Original Article

Hydroxychloroquine For Improvement Of Pregnancy Outcome In Unexplained Recurrent Miscarriage: A Randomized Controlled Trial

Mostafa Ibrahim, Abdelrahman M. Mohammed, Mohamed M. F. Fathalla, Mohamed A. Youssef, Safwat A. Salman, Seif Ali

Department of Obstetrics and Gynecology,Women Health Hospital, Faculty of Medicine, Assiut University, Egypt.

ABSTRACT

Background: Recurrent miscarriage (RM) is unexplained in about 50% of cases. We evaluate the efficacy of hydroxychloroquine in improving ongoing pregnancy rate at 20 weeks' gestation in women diagnosed with unexplained recurrent miscarriage.

Methods: This is a randomized controlled trial, prospectively registered on ClinicalTrials.gov (NCT04228263).It was conducted at outpatient clinic, Women's Health Hospital (WHH), Assiut University, Egypt from January 1, 2020, to July 8, 2023. Eligibleparticipants were prospectively randomized to either Group I (*n*= 78) received 200 mg of oral HCQ twice daily, alongside folic acid supplementation or Group II (*n*= 78) received folic acid alone.Low-dose aspirin (75mg)was started upon confirmed pregnancy in both groups.

Results: The Ongoing pregnancy rate at 20 weeks gestation consistently trended higherin Group I (HCQ) *n*= 53/78(67.9%) than those in Group II (control) *n*= 45/78(57.7%). Analysis of ongoing pregnancies at 20 weeks found that the absolute risk reduction (ARR) was 10.3% (CI= -4.83%, 25.34%) so the number needed to treat (NNT) was 10.There was no statistical difference between both study groups regarding live birth rate, neonatal outcomes and pregnancy complications (FGR, preeclampsia, preterm delivery).

Conclusion: HCQ did not significantly enhance the ongoing pregnancy rate at 20 weeks gestation and had no effect on the risk of preeclampsia, FGR and preterm birth in women with unexplained recurrent miscarriage. HCQ appears to be safe to the fetus with few maternal side effects to mothers.

Key Words: Hydroxychloroquine; recurrent miscarriage: unexplained recurrent miscarriages; randomized controlled trial.

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Corresponding Author: Mostafa Ibrahim, MD, Department of Obstetrics and Gynecology, Women Health Hospital, Faculty of Medicine, Assiut University, Egypt. **Tel.:** + 201021216060, **E-mail:** m_nasr6206@aun.edu.eg

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INTRODUCTION

Recurrent Miscarriage (RM) is defined by the American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE), this condition entails the loss of two or more consecutive pregnancies prior to fetal viability, irrespective of prior live births[1,2]. RM approximately affects 1–5% of women within the reproductive age group[3]. While multiple causes are contributed to recurrent miscarriage, the underlying etiology remains unknown in 50-70% of cases[4]. Different therapeutic options were used in management of URM including low dose aspirin, LMWH, Progesterone supplementation, IVIG, corticosteroids and GCSF, but no treatment was found to be definitely effective[5].

Recent basic research suggested that disruptions in the intricate maternal immune tolerance towards the semi-allogeneic fetus might play animportant role in URM[6,7]. Many abnormal immune responses are contributed to URM including TNF overproduction, low levels of immunosuppressive T regulatory cells, elevated levels of natural killer cells and the presence of autoantibodies[8,9]. This strong evidence thatexplain the rationale of immunomodulatory therapies as a promising strategy for URM treatment[6].

Hydroxychloroquine (HCQ), an immunomodulatory agent, has demonstrated potential in enhancing placental function and improving pregnancy outcomes when

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employed to manage systemic lupus erythematosus and antiphospholipid syndrome (APS)[10,11]. It may exerts its effects through dampening Th17 cell differentiation and promotion of TH2 immune response[12,13]. Few studies addresses the role of HCQ in URM but were either of limited sample size or suffered from methodological limitations[14,15].

Therefore, the current study was conductedto evaluate the efficacy of HCQ in enhancing the ongoing pregnancy rate at 20 weeks' gestation in women diagnosed with URM. Also, the study aimed to assess the adverse effect of HCQ and the effect of HCQ on live birth rate, preeclampsia, FGR and neonatal outcomes.

