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Hydroxychloroquine for preventing hypertensive pregnancy disorders in recurrent spontaneous abortion: a retrospective cohort study in a single referral center

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Abstract

Objective We aimed to assess the effectiveness of hydroxychloroquine (HCQ) in preventing hypertensive pregnancy disorders (HPD) among women with recurrent spontaneous abortion (RSA).

Study design This retrospective cohort study included 462 pregnant women with RSA. Inverse probability of treatment weighting (IPTW) and propensity score matching (PSM) were used to balance baseline characteristics between HCQ and non-HCQ groups. The primary outcome comprised a composite of HPD, including preeclampsia, eclampsia, and gestational hypertension. Secondary outcomes included maternal complications and neonatal outcomes.

Results HCQ was associated with a 62% decreased risk of HPD compared to no HCQ (weighted hazard ratio 0.38, 95% CI 0.16–0.94, $P < 0.001$). The cumulative incidence of HPD at 34 weeks was lower among HCQ users (5% vs 14%, $P = 0.03$). HCQ demonstrated greater efficacy in preventing HPD among women aged < 35 years, a body mass index (BMI) of ≥ 28, non-in vitro fertilization (IVF) pregnancies, and fewer than three prior miscarriages (P-interaction < 0.05). Notably, the risk of HPD was significantly lowered by 56 and 53% in combined HCQ and aspirin with/without low-molecular-weight heparin (LMWH) group compared with no HCQ counterpart, respectively.

Conclusions HCQ demonstrated promising efficacy in reducing HPD, particularly when used in conjunction with aspirin and/or LMWH therapy.

Keywords Hydroxychloroquine, Recurrent spontaneous abortion, Hypertensive pregnancy disorders, Aspirin

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Introduction

Hypertensive pregnancy disorders (HPD), which include preeclampsia, eclampsia, gestational hypertension, and chronic hypertension with superimposed preeclampsia, pose significant risks to maternal and fetal health [1–3]. Despite the substantial adverse impacts of HPD, there is a lack of definitive preventive measures or treatments, aside from pregnancy termination [4]. Previous studies have explored the use of low-dose aspirin as a prophylactic measure, showing moderate benefits but falling short in preventing all aspects of HPD [5]. Nevertheless, possible increases in neonatal bleeding as well as antepartum and postpartum hemorrhage caused by aspirin, may raise concerns for health-providers [6–8]. Given persistent challenges in HPD management, it is imperative to advance innovative interventions to address complex pregnancy disorders like preeclampsia and enhance maternal–fetal wellbeing.

Hydroxychloroquine (HCQ), an antimalarial and anti-inflammatory medication, has been used to treat autoimmune diseases during pregnancy and has demonstrated favorable safety in pregnant women with systemic lupus erythematosus (SLE) [9]. While smaller studies have suggested that HCQ may provide protection against preeclampsia, robust clinical evidence remains limited [10]. The anti-inflammatory, antioxidant, and vascular protective properties of HCQ make it a biologically plausible agent for mitigating the systemic inflammation and endothelial dysfunction that are central to the pathogenesis of preeclampsia [11]. In addition to its potential benefits for autoimmune conditions, HCQ may also hold promise for patients with a history of recurrent spontaneous abortion (RSA), which shares aberrant inflammatory responses as an underlying mechanism [12]. However, there is an extreme scarcity of clinical research on HCQ in patients with RSA.

While the initial evidence is promising, most