RESEARCH
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HYDROXYCHLOROQUINE IS A POTENTIAL THERAPEUTIC OPTION FOR PREECLAMPSIA PREVENTION AMONG PREGNANT WOMEN WITH PREVIOUS PREECLAMPSIA: A PILOT RANDOMIZED CONTROLLED TRIAL

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Abstract

Objectives

Abnormal immune response towards the fetus, impaired early placentation, and maternal endothelial dysfunction are possible pathogenesis of preeclampsia. The study aim was to investigate the role of Hydroxychloroquine (HCQ) in preeclampsia prevention among pregnant women with previous history of preeclampsia.

Methods

This was a pilot open label randomized controlled trial, prospectively registered on Clinical Trials (NCT04755322). This study conducted at the Women's Health Hospital, Assiut University, Egypt, from March 1, 2021, to July 30, 2023. Participants were randomized to receive either Group I (n=25) received 200 mg of oral HCQ twice daily, alongside low dose aspirin or Group II (n=25) received low dose aspirin alone. Both interventions were started in the first 6 weeks of gestation and continued till 36 weeks of gestation.

Results

The baseline characteristics were homogenous between both study groups. The study showed that preeclampsia rate was (12%) in HCQ group versus (20%) in the control group but the difference was not statistical significant (p=0.702). There was no significant differences between both groups regarding neonatal outcomes and preeclampsia associated complications. The side effects of the therapy were minimal and no serious adverse effects was reported.

Conclusion

HCQ may be beneficial treatment for prevention of preeclampsia but we needed a properly designed studies to prove its efficacy. Also, HCQ could be considered as an adjunctive therapy to low-dose aspirin for PE prevention in high-risk women. In women with prior preeclampsia, there was no benefit of HCQ regarding fetal growth restriction, preterm birth, neonatal outcomes and preeclampsia associated complications. HCQ appears to be safe to the fetus with few maternal side effects.

Keywords: Hydroxychloroquine, preeclampsia.

INTRODUCTION

Preeclampsia (PE) affects approximately 3-8 % and responsible for over 70,000 maternal deaths annually **[1]**. Preeclampsia is characterized by endothelial dysfunction and diagnosed by the development of hypertension and significant proteinuria at or beyond 20 weeks' gestation **[2, 3].** Alternatively, a diagnosis can be made based on the emergence of one or more specific maternal organ dysfunctions, including renal, hepatic, neurological, pulmonary, or placental insufficiency, or the development of thrombocytopenia, even in the absence of proteinuria **[2].** Preeclampsia pathogenesis may be related to immunological abnormalities towards the fetus and impaired early placentation which usually associated with higher ratio of circulating Th1/Th2 lymphocytes with release the proinflammatory cytokines **[3].** Therefore, prevention of preeclampsia should be focused to correct the abnormal immune response and suppress the endothelial dysfunction through immunomodulatory and vasculo-protective treatments **[4].**

Hydroxychloroquine (HCQ) is an antimalarial drug used to enhance the placental function and treating endothelial

dysfunction and abnormal immune response during pregnancy in specific immunological disorders linked to adverse perinatal complications as SLE and antiphospholipid syndrome [5, 6]. Hydroxychloroquine has been proposed as a potential preventive treatment for preeclampsia because it may interrupt the pathogenesis through antioxidant, immunomodulatory and vasculo-protective effects [7]. Also, it acts on target toll-like receptors to prevent proinflammatory cytokine production (IL 1, IL-6, TNF alpha), reduces the levels of angiotensin II type 1 receptor antibodies, inhibits endothelin 1 which associated to preeclampsia [2, 7].

Previous studies [8-12] evaluated the role of HCQ in preeclampsia prevention included only pregnant women with autoimmune disease. In this study, we aimed to investigate HCQ efficacy in preeclampsia prevention in women with previous history of preeclampsia.

PATIENTS AND METHODS

This prospective, open label pilot randomized controlled trial, conducted at the Women's Health Hospital (WHH), Assiut University, Egypt from March 1, 2021, to July 30, 2023, evaluated the efficacy of HCQ in improving pregnancy outcomes for women with a prior history of preeclampsia. The study protocol was registered at ClinicalTrials.gov (NCT04755322).

