

# IS Hydroxychloroquine having Arole for Prevention of Unexplained Recurrent Miscarriage?

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## ABSTRACT

**Background:** Recurrent miscarriage (RM) impacts 1%–2% of fertile couples and is characterized by 3 or more consecutive miscarriages during the 1st trimester of gestation. It's a prevalent reproductive burden on public health, producing both emotional and physical anguish. There is no therapy that has been proven to be beneficial to date.

**Aim of the work:** To determine whether hydroxychloroquine (given orally prior to conception and for the first ten weeks of pregnancy) could increase the live birth rate by 15% or more in women with a prior RM.

**Patients and methods:** We conducted a double-blind, randomized, placebo-controlled study on 300 female participants suffering from recurrent miscarriages. At randomization, the minimization approach will be utilized to balance the two groups and two major predictors of miscarriage recurrence: mother age ( $\leq 35$  or  $> 35$  years) and the number of prior miscarriages (3 or  $\geq 4$ ).

**Results:** The current study showed that 30% of study female patients completed their pregnancy after taking hydroxychloroquine (HCQ), while 70% of them did not complete the pregnancy. The difference in mean age between cases and controls was statistically significant ( $P = 0.001$ ).

**Conclusion:** We obtained some significant positive results regarding the orally administrated HCQ usage to increase the live birth rate in women suffering from recurrent miscarriages.

**Keywords:** Recurrent miscarriage; Hydroxychloroquine; Pregnancy outcome.

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## INTRODUCTION

Recurrent miscarriage (RM) impacts 1%–2% of fertile couples and is characterized by 3 or more consecutive miscarriages during the 1st trimester of gestation. In around half of the cases, standard examinations uncover no obvious reason.<sup>1</sup>

There is currently no therapy whose effectiveness has been clearly demonstrated, even in the context of well-known risk variables for RM.<sup>2</sup>

In about 10%–15% of conceptions, a sporadic abortion is clinically observed. Usually, fetal growth ceases before the age of ten weeks. Aside from the discovery of a fatal chromosomal defect in pregnancy products.<sup>3</sup>

In 1955, HCQ, a quinacrine-derived molecule, was first employed as an antimalarial drug. Soon after, HCQ was widely applied as an anti-inflammatory as well as immunomodulatory drug at dosages ranging from 200–400 mg/day for the therapy of autoimmune illnesses like systemic erythematous lupus (SLE) and rheumatoid arthritis (RA). Prior to the routine usage of LMWH, HCQ was briefly utilized as a

thromboembolic prophylactic drug following total hip replacement in certain centers in the 1970s at a higher dosage (600–1200 mg/day).<sup>4</sup>

HCQ is a molecule with a long track record of safety in pregnant women. HCQ's pharmacological characteristics (antithrombotic, vascular protecting, immunomodulatory, enhanced glucose tolerance, lipid reducing, and anti-infective, for example).<sup>3</sup>

## PATIENTS AND METHODS

### Study design

This is a prospective, double-blind, randomized, 1:1 placebo-controlled trial on 300 patients (containing 2 parallel groups [HCQ 400 mg or placebo]). The minimization approach would be used at randomization to balance the two groups and two primary predictors of miscarriage recurrence: mother age ( $\leq 37$ ) and number of prior miscarriages ( $\geq 3$ ), with an upper limit of 8 months for giving hydroxychloroquine, if not get pregnant, we stop giving hydroxychloroquine.

### Place of the study

Sayed Galal University Hospital.

### Period of the study

2 years at Sayed Galal University Hospital from January 2020 to December 2021.

### Population

The study participants are made up of women who are trying to conceive and have suffered at least 3 consecutive losses during the first trimester of their pregnancy (normal parental karyotypes and no abnormalities in the uterine cavity that could explain the miscarriages). All obstetricians as well as internal medicine practitioners operating in the catchment region of every participating center were notified about the hydroxychloroquine trial via medical meetings, emails, and letters. All of them are urged to refer possibly eligible women to the study's screening unit. Every center ensures patient recruitment by utilizing existing settings like specialist RM consults and other OBS/GYN patient treatment units. Additionally, as part of this recruitment technique, posters are placed in consultation waiting rooms to reach out to additional patients.