PATIENTS AND METHODS

Thissingle-center, open-label, parallel-randomized controlled trial was conducted at the Women's Health Hospital (WHH), Assiut University, Egypt from January 1, 2020, to July 8, 2023 after approval by the Assiut Medical School Review Board (IRB: 17200427) and registration with clinicaltrials.gov (NCT04228263).

Our study enrolled women who met the following inclusion criteria: (1) age between 20 and 40 years; (2) Body Mass Index (BMI) within the range of 18.5-35kg/m^2; (3) documented history of at least two prior spontaneous miscarriages before 20 weeks' gestation; (4) expressed desire to conceive; (5) written informed consent to participate. The exclusion criteria included those already pregnant, women had uterineabnormalities, thyroid abnormalities, diabetes mellitus, polycystic ovary syndrome,, history of chromosomal or genetic abnormalities or positive serological test for antiphospholipid antibody syndrome(Lupus anticoagulant, Anticardiolipin IgM, IgG and Anti-B2glycoprotein), women already receiving HCQtreatment for conditions such as rheumatoid arthritis, lupus erythematosus,women had contraindications to HCQ therapy, including retinopathy, hypersensitivity to chloroquine or HCQ, G6PD deficiency, chronic liver or kidney insufficiency, heart block, significant chronic digestive or hematologic disease[16] and women who failed to achieve pregnancy within 12 months of HCQ administration.

Randomization:

Eligible women were randomly assigned in equal proportions to either the HCQ group (Group I) or control group (Group II). Blocked randomization was employed using a web-based random number generator accessible through https://www.sealedenvelope.com. Upon confirmation of eligibility and securing written informed consent, participants were allocated to their respective groups. All participants were informed of their group assignment (study or control). Once randomized, group allocation remained irreversible.

Intervention:

The women who accepted to participate were entered in a screening phase of the study after the signed informed consent. This phase included (1) History taking (including detailed obstetric history and exclude history of genetic and chromosomal abnormalities). (2) Clinical examination included body mass index (BMI). (3) 2D Ultrasound to exclude PCOS and adenomyosis.(4) Evaluation of uterine cavity by Hysterosalpingiography (HSG), hysteroscopy or 3D ultrasound.(5)Laboratory investigations (Lupus anticoagulant, Anticardiolipin IgM, IgG and Anti-B2glycoprotein, Hemoglobin A1C, Serum TSH and Serum Prolactin).

Eligible patients were prospectively assigned to one of two pre-conception treatment regimens. Group I received 200mg of oral HCQ twice daily alongside folic acid (5mg). The dose was used in previous research of HCQ in pregnancy[14]. Group II received folic acid (5mg) only. Low-dose aspirin (75mg) was started upon confirmation of pregnancy in both groups. HCQ and folic acid administration was discontinued at 12 weeks' gestation (end of the first trimester where most unexplained recurrent miscarriages take place), while low-dose aspirin continued until 36 weeks gestations.

Follow-up:

Prior to conception, eligible patients participated for ovulation monitoring to enhance their probability of achieving pregnancy. Upon confirmation of pregnancy, both groups were followed up as the following. At 6 weeks' gestation, a transvaginal scan utilizing the Mindray DC-30HD system assessed fetal viability. Five subsequent transabdominal scans were conducted at key gestational intervals (approximately 12, 20, 28, 32, and 37 weeks), confirming fetal viability, screening for potential congenital malformations, and monitoring for any pregnancy complications or therapy side effects. During each clinic visit, thorough clinical examinations ensured both fetal well-being and maternal health by assessing for complications and potential therapy-related adverse events. Finally, upon delivery, detailed data were collected regarding gestational age, mode of delivery, birth weight, and any neonatal intensive care unit (NICU) admission requirements.

Outcomes:

This study assessed the HCQ's efficacy by monitoring a range of outcomes. Its primary outcome was ongoing pregnancy at 20 weeks' gestation. Secondly, we aimed to report pregnancy complications like fetal growth restriction (FGR), preeclampsia after 20 weeks. We also aimed to examine the prevalence of major congenital anomalies in newborns, the live birth rate, and the rate of preterm delivery before 37 weeks' gestation.