Inclusion and exclusion criteria

Eligible participants were pregnant women aged 20-40 years, within the first six weeks of gestation, and with a documented history of preeclampsia in a previous pregnancy. All participants provided written informed consent. Exclusion criteria included major risk factors for Preeclampsia (e.g., multiple gestation, chronic hypertension, chronic renal disease), known contraindications to HCQ therapy as outlined by **[13]** (e.g., retinopathy, hypersensitivity, G6PD deficiency, chronic organ insufficiency, heart block, significant chronic digestive, hematologic, or neurologic diseases, epilepsy, or psychotic disorders), current use of HCQ for other medical conditions, and anticipated difficulty adhering to the study protocol and follow-up procedures.

Randomization

Eligible women were allocated to either the HCQ group (Group I) or the control group (Group II) in equal proportions using a blocked randomization design. This process employed a web-based random number generator accessible at https://www.sealedenvelope.com. Following confirmation of eligibility and acquisition of written informed consent, participants were assigned to their respective groups. Both study and control participants were notified of their group assignment. Group allocation was irreversible after **Intervention**

Following written informed consent, participants were enrolled in a screening phase that assessed eligibility for the subsequent intervention phase. This screening phase comprised two components: (1) a detailed medical history, including a comprehensive obstetric history, and (2) a clinical examination encompassing the calculation of body mass index (BMI). Upon confirmation of eligibility and a positive pregnancy test, participants were allocated to receive either 200 mg of oral HCQ twice daily combined with daily low-dose aspirin (75 mg) or daily low-dose aspirin (75 mg) alone. Both interventions continued throughout pregnancy until 36 weeks of gestation.

Follow-up

Beyond standard antenatal care, participants underwent a tailored follow-up schedule. Initial fetal viability was assessed via transvaginal ultrasound at 6 weeks. Two subsequent transabdominal scans at 20-24 weeks assessed for malformations, followed by a final scan at 36 weeks. Clinic visits adjusted frequency based on gestational age: monthly (20-28 weeks), bi-weekly (28-36 weeks), and weekly (>36 weeks), focusing on blood pressure and proteinuria. Antenatal records documented fetal viability, complications, treatment side effects, and delivery data (gestational age, mode, birth weight, NICU needs). This comprehensive follow-up ensured close monitoring and detailed data collection.

Outcomes

This study assesses the impact of HCQ on PE prevalence in pregnant women. According **ACOG 2020 [14]**, PE diagnosis after 20 weeks gestation hinges on elevated blood pressure (systolic ≥140mmHg or diastolic ≥90mmHg) and either proteinuria (≥300mg/24h or dipstick ≥2+) or severe features like new onset headache thrombocytopenia, HELLP syndrome or maternal organ dysfunctions, including renal, hepatic, neurological, and pulmonary. Early-onset PE occurs before 34 weeks, late-onset afterwards. Secondary outcomes include fetal malformations, complications like gestational hypertension and preterm birth, and neonatal birth weight.

Statistical analysis

Statistical analysis was performed using SPSS 27. Data distribution was assessed with the Shapiro-Wilk test. Parametric quantitative data were analyzed using independent t-tests and presented as mean ± SD. Non-parametric data were analyzed using Mann-Whitney U tests and presented as median (Q1, Q3). Categorical variables were analyzed using chi-square tests and presented as frequency (%). Statistical significance was set at $p < 0.05$.

Sample size

This was a pilot study so, convenience sampling of 25 patient in each study group was chosen (total 50 patients).

Ethical approval

The study protocol was approved by Assiut Medical School Review Board (IRB: 17200427) as presented as **supplementary file 1**.

RESULTS

A total of 72 women were counseled for participation in the study. Of these, 22 were excluded: 12 declined to participate, and 10 did not meet the inclusion criteria. The remaining 50 women consented and were randomly assigned to two groups of equal size (n=25): the HCQ group and the control group. Two participants in the HCQ group and one in the non-HCQ group were lost to follow-up, and one participant in the non-HCQ group experienced a miscarriage. Therefore, the final analysis included 23 women in the HCQ group and 23 women in the non-HCQ group as presented in **Figure 1**.