### Intervention

The medical examiner evaluates the inclusion and exclusion criteria of nearly 1,000 eligible women during the inclusion visit. 300 women only were finally concluded and divided into 2 groups by randomization system (envelops) and listed by serial numbers and telephone numbers on computer data

**Group A:** 150 women were given Hydroxychloroquine 400mg daily and up to 8 months.

**Group B:** 150 women were given placebo.

All women informed to communicate with us by telephone number for follow up or if get pregnant within 8 months. Follow up persisted till the end of pregnancy by their serial number.

### Inclusion criteria

Females between the ages of 18 and 37 years old.

Women who are trying to conceive a child.

Women who have had at least 3 prior consecutive losses of unclear aetiology in the 1st trimester of gestation, described as

Parental karyotypes that are normal.

There are no uterine cavity abnormalities that could explain the RM (hystero-graphy, hysteroscopy, or ultrasound scan).

No prior thrombotic or obstetrical incident described in APS, with the exception of RM in the first trimester if APL antibodies are persistently positive according to Myakis' biological criteria.

Women who gave written consent.

### Exclusion criteria

An ongoing pregnancy.

Since the previous miscarriage, a normal pregnancy (living and viable delivery) has occurred.

A uterine cavity anomaly, which could explain RM during the first trimester.

APS defined as both

Persistently positive APL antibodies: titers of lupus anticoagulant and/or APL (anticardiolipin or anti-beta2 GPI, IgG or IgM) greater than the 99th percentile or greater than 40 with a 12-week interval between two positive findings (persistent antibodies).

A particular clinical setting of APS based on the Myakis criteria (thrombotic or obstetrical, excluding RM in the 1st trimester of gestation).

Recognized uncommon lactose metabolic disorder (excipient) or known HCQ contraindications (hypersensitivity to chloroquine or HCQ, retinopathy, G6PD deficient, severe intermittent porphyria, chronic hepatic or renal failure, widespread cutaneous psoriasis not managed by local therapy, significant chronic digestive or hematological illness).

A history of epilepsy or psychotic diseases in the past.

Impossible to follow-up.

**Sampling Method:** Convenient sample.

**Sample Size:** 300 women with unexplained recurrent miscarriage.

This number of cases was adopted by using Medcalc 19 program by setting alpha error of 5%, 95% confidence level and 80% power sample.

### Sample size justification:

The sample size for this study was calculated from the prevalence of the live birth rate in cases taking HCQ (67%), according to a prior study by **Sciascia et al., 2016**. Equations are described in **Plantone and Koudriavtseva (2018)**.

The sample size is computed according to the following formula:

$$n = P \left( 1 - P \right) \left( \frac{Z}{E} \right)^2$$

**Z** = 1.96 (The critical value that separates the Z distribution's central 95% from the tail's 5%).

**P:** prevalence of live birth rate in cases taking HCQ, according to prior study of **Sciascia et al., 2016**. (=67%)

**E:** The desired margin of error (alpha error =0.05)

$$n = 0.67 \times 0.33 \times 1536.64 = 339.75$$

Sample size before correction is **340** cases.

### Correction of sample size

Correction of this size for finite population by the following formula:

**Sample size for finite population** =  $n / [1 + \{(n - 1)/Pop\}]$

**Where,**

**n:**calculated sample size for infinite population (=340)

**Pop:** finite population, considering it nearly 2600 cases according to registered data of average yearly flow of the outpatient clinic.

**Sample size** =  $340 / 1 + \{339/2600\}$

$$= 340/1.13$$

$$= 300.88$$

### Statistical Analysis

The Statistical Package for Social Sciences (SPSS) version 21 was used to sort and analyze the data.

Numbers and percentages were used to describe qualitative data in this research.

To present quantitative data, the mean, standard deviation (SD), and range have been used.

Categorical variables were analyzed and compared using the Chi-square test.

Multivariate analysis (Binary Logistic regression) was employed for multiple risk factor analysis.

The significant level has been set at  $P < 0.05$ .

## RESULTS

This study is a randomized, placebo-controlled, double-blind study. It included 300 women who were trying to get pregnant and had suffered at least three miscarriages in the first trimester.

The patients in the study have been split into two groups:

Group I: 150 patients who received hydroxychloroquine.

