of LDA and LMWH was used during pregnancy.
4. In antenatal visits, compliance was assessed and all data was collected in a case record file.
5. After confirmation of fetal viability by ultrasound, LMWH was started in thrombo-prophylactic dose according to patient weight according to **Nelson-Piercy, [20].**
6. Follow-up visits were scheduled once every three weeks in 1st trimester, one every two weeks in 2nd trimester and once weekly in third trimester.
7. All patients received routine antenatal steroid from 24-34 weeks gestation. It was in the form of four doses of dexamethasone 6 mg, intramuscularly 12 hours apart.
8. In the absence of standard medical or obstetric indications for early delivery, delivery was scheduled (induction of labor under continuous fetal monitoring or elective C-section) at 38 weeks of gestation to control the timing of discontinuation of antithrombotic drugs.
9. Women were instructed to stop HCQ on the day of delivery.
10. LDA was stopped at 36 weeks of gestation in women with no history of thrombosis.
11. LMWH was discontinued 24 hours before labor and delivery, continued for 3–6 weeks during the postpartum period
12. The postpartum visit was completed 6 weeks postpartum.

V. Study outcomes:

- **Primary outcome:** Live birth rate, defined as delivery of a viable fetus that subsequently shows any sign of life; at gestational age > 28 weeks.
- **Secondary outcomes:** Rate of miscarriage with or without HCQ, Birth weight, Mode of delivery either vaginal delivery or Cesarean Section, Apgar score <7 at 5 minutes, Neonatal morbidity (bleeding or thrombotic complications, infections, congenital abnormalities), Days to hospital discharge following delivery (mother), Thrombotic events in the mother during pregnancy and 6 weeks postpartum, and Rate of NICU admission.

Statistical analysis:

The statistical software for social sciences, version 23.0, (SPSS Inc., Chicago, Illinois, United States) was used in order to do the analysis on the data that was recorded. For parametric (normal) distributions, quantitative data were presented as mean plus standard deviation and ranges. On the other hand, for non-normally distributed variables, the median was supplied together with the inter-quartile range. In addition, qualitative features were given numerical and percentageal representations in the report. For the purpose of determining whether or not the data were normal, the Kolmogorov-Smirnov and Shapiro-Wilk tests were used. To determine whether or not there was a significant difference between two means, the independent-samples t-test was performed. The Chi-square test and Fisher's exact test were used in order to compare groups that were based on qualitative data. Only in situations where the expected number of cells in any given cell was lower than five was the Chi-square test used. A P-value that was less than 0.05 was considered to be statistically significant.

3. RESULTS

Table (1): showed no differences between study groups regarding age, BMI, abortions, and antiphosphospholipid markers,

p value > 0.05.

Table 1: Demographic characteristics and serum antiphosphospholipid markers among the studied groups

Items	Measure	HCQ group (N=50)	Control Group (N=50)	P-value
Age (years)	Mean±SD	28.2±6.3	30.1±4.1	0.524
	Range	18.0–39.0	19.0–39.0	
BMI (kg/m^2)	Mean±SD	24.4±3.6	27.8±1.9	0.315
	Range	21.8–3.5	20.2–29.5	
Previous Abortions	Mean±SD	5±1.0	4.4±1.0	0.752
	Range	3.0–7.0	3.0–7.0	
Lupus anticoagulant (LA)	Number (%)	23 (46.0 %)	20 (40.0%)	0.413
Anti-cardiolipin (aCL)	Number (%)	18 (36.0 %)	20 (40.%)	0.215
Antiβ2glycoprotein1(anti-β2GP1)	Number (%)	9(18 %)	10 (10.0%)	0.356

t-Independent, sample t-test for mean ± SD; x2: Chi-square test for Number (%) or Fisher's exact test, *p-value <0.05 is significant