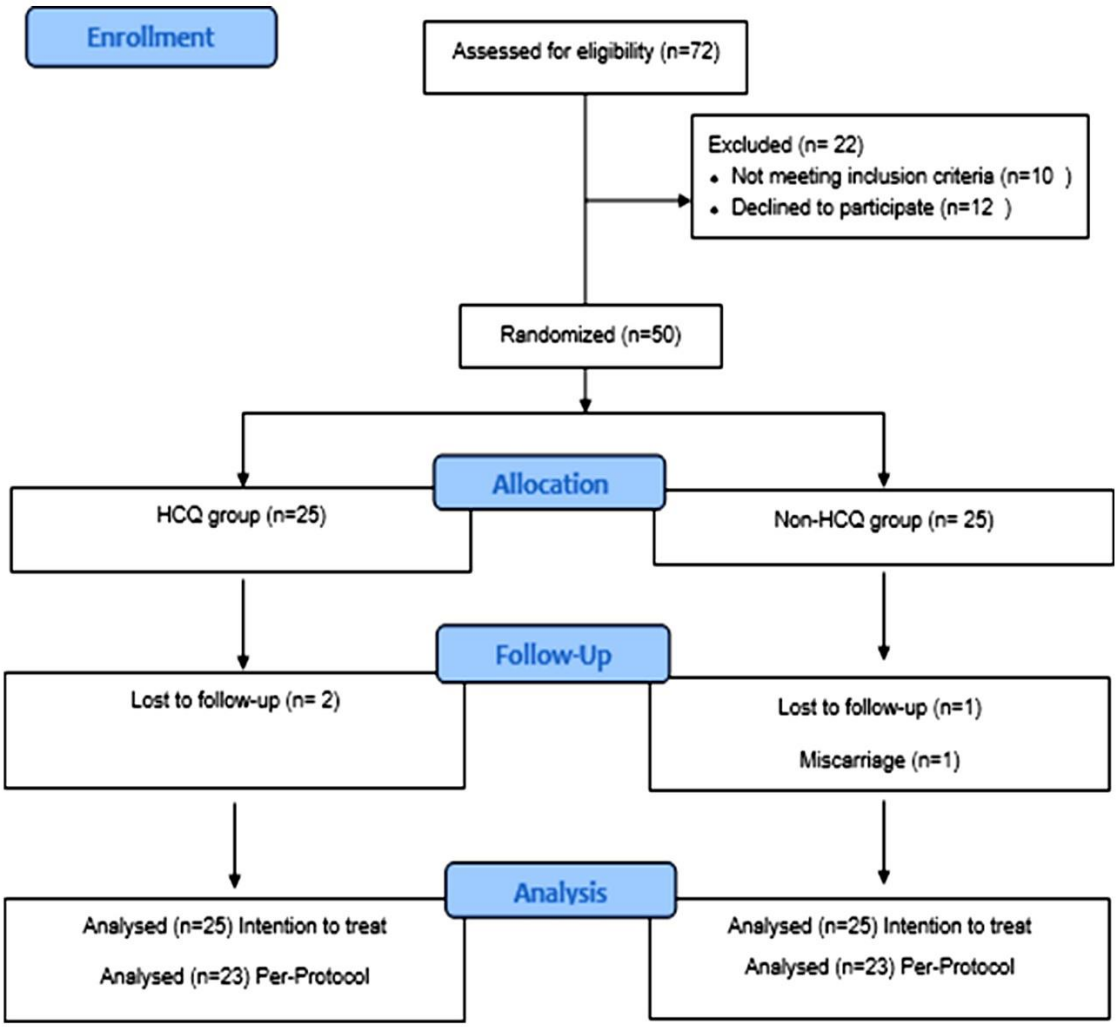

Figure 1: Consort flow chart.

Baseline characteristics were comparable between the two groups, with no statistically significant differences identified. The mean age of participants was approximately 25.3 years, and the mean BMI was 24.04 kg/m². Similarly, average systolic and diastolic blood pressures were 119.16 mmHg and 68.08 mmHg, respectively. Further analysis, detailed in **Table 1**, revealed no significant differences between the groups regarding, parity, FGR history, miscarriage history, PE type, or history of congenital malformations.