Group II: 150 controls who received placebo only did not receive hydroxychloroquine.

n=300			
<b>Age</b>			
Mean± S.D.	29.09	±	5.20
Range	19	-	42
Median			29

**Table 1:** shows that the average age of the study participants was  $20.09 \pm 5.20$  years.

n=300		
<b>Gravidity</b>	N	%
4	36	12.0
5	84	28.0
6	52	17.3
7	56	18.7
8	32	10.7
> 8	40	13.3
<b>Parity</b>		
0	108	36.0
1	136	45.3
2	40	13.3
3	16	5.3
<b>Number of miscarriages</b>		
3	80	26.7
4	96	32.0
5	64	21.3
6	28	9.3
> 6	32	10.7

**Table 2:** shows the obstetric history of the study patients. Regarding gravidity, 28.0% of the patients were gravida five, 17.3% were gravida six, and 18.7% were gravida seven. Regarding parity, 45.3% were para one, and 36.0% were para zero. As for number of miscarriages, 32.0%, 26.7%, and 21.3% had four, three, and five miscarriages, respectively.

n=300		
<b>APS antibodies</b>	N	%
Yes	74	24.7
No	226	75.3
<b>Anatomical insult</b>		
No	300	100.0

**Table 3:** shows that 24.7% of the patients had positive APS antibodies and 100% didn't have anatomical insult that may explain the recurrent miscarriages.

n=300		
<b>Cases</b>	N	%
Hydroxychloroquine	150	100.0
<b>Controls</b>		
No	118	78.7
Clexane	32	21.3

**Table 4:** shows that 21.3% of the control patients were on clexane therapy during the study.

n=300		
<b>Completing pregnancy</b>	N	%
Yes	90	30.0
No	210	70.0
<b>Post-natal</b>		
NAD	300	100.0

**Table 5:** shows that 30.0% of all study patients completed their pregnancy while 70.0% did not complete it. Comparison of the cases and controls:

	Cases (n=150)		Controls (n=150)		T	P
<b>Age</b>						
Mean± S.D.	30.64	± 4.47	27.51	± 5.39		
Range	20	- 41	19	- 42		

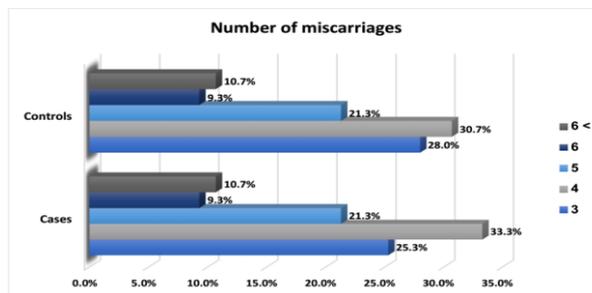
*t: Independent samples t-test \*: Statistically Significant*

**Table 6:** demonstrates that the average age was 30.64±4.47 years for cases and 27.51±5.39 years for controls. At a p value of 0.001, the difference between them was statistically significant.

	Cases (n=150)		Controls (n=150)		χ <sup>2</sup>	P
	N	%	N	%		
<b>Gravidity</b>						
4	18	12.0	18	12.0		
5	42	28.0	42	28.0		
6	26	17.3	26	17.3		
7	28	18.7	28	18.7		
8	16	10.7	16	10.7		
> 8	20	13.3	20	13.3		
<b>Parity</b>						
0	54	36.0%	54	36.0%		
1	68	45.3%	68	45.3%		
2	20	13.3%	20	13.3%		
3	8	5.3%	8	5.3%		
<b>Number of miscarriages</b>						
3	38	25.3%	42	28.0%		
4	50	33.3%	46	30.7%		
5	32	21.3%	32	21.3%		
6	14	9.3%	14	9.3%		
> 6	16	10.7%	16	10.7%		

χ<sup>2</sup>: Chi-square test

**Table 7:** shows that both study groups had equal percentages regarding gravidity and parity. At a p value of 0.985, the association between the number of miscarriages was statistically insignificant.