In table (2): The mean gestational age at delivery, for all studied cases, was 33.1±5.5 week of gestation in the HCQ group, and 24.8±7.5 week of gestation in the control group, while it was 34.0±3.1 week of gestation in the live births in HCQ group and 32.5±4.0 week of gestation in control group. Furthermore, the mean gestational age at delivery, for fetal losses, was 22.8±2.3 week of gestation in HCQ group, and 24.2±5.4 week of gestation in control group. Gestational age at delivery was significantly higher in HCQ group than in control group as regard all cases. Mode of delivery among the studied groups was non-statistically significant. In HCQ group, as regard all cases, 28 (56.0%) women delivered by CS and 22 (44.0%) women delivered vaginally. As regard live births, 23 (71.8%) women delivered by CS, and 10 (23.2%) delivered vaginally. Maternal thrombotic events was non-statistically significant lower during pregnancy and statistically significant lower among HCQ group postpartum, p = 0.658 and 0.04 respectively. There were no differences between study groups as post-delivery hospital stay, p = 0.859.

Table 2: Maternal outcomes among the studied groups

Cases		**HCQ group (N=50)**	**Control Group (N=50)**	**P-value**
Gestational age at delivery (Weeks)				
All cases	**Mean±SD**	33.1±5.5	24.8±7.5	**0.011***
	Range	18.0–40.0	14.0–38.0	
Live	**Mean±SD**	34.0±3.1	32.5±4.0	**0.025***
	Range	26.0–40.0	28.0–39.0	
Fetal loss	**Mean±SD**	22.8±2.3	24.2±5.4	0.552
	Range	15.0–26.0	13.0–33.0	
Mode of delivery				
All cases	**Cesarean**	28(56.0%)	19(36.5%)	0.22
	Vaginal	22(44.0%)	33(63.5%)	

Live birth	**Cesarean**	23(71.8%)	16(72.7%)	0.56
	Vaginal	10(23.2%)	6(27.3%)	
Fetal death	**Cesarean**	3(17.7%)	3(10.0%)	0.89
	Vaginal	16(82.3%)	27(90.0%)	
Maternal thrombotic events				
During pregnancy		3 (6.0%)	5 (10.0%)	0.658
Postpartum		1 (2.0%)	7 (14.0%)	**0.04**
Maternal post-delivery hospital stay				
One day		46(92.0%)	45(90.0%)	**0.859**
More than one day		4(8.0%)	5(10.0%)	

t-Independent sample t-test for mean ± SD; x2: Chi-square test for number (%) or Fisher's exact test, when appropriate p-value >0.05 is insignificant; *p-value <0.05 is significant; **p-value <0.001 is highly significant.

In table (3): live birth rate was statistically significant higher among HCQ group, p value = 0.012. Neonatal birth weight was statistically significant higher among HCQ group, p value = 0.002. Apgar score at 5 min that was less than7, presented in 9 (18.0%) live births in **HCQ** group, and 17 (34.0%) live births in control group. Apgar score at 5 minute that was less than 7.0 was significantly less frequent in **HCQ** group than in control group (p value =0.001). Bleeding or thrombotic attacks were statistically significant lower among **HCQ** group, p value = 0.031. On the other hand, no differences were noted between study groups regarding incidence of infection and congenital anomalies. NICU admission was statistically significant higher among control cases compared with **HCQ** group, p = 0.021. postnatal mortality was statistically significant lower among **HCQ** group, p = 0.01.

Table 3: Neonatal outcomes among the studied groups

Outcomes	**HCQ group (N=50)**	**Control Group (N=50)**	**P-value**
Live birth (n,%)	36(72.0%)	24(48.0%)	**0.012***
Fetal loss (n,%)	14(28.0%)	26(52.0%)	
Neonatal birth weight among live births			
Mean ± SD	2.600±0.611	2.125±0.215	**0.002***
Range	1.458–3.458	1.585–3.125	
Neonatal Apgar score at 5 min among live births			
<7.0	9(18.0%)	17(34.0%)	**0.001***
≥ 7.0	27(54.0%)	10(20.0%)	
Morbidities			
Bleeding or thrombotic (n,%)	4 (8%)	10 (20.0%)	**0.031***
Infection (n,%)	9 (18%)	5(10.0%)	0.215
Congenital anomalies (n,%)	3 (6%)	1(2.0%)	0.412
NICU admission(n,%)	3(6.0%)	16(32.0%)	**0.021***