Sample size calculation using (Epi-info 7 Version 3 software). The ongoing pregnancy at 20 weeks' gestation in

women with URM was set to be the primary outcome of the study. An effect size of 25% increase from the 48% ongoing pregnancy rate in a previous study in a similar population of unexplained recurrent miscarriage[17]. justifies the use of a drug which may have potential side effects as HCQ. We used 95% confidence and 85% power cut-off limits. Accounting for a 10% anticipated drop-out rate, about 156 participants was determined as a target recruitment.

Statistical analysis:

Data were analyzed in SPSS 27. Normality was checked with Shapiro-Wilk. Continuous data were summarized as mean±SD or median±IQR using appropriate tests. Categorical data got frequencies (%) and Chi-square tests. Significance was set at $p<0.05$.Additionally we evaluated the effectiveness of the treatment by calculating metrics such, as experimental event rate (EER) control event rate (CER) relative risk, relative risk reduction (RRR) absolute risk reduction (ARR) and number needed to treat (NNT).

RESULTS

Among 342 counseled women, 186 were excluded (refusal: 80, endocrine abnormalities: 38, APS+: 36, uterine issues: 22, existing HCQ use: 10). The remaining 156, equally randomized to HCQ (*n*= 78) or control (*n*= 78) groups. Before 20 weeks gestations six women were lost to follow-up (3/group). One woman in group II was found to have ectopic pregnancy which was terminated .After 20 weeks and until delivery, 4 women lost follow-up, with one case in HCQ group and three cases in control group.

Baseline demographic characteristics were statistically homogenous between the two groups, as shown in Table (1). An assessment of pregnancy status at 20 and 37 weeks gestation, as well as live birth rate, revealed no statistical significant differences between the HCQ and control groups, regardless of the employed analytical approach (intention-to-treat or per-protocol) (Table 2). Analysis of ongoing pregnancies at 20 weeks found that Absolute risk reduction was 10.3 % so the number needed to treat (NNT) was 10. Furthermore Analysis of live birth rate found that Absolute risk reduction was 12.8 % so the number needed to treat (NNT) was 8 (Table 2).

In addition, our investigation revealed no statistical significant differences between the two groups regarding neonatal outcomes(preterm delivery, congenital anomalies, gestational age at delivery, mode of delivery, birth weight at delivery, or need for NICU admission). These findings are further detailed in Table (3).There were no significant differences in the rates of pregnancy complications between both groups. The rates of fetal growth restriction, preeclampsia, intrauterine fetal death and antepartum hemorrhage were all low and similar in both groups (Table 4).

Furthermore, participants in the HCQ group reported a higher rate of any side effects compared to the non-HCQ group. This difference, however, did not reach statistical significance. The most common side effect in the HCQ group was nausea or vomiting (6.4%), followed by headache (1.3%), itchy skin (1.3%), and facial flushing (1.3%). Notably, these side effects were less frequent or absent in the control group (Table 5).

Table 1: Comparison of patient characteristics between the two groups:

		Group		*P* value
		HCQ group *N*= 78	Control Group *N*= 78	
		N(%)	*N*(%)	
Age(years)	Mean±SD	27.33±5.03	27.68±5.22	0.669
BMI(Kg/m^2)	Mean±SD	24.62±3.20	25.23±3.19	0.239
No.of PreviousMiscarriage	Median(Q1-Q3)	3(2-4)	3(2-4)	0.705
No.ofPreviousMiscarriage	2	27(34.6%)	32(41%)	0.507
	3	24(30.8%)	20(25.6%)	
	4	16(20.5%)	11(14.1%)	
	≥5	11(14.1%)	15(19.2%)	
Parity	Nulliparous	44(56.4%)	41(52.6%)	0.630
	Multipara	34(43.6%)	37(47.4%)	
Paritycategories	Nulliparous	44(56.4%)	41(52.6%)	0.792
	1-2deliveries	23(29.5%)	23(29.5%)	
	>3deliveries	11(14.1%)	14(17.9%)	
History.Of.previousCS		22(28.2%)	23(29.5%)	0.860
No.of PreviousCS	1	12(15.4%)	15(19.2%)	
	2	7(9%)	6(7.7%)	
	≥3	3(3.8%)	2(2.6%)	
PreviousFGR		0(0%)	1(1.3%)	>0.999
Previouspreeclampsia		2(2.6%)	1(1.3%)	>0.999
PreviousCongenitalAnomalies		0(0%)	1(1.3%)	>0.999