**Fig. 1:** Number of miscarriages among study groups

	Cases (n=150)		Controls (n=150)		χ <sup>2</sup>	P
	N	%	N	%		
<b>APS antibodies</b>						
Yes	42	28.0%	32	21.3%		
No	108	72.0%	118	78.7%		
<b>Completing pregnancy</b>						
Yes	27	18.0%	30	20.0%		
No	123	82.0%	120	80.0%		

*\*: statistically significant χ<sup>2</sup>: Chi-square test*

**Table 8:** shows that 28.0% of cases and 21.3% of controls had APS antibodies, and the association between them was statistically insignificant at p values of 0.180.

Regarding outcome, 18.0% of cases completed their pregnancy while 82.0% did not complete it. For controls, 20.0% of them completed their pregnancy while 80.0% did not complete it. The association between them was not statistically significant at p values of 0.659.

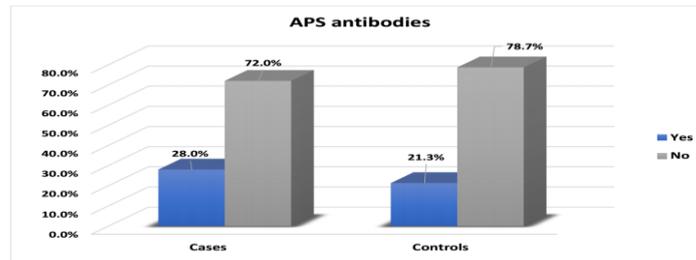


Fig. 2: APS antibodies among study groups

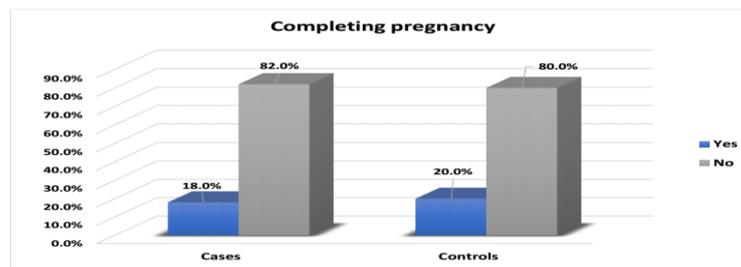


Fig. 3: Percentages of pregnancy completion among study groups

## DISCUSSION

Two or more clinical pregnancy miscarriages (verified by ultrasound or histopathologic investigation) are defined as recurrent miscarriages, but they do not have to be consecutive.<sup>5</sup>

Recurrent miscarriage affect around 1% of couples, it became important to address such problems properly and try to find a significant intervention. It is considered as a frustrating condition for both physicians and patients as well. In spite of extensive testing, at least half of the couples do not have a definite underlying disease.<sup>6</sup>

We conducted a double-blind, randomized, placebo-controlled study on 300 female subjects suffering from recurrent miscarriages. At randomization, the minimization approach will be utilized to balance the two groups and two major predictors of miscarriage recurrence: mother age ( $\leq 35$  or  $>35$  years) and the number of prior miscarriages (3 or  $\geq 4$ ).

In our research, we applied 300 female patients to the trial. Regarding some of their demographics, those females are trying to get pregnant, and they've had at least 3 losses in their first trimester. Their ages range between 19 and 42 years old, with an average of 29.09 5.2 years. 28.0% of the patients were gravida-five, 17.3% were gravida-six, and 18.7% were gravida-seven. In terms of parity, 45.3% were para-one, and 36.0% were para zero. 26.7% had three miscarriages, 32.0% had four miscarriages, and 21.3% had five miscarriages. 24.7% of the patients had positive APL antibodies, and 100% had anatomical insults that may explain the recurrent miscarriages. Regarding Clexane usage by the studied participants, 21.3% of the control patients were on Clexane therapy during the study period.

The current research showed that 30% of study female patients completed their pregnancy after taking hydroxychloroquine (HCQ), while 70% of them did not complete the pregnancy. Between cases

and controls, we found a statistically significant difference in mean age ( $P = 0.001$ ). However, no statistically significant difference existed between the two groups in terms of obstetric history, including gravidity, parity, and the number of miscarriages, having P- values of 0.1, 0.1, and 0.985, respectively. The frequency of miscarriages was at its highest level, with four miscarriages between either cases or the control group. Also, there had been no significant difference regarding the APL antibodies, with a P-value of 0.18. On the other hand, the study showed a statistically significant difference regarding the pregnancy completion rate, having a P-value of 0.001 favoring the hydroxychloroquine intervention.