NICU>1week (n,%)	2(4.0%)	3(6.0%)	0.885
Postnatal mortality			
Mortality	20(40%)	34(68%)	**0.01***
Survival	30(60%)	16 (32.0%)	

t-Independent Sample t-test for Mean±SD; x2: Chi-square test for Number (%) or Fisher's exact test, when appropriate p-value >0.05 is insignificant; *p-value <0.05 is significant; **p-value <0.001 is highly significant

4. DISCUSSION

Preventing obstetric complications in patients with APS is standard practice, and it requires taking low-dose aspirin and low molecular weight heparin together. But refractory obstetrical APS still affects 20–30% of women **[21]**. HCQ, an immunomodulatory drug, has been studied in the lab and found to lower the risk of thrombosis, assist in placentation, and lessen the harmful effects of aPL **[22]**. Because pregnant women with APS lose pregnancies over and over again, and the condition doesn't respond to standard treatment with LDA and prophylactic LMWH, this study looked at how well adding HCQ to standard treatment would affect pregnancy outcomes.

Our study revealed that regarding obstetric outcome, the main finding of current study that gestational age at delivery was statistically significant higher among hydroxychloroquine group 33.1±5.5 vs. 24.8±7.5 weeks with higher live birth rate and lower percent of fetal loss; 34.0±3.1 vs. 32.5±4.0 and 22.8±2.3 vs. 24.2±5.4 respectively. Also, bleeding or thrombotic events were statistically significant lower among hydroxychloroquine group 4 (8%) vs. 10 (20.0%) respectively. Additionally, during pregnancy and postpartum maternal thrombotic events were 3 (6.0%) vs. 5 (10.0%) and 1 (2.0%) vs. 7 (14.0%) respectively. Additionally neonatal outcomes were better; neonatal birth weight and Apgar score ≥ 7.0 were statistically significant higher among hydroxychloroquine group; 2.600±0.611 vs. 2.125±0.215 gram and 27(54.0%) vs. 10(20.0%) respectively. also, need for NICU admission was lower among Hydroxychloroquine group; 3(6.0%) vs. 16(32.0%). Finally, postnatal maternal mortality rates were lower among hydroxychloroquine group; 20(40%) vs. 34(68%). On the other hand, no differences were noted between study groups regarding maternal age, BMI, number of previous abortions, serum antiphosphospholipid markers, mode of delivery and maternal post-delivery hospital stay.

In line with our findings, **Hooper** et al. **[11]** discovered that taking HCQ with aspirin and heparin greatly decreased the number of problems mothers had during pregnancy that were caused by aPL in people who had APS. Their incidence of miscarriage was lower than average. When compared to previous obstetrical outcomes, two case studies showed that HCQ was beneficial. In a recent study, **Gerde et al. [23]** examined an Argentine retrospective single-center cohort. The study compared the results of 31 patients (32 pregnancies) receiving standard treatment alone with those of 56 patients (69 pregnancies) who received HCQ medication in addition to conventional therapy for refractory primary APS. Previous pregnancies involving HCQ-treated women were more likely to have had catastrophic obstetrical outcomes, even after receiving standard medical care. A live birth rate of 97.1% (67/69) was achieved with HCQ in contrast to the standard care rate of 62.5% (20/32) in a study where people treated just with LDA and LMWH had a live birth rate of 62.5% (p <.001). In addition, the use of HCQ medicine significantly decreased the occurrence of pregnancy complications, going from 37.5% (12/32) to 8.7% (6/69) (p <.001). **Gerde et al. [23]**looked at HCQ for primary refractory obstetrical APS and found that it increased the number of live births and decreased the number of pregnancy complications compared to the gold standard treatment, which includes LDA and LMWH. **Another study** , also found that HCQ had a somewhat longer half-life and eliminated over a period of 40 to 60 days, supported our results. The extensive tissue sequestration causes the immunomodulatory therapy advantages to take several weeks, if not months, to become apparent **[24]**. **Skorpen** et al. **[25]** found that giving HCQ to women before they get pregnant, during pregnancy, and while they are breastfeeding is safe. According to **Schrezenmeier and Dörner [26]**, the majority of patients take HCQ treatment well; nonetheless, the most common side effect was gastrointestinal distress, which includes nausea, vomiting, and diarrhea. Myopathy and retinopathy caused by HCQ are, however, more serious outcomes. Higher dosages and longer durations of medicine are associated with an increased risk of retinopathy **[27]**. Never exceed 5 mg/kg of actual body weight as a dose. A total of four retrospective observational studies have shown that HCQ increased the rate of live births and decreased the incidence of unfavorable neonatal outcomes **[28- 31]**.