Table 2: Comparison of the pregnancy statusat20weeks,37weeksgestation and live birth in the two groups:

	HCQ group	Control group	*P* value	95% CI
	n/*N*(%)	*n*/*N*(%)		
Intentionto treat				
Ongoingpregnancy20thweek	53/78(67.9%)	45/78(57.7%)	0.185	-4.83%, 25.34%
Ongoingpregnancy37thweek	48/78(61.5%)	39/78(50%)	0.147	-3.94%, 27.02%
Livebirthrate	51/78(65.4 %)	41/78(52.6 %)	0.104	-2.49%, 28.13%
Per-protocolanalysis				
Ongoingpregnancy20thweek	53/75(70.7%)	45/74(60.8%)	0.205	-5.31%, 25.02%
Ongoingpregnancy37thweek	48/74(64.9%)	39/71(54.9%)	0.222	-5.95%, 25.82%
Livebirthrate	51/74(68.9 %)	41/71(57.7 %)	0.163	-4.42%, 26.77%

Table 3: Comparison of the neonatal outcomes in the two groups:

		HCQ group	Control group	*P* value
		n(%)	*n*(%)	
Term		48/53*(90.6%)	39/45*(86.7%)	0.542
Preterm		3 /53*(5.7%)	2 /45*(4.4%)	>.999
Modedelivery	VD	15/53**(28.3%)	16/45**(35.5%)	0.442
	CS	37/53**(69.8%)	26/45**(57.8%)	0.215
Gestationalagedelivery	Mean±SD	38.46±2.25	38.32±1.6	0.749
Birthweight	Mean±SD	3124.51±448.23	3018.78±461.08	0.270
Apgarscore	<7	5/ 53*(5.4%)	3/45*(6.6%)	0.728
	>7	46/53*(86.8%)	38/45*(48.4%)	
NeedNICU		5/53*(9.8%)	3/45*(7.3%)	0.728
Presenceof Cong anomalies		1/53*(1.9%)	0/45*(0%)	>0.999

* Term, preterm, Apgar score: 1 Case lost to follow up and 1 case IUFD in HCQ group, 3 cases loss of follow up and 1 case IUFD in Non-HCQ group; **: Mode of delivery, 1 case lost to follow up HCQ group, 3 cases loss of follow up Non-HCQ group.

Table 4: Comparison of the secondary outcomes in the two groups:

	HCQ group	Control group	*P* value
	n/*N*(%)	*n*/*N*(%)	
Preeclampsia	1/53(1.9%)	2/45(4.4%)	0.592
IUFD	1/53(1.9%)	1/45(2.2%)	>0.999
FGR	1/53(1.9%)	3/45(6.7%)	0.331
Antepartumhemorrhage	1/53(1.9%)	0/45(0%)	>0.999

Table 5: Comparison of the side effects of interventions in the both study groups:

		HCQ Group	Control group	*P* value
		n/*N*(%)	*n*/*N*(%)	
Presence of side effects		7/78(9%)	2/78(2.6%)	0.167
Sideeffects	No	71(91%)	76(96.4%)	
	Nauseaorvomiting	5(6.4%)	1(1.3%	
	Headache	1(1.3%)	1(1.3%)	
	Itchyskin	1(1.3%)	0(0%)	
	Facialflushing	1(1.3%)	0(0%)	

DISCUSSION

The current study demonstrated a potential trend towards improved ongoing pregnancy rate at 20 weeks' gestation and live birth rates among women with URM receiving HCQ compared to those did not receive HCQ. However,the difference was not statistical significant. HCQ did not appear to significantly reduce the risk of preeclampsia, fetal growth restriction, preterm birth, or intrauterine fetal

deaths. Additionally, no statistically significant differences in neonatal outcomes were observed between the study groups. Notably, HCQ was well-tolerated, with no reports of serious maternal or fetal complications associated with its short-term use.