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

		Group		P value
		HCQ group N= 25	Control group N=25	
		N (%)	N (%)	
Age (years)	**Mean ± SD**	24.9± 3.58	25.7±4.19	0.461
BMI (Kg/m²)	**Mean ± SD**	24.09 ± 2.79	23.98± 3.05	0.899
Baseline BP (mmhg)				
Systolic BP	**Mean ± SD**	118.68 ± 7.29	119.64 ± 6.88	0.634
Diastolic BP	**Mean ± SD**	67.88 ± 8.97	68.28 ± 9.54	0.930
Parity categories	1	17 (68%)	15 (60%)	0.414
	2	4 (16%)	3 (12%)	
	3	2 (8%)	4 (16%)	
	≥4	2 (8%)	3(12%)	
Previous Preeclampsia				0.762
Early onset		7 (28%)	9 (36%)	
Late onset		18 (72%)	16 (64%)	
Previous FGR		8 (32%)	11(44%)	0.382

Previous IUFD		2 (8%)	3 (12%)	>0.999
Previous HELLP		1 (4%)	1 (4%)	>0.999
Previous Eclampsia		0 (0%)	1 (4%)	>0.999
Previous ICU admission		1 (4%)	2 (8%)	>0.999
Previous PTL		13 (52%)	15 (60%)	0.766
Previous placentalAbruption		2 (8%)	1 (4%)	>0.999
Previous Miscarriage		5 (20%)	3 (12%)	0.702

CS: Cesarean section, FGR: Fetal growth restriction, HELLP (Hemolysis, Elevated liver enzyme, Low Platelets) ICU: Intensive care unit, BP: blood pressure HCQ: Hydroxychloroquine, BMI: Body Mass Index, SD: Standard deviation, N (%), number and percentage.

The study releveled that preeclampsia rate trended to be lower in Group I than Group II but the difference was not statistical significant as presented in **Table 2**.

Table 2: Primary outcome (Preeclampsia) between the two groups.

	HCQ group	**Control group**	**P value**
	n/N (%)	**n/N (%)**	
Preeclampsia	3/25 (12 %)	5/25 (20 %)	0.702
Early onset	1 /3(33.3%)	2 /5(40%)	
Late onset	2/3 (66.7%)	3/5 (60%)	
Preeclampsia without severe features	2/3 (66.7%)	1/5 (20%)	
Preeclampsia with severe features	1/3 (33.3%)	4/5 (80%)	

In addition, no statistically significant differences were observed between the two groups regarding neonatal outcomes, including preterm delivery, fetal growth restriction, and gestational age at delivery, birth weight, or NICU admission. Notably, there was no cases of intrauterine fetal death or congenital anomalies were reported either in group I or group II as represented in **Table 3**.

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

		HCQ group	**Control group**	**P value**
		n/N (%)	**n/N (%)**	
Livebirth		23/25(92%)	23/25 92%	>0.999
Term		21/23 90.6%	20/23 86.7%	>0.999
Preterm		2/23 5.7%	3/23 4.4%	>.999
FGR		2/23 (1.9%)	3/23 (0.7%)	>0.999
Mode delivery	VD	9/23 (28.3%)	7/23 (35.5%)	0.536
	CS	14/23 (69.8%)	16/23 (57.8%)	
Gestational Age at delivery (weeks)	**Mean ± SD**	38.23 ± 1.76	37.25 ± 2.63	0.429
Birth weight (gm)	**Mean ± SD**	2833.48 ± 532.7	2781.74 ± 713.9	0.956
Apgar score	<7	2/23 (9.8%)	4/23 (7.3%)	0.728
	>7	21/23 (90.2%)	19/23 (92.7%)	
Need NICU		2/23 (9.8%)	4/23 (7.3%)	0.728
ICU admission		1 (4.3%)	1 (4.3%)	>0.999

IUFD: intrauterine fetal death, FGR: Fetal Growth Restriction, NICU: Neonatal intensive care unit, CS: cesarean section, VD: vaginal delivery HCQ: Hydroxychloroquine, N (%), number and percentage, SD: standard deviation.

NICU: Neonatal Intensive Care Unit, IUFD: Intrauterine fetal demise, FGR: Fetal growth restriction, HCQ: Hydroxychloroquine, N (%), number and percentage, SD: standard deviation.

Furthermore, the analysis of the study revealed there was no statistically significant differences between the groups regarding miscarriage, gestational hypertension, HELLP syndrome, pulmonary edema, ICU admission, or reported side effects of the assigned drugs. Additionally, no cases of eclampsia, placental abruption, or maternal deaths were reported in either group as presented in **Table 4**.

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

		HCQ group	**Control group**	**P value**
		n/N (%)	**n/N (%)**	
Miscarriage		0	1 (4.3%)	>0.999
Gestational Hypertension		0	2	0.489
HELLP syndrome		0	1 (4.3%)	>0.999
Pulmonary edema		0	1 (4.3%)	>0.999

In addition, the study found that women in the HCQ group reported a higher rate of side effects compared to the control group (16% Vs 8%). But there was no statistical significance difference between both groups (P = 0.667). The most common side effect in the HCQ group was nausea or vomiting (4%), stomach pain (4%) and headache (8%). The control group reported only 2 cases with vomiting and headache.

DISCUSSION

This pilot study suggests a potential, albeit statistically non-significant, benefit of HCQ in reducing PE recurrence among women with a history of preeclampsia. While HCQ treatment did not demonstrate a reduction in miscarriage, gestational

hypertension, fetal growth restriction, preterm birth, or intrauterine fetal deaths. Importantly, neonatal outcomes remained comparable between the study groups. Hydroxychloroquine was well-tolerated with minimal maternal side effects and no cases of fetal malformations was reported.

The strength points of the present study, including a randomized controlled design with group allocation and minimal loss to follow-up (less than 10%). However, its pilot open-label nature remains a limitation. Also generalization of findings should be cautious in extrapolation beyond the eligible participants.

This pilot trial reported a trend towards decreased PE risk in women with a history of PE more with HCQ than control group, but the difference was not statistically significant. The non-significant reduction of the preeclampsia risk aligns with previous studies which reported no significant reduction in PE prevalence with HCQ use among women with SLE and antiphospholipid syndrome **[15-18]**. On the other hand, several studies showed significant positive effect of HCQ in reduction of preeclampsia risk among selected rheumatological disorders **[8-12]**. However, the previous studies were observational, retrospective and focusing on women with SLE.

Although numerous interventions have been explored for PE prevention, including low-dose aspirin (LDA), calcium, metformin, L-arginine, statins, esomeprazole, vitamin D, and LMWH **[19]**, only LDA remains recommended by NICE (2019) and ACOG (2020) for moderate and high-risk women **[15, 20].** However, a study evaluated the role of LDA in preeclampsia prevention, demonstrating a significant reduction in PE among low-risk non-Hispanic white women but not overall or in other racial/ethnic groups **[21]**. Calcium supplementation demonstrated a significant risk reduction of preeclampsia primarily among women with low baseline calcium intake **[22]**. This means that there is no definitive therapy for preeclampsia prevention and we need to explore new potential preventive measures for preeclampsia.

In the current study, HCQ was well tolerated, and no serious adverse effects were observed. HCQ had good safety profile to the fetus with few maternal side effects to mothers. The finding aligns with several studies which reported that there was no increase in the risk of congenital fetal malformations among newborn delivered to mothers given HCQ during pregnancy **[23, 24**]. Also, a literature reported that HCQ may have tolerated side effects like gastrointestinal disturbances and skin manifestation which resolve with time but serious adverse events like retinal and cardiac toxicity related to HCQ are very rare and needs high doses (>5 g/day) and long durations of use (>5 years) **[25]**

CONCLUSION

HCQ may be beneficial treatment for prevention of preeclampsia but we needed a properly designed studies to prove its efficacy. HCQ could be considered as an adjunctive therapy to low-dose aspirin for PE prevention in high-risk women. In women with prior preeclampsia, there was no benefit of HCQ regarding fetal growth restriction, preterm birth, neonatal outcomes and preeclampsia associated complications. HCQ appears to be safe to the fetus with few maternal side effects to mothers.

Competing interests

The authors declare that they have no competing interests.

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