In the result of pregnancy completion rate, our results showed significant positive results favoring the hydroxychloroquine intervention over the control group. Some studies demonstrated similar results as Kravvariti et al. and Costedoat-Chalumeau et al.<sup>7&8</sup>

They reported that HCQ is also being studied and tested as a possible adjunctive therapy for refractory obstetric antiphospholipid syndrome (APS) during gestation by Costedoat-Chalumeau et al. and Kravvariti et al. as they reported similar results to ours regarding the pregnancy completion rate.

A propensity-score matching retrospective chart review study conducted prior to our trial produced similar results to ours. They reported that HCQ-exposed patients who took PAPS had a lower yearly rate of recurrent thrombosis than non-HCQ user.<sup>9</sup>

Due to HCQ's immune-modulatory characteristics, this finding could be interpreted. Moreover, HCQ has been shown to limit antigen presentation, and its immunomodulatory effects are owing to its antigen processing interference. In vitro, HCQ seems to modify antigen processing via raising the pH of intracellular vacuoles, causing the invariant chain to separate from MHC class II molecules and inhibit antigen-binding.<sup>10</sup>

A previous trial was done by Abd Rahman et al.<sup>11</sup> Our results agree with their finding regarding mean birth weight. According to Abd Rahman et al., the HCQ group had a significantly longer pregnancy (36.74 compared to 34.79,  $P = 0.001$ ), which resulted in a significantly bigger mean birthweight (2.52 compared to 2.13,  $P = 0.02$ ).

The analysis of our trial revealed a significant association between both groups regarding the age and the effectiveness of the treatment; however, according to Rahman et al.<sup>11</sup> They demonstrated no significant effect regarding the mean age of both groups (32.03 versus 31.5,  $P = 0.82$ ). The interpretation of these results is that the probability of miscarriage is low in women aged 25–29 (10%) and quickly increases following age 30, hitting 53% in women aged 45 and above.<sup>12</sup>

In terms of gravidity frequency and HCQ, the analysis revealed no significant differences between the case and control groups. According to a recent trial conducted by Schreiber et al.<sup>13</sup>, approximately 70% of pregnant women with APL/APS will have a viable baby. They suggested that HCQ has a positive influence on women with APL since it was linked to a greater incidence of live births (67 versus 57%,  $P = 0.05$ ) and a reduced incidence of APL-related pregnancy illness.<sup>14&15</sup>

There has been no significant difference in the parity outcome between the case and control groups. This result was similar to Rahman et al.<sup>15</sup> Regarding the number of miscarriages, we agree with Rahman et al. 2020. Recurrent miscarriages were significantly more common ( $P = 0.003$ ) in non-hydroxychloroquine patients. However, there have been no statistically significant differences in the number of miscarriages between the two groups ( $P = 0.985$ ).

In this retrospective cohort conducted by Nuri et al.<sup>9</sup>, they studied APL levels at the beginning and end of the follow-up and found no significant differences had been noted in the HCQ-group. We found the same insignificant findings with a  $P$ -value of 0.180.

Finally, in the antiphospholipid (APL) syndrome, the clinical advantage of HCQ has been proposed in the avoidance of thrombotic and late obstetric complications by Prevention of systemic inflammation and oxidative stress by; Inhibition of TLR9 overactivated in decidua. And Inhibition of peptide MHC and proinflammatory cytokines.

Prevention of maternal endothelial dysfunction and of hypercoagulability state by; Inhibition of endothelin1 secretion and VCAM1 expression and act as antiplatelet effect and by Inhibition of aPL-B2GPI complexes binding to phospholipid bilayers in trophoblast and contracting aPL action on annexin5.

In the presence of APL antibodies, no evidence of HCQ's benefits in RM has been reported.<sup>16</sup>

## CONCLUSION

Orally administrated HCQ usage can improve the live birth in women suffering from recurrent miscarriages. In individuals having systemic lupus

erythematosus, it's been suggested that HCQ can help lower APL antibody titers and prevent thrombotic recurrences.

Conflict of interest : none

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