In addition, our analysis revealed no statistically significant difference in ongoing pregnancy rates at 20 weeks' gestation between the two groups. This finding aligns with previous studies[14,18-20] which reported no significant positive impact of HCQ on ongoing pregnancy rates at 20 or 24 weeks' gestation in various groups, including those with URM, antiphospholipid antibodies, SLE and IgA nephropathy.One study concluded that HCQ was recommended for unexplained recurrent miscarriage[21]. Thisstudyincluded different population from those included in our study and different treatment regimen was applied plus LDA and heparin in both groups[21].

Regarding live birth rate,our study observed a higher live birth rate in the HCQ group than control group but the difference did not reach statistical significance.These findings agreed withprevious studies[18-20] investigating HCQ use in women with autoimmune-related RM. A RCT of HCQ in URM claimed a significant improvement in live birth rate[15]. The study suffered from the following limitations, age discrepancy between groups and the inclusion of participants with positive APL antibodies and enoxaparin use in both groups. Hence, reliance on the results of this particular study would be imprudent in light of these concerns[15].

Regarding to neonatal outcomes, our study revealed no significant differences in neonatal outcomes between the two study groups, aligning with the findings of[20,22] who observed no improvement in neonatal outcomes among women with autoimmune disease taking HCQ. However, in contrasts to our study, previous trial reported positive neonatal impact of HCQ use during pregnancy in pateints with autoimmune diseases[18]. This study was retrospective included unmatched number of pateints between both groups.

Regarding to HCQ safety profile, our study revealed good tolerability of HCQ in the study population, with no serious side effects was reported. While seven patients in the HCQ group experienced mild side effects such as headache, vomiting, itchy skin, and facial flushing, only two experienced any side effects in the control group. Furthermore, our findings demonstrated no evidence of increased risk of fetal malformations associated with HCQ use. This aligns with existing literature, a study reported gastrointestinal issues in 7-37% and cutaneous manifestations in 5-25% of HCQ users, though these typically resolved over time[23]. Additionally, another study emphasized that serious consequences like cardiac and retinal toxicity associated with HCQ are exceptionally rare and necessitate higher doses (>5g/day) and longer durations of use (>5 years)[24].

Our study possessed several merits, including its robust randomized design, ensuring un-biased group allocation. Furthermore, we achieved our pre-calculated sample size, and notably, maintained a follow-up rate exceeding 90%. However, certain limitations warrant acknowledgement, including the high cost of a placebo medication precluded its inclusion, necessitating an open-label design. Additionally, pre-study chromosomal analysis of participants was not feasible, this may explained as ESHRE guidelines (2017), updated (2022), recommended parental karyotyping in recurrent miscarriage cases only with history of genetic or chromosomal abnormalities[25].Therefore karyotyping is not necessary for all women with recurrent miscarriage. Finally, although maternal and neonatal outcomes, as well as live birth rates, were monitored, the study design may be underpowered for definitive conclusions in these secondary outcome measures.

CONCLUSION

Our study involving women with URM revealed that HCQ administration during the pre-conceptional period and first 12 weeks of gestation did not demonstrably improve ongoing pregnancy rates at 20 weeks compared to the absence of treatment. In addition, our data suggest HCQ appears to be safe to the fetus with few maternal side effects to mothers and no apparent increase in the risk of congenital anomalies among newborns exposed to HCQ in utero.

Ethics approval and consent to participate:

The ethical approval was obtained from Assiut Medical School Review Board (IRB Code: 17200427).

Informed consent:

Eligible participants who agreed to participate in the study provided written informed consent.

Consent for publication:

Written informed consent for publication of anonymized data and study results was obtained from all participants.

Availability of data and materials:

In support of transparency and reproducibility, the datasets utilized and/or analyzed in this study are accessible upon reasonable request from the corresponding author.

CONFLICT OF INTERESTS

There is no conflict of interests.

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