While earlier observational studies only included women who tested positive for conventional aPL, our investigation relied more on clinical than laboratory criteria when selecting study patients in order to weed out erroneous negative results for conventional aPL (seronegative APS). Following their inclusion in the trial, the individuals were instructed to conduct traditional aPL twice, separated by 12 weeks (aCL, anti-β2GP1, LA). 42.5% of study cases had positive aPL, according to the study's results, and the remaining 57.5% were regarded as seronegative for conventional aPL. Seronegative APS is a new entity that has been around since 2003, as the present RCT has shown. While seronegative APS patients lack aß2GP1, aCL, or LA, they still exhibit a number of clinical traits that are consistent with classical APS, including positive non-criteria aPL **[32].** The primary objective of **Zhou et al. [33]**, a retrospective observational cohort carried out in a single Chinese

facility, is to examine patient data pertaining to obstetric APS from 2000 to 2017. In their cohort of 450 pregnancies, 180 individuals with obstetric APS were included; of them, 66 were exposed to HCQ and 26 were not. Forty of the pregnancies exposed to HCQ had recorded pregnancy outcomes; however, the HCQ dose and whether or not the HCQ addition was protocolized were not specified. However, it was reported that their population used a variety of drugs, including LMWH, glucocorticoids, IVIG, azathioprine, and corticosteroids. Thirty-seven patients experienced placental insufficiency or lost their pregnancies in the second or third trimester out of the sixty-six patients exposed to HCQ. Twenty of the 40 pregnancies that were not exposed to HCQ resulted in a live birth, but it was not possible to estimate how many of these pregnancies also had features of placental insufficiency or experienced a second or third trimester pregnancy loss; nevertheless, four patients in the non-exposed group and five patients in the exposed group experienced any pregnancy complications. After exposure to HCQ, no negative effects were noted**.**

Ruffatti et al. [29]did retrospective observational multicenter cohort research in Europe using data gathered from 20 sites in the European Forum of Antiphospholipid Antibodies network from 1999 to 2006. The study included 194 patients. There were a total of 194 individuals; 94 (or 83% of the total) were able to have a live birth after receiving HCQ. Five percent of the women given 200 mg of HCQ and one percent given 400 mg had miscarriages before 10 weeks of pregnancy, and another five percent lost their pregnancies in the second or third trimester. There was no mention of how many HCQ patients had symptoms of placental insufficiency. According to **Ruffatti et al. [29],** forty pregnant patients, or 35% of the total, who were exposed to HCQ, and thirty-one patients, or 38% of the total, who were not exposed, reported experiencing some form of difficulty. Unfortunately, previous studies that looked back at this issue used different approaches and had smaller sample sizes **[28-31]**. There is a lack of forward-looking information and evident limitations in the current data. The fact that patients received HCQ for a specific reason makes these retrospective cohort studies highly susceptible to bias. In three trials, the majority of patients received HCQ as a treatment for a concomitant mixed connective tissue disorder, the most common of which was systemic lupus erythematosus (SLE). The studies did not employ propensity score matching to account for treatment-indication confounding. Utilizing data from a single-center retrospective observational cohort in the UK, the third study evaluated pregnancy outcomes in aPL-positive women who were given the HCQ. Out of the 170 documented pregnancies, 51 underwent HCQ exposure, while 119 served as controls. 34 (or 67%) of the pregnancies exposed to HCQ and 60 (or 50%) of the pregnancies not exposed resulted in a live birth. **Sciascia et al. [30]**reported that, 20 patients (42% exposed to HCQ) and 75 individuals (63% not exposed) in this cohort experienced pregnancy-related complications. **Mekinian et al. [31]** published the results of a retrospective single-center cohort study in France, which included 30 women diagnosed with aPL or APS and treated with HCQ. **Mekinian et al. [31]** gave HCQ to twenty pregnancies, but not to the other twenty-five. The sixteen pregnancies exposed to HCQ (20%) yielded twelve live births, while the twenty-three pregnancies not exposed to HCQ (92%), yielded twenty-three live births. It was difficult to extract data on specific pregnancy outcomes. Through a comprehensive review and meta-analysis of four prior investigations, researchers were able to identify medium-quality retrospective observational studies, including 214 aPL-positive women. Of these, 250 had pregnancies exposed to HCQ and 521 did not. Extractable data on live birth outcomes corroborated a meta-analysis that found a medium level of evidence for a non-significant influence on live births (OR 1.33; 95% CI 0.62-2.85). Our meta-analysis made use of data from three out of four studies that looked at the effects of pregnancy problems caused by aPL. Three randomized controlled trials with medium-quality follow-up data found no statistically significant difference between the two groups (OR0.66; 95% CI 0.32-1.38). **Frishman** et al. **[34]** conducted research in 2020. The results of this meta-analysis showed that HCQ had a low risk of adverse effects in pregnant women. However, the current evidence remains inconsistent, leaving the question of whether this medication could be beneficial during pregnancy for women with aPL (or certain subgroups thereof) unanswered. Research by **Abisror** et al. **[35]** has shown that using just LDA and LMWH during obstetric APS might have negative effects on the health of the developing baby. The most common causes of neonatal complications includes being born prematurely, having a baby that is undersized for their gestational age, infections, and other related difficulties. **Mekinian** et al. **[36]** found that out of 39 pregnancies in which mothers had primary obstetrical APS, 22% resulted in premature birth, 19% had infants weighing less than 2500 g, and 5% experienced early neonatal complications, despite the mothers receiving LDA and LMWH. **Ruffatti et al. [29]** demonstrated similar rates of infant complications. The European registry of 133 APS mothers receiving the usual APS therapy confirmed the persistently high prevalence of preterm and small-for-gestational-age children **[37]**. In the retrospective observational cohort study **[30]**, HCQ slightly reduced the occurrence of preterm births (P = 0.06) and increased the total duration of gestation (P = 0.034). Afterwards, **Ruffatti** et al. **[29]** looked at the outcomes of other therapies in addition to standard therapy in high-risk primary antiphospholipid syndrome patients to determine the most effective treatment regimen. The researcher found that those who were given HCQ had a significantly later average gestational age than those who were treated with plasma exchange alone ($p < 0.001$). Premature vaginal birth was more common in the HCQ group (37.3% vs. 14.3%; P = 0.01), according to a retrospective observational cohort study **[30]**.

5. CONCLUSION

According to our findings, HCQ has the potential to improve obstetrical outcomes for individuals suffering from obstetrical APS. Although HCQ has shown effectiveness in improving live birth rates, decreasing pregnancy loss, and alleviating issues

with both mothers and newborns, the results of future research are vital in confirming these findings. We need randomized controlled studies that test how well HCQ works as a treatment for refractory APS and make sure that all patients meet the same criteria. Only then can we give more specific advice on how to care for this particular group of patients. Our present study has the potential to shed light on the topic and pave the way for future prospective studies with larger samples to reassess our findings.

REFERENCES

[1] Rudra A, Chatterjee S, Sengupta S, Wankhede R, Nandi B, Maitra G, Mitra J. Management of obstetric hemorrhage. Middle East J Anaesthesiol 2010;20:499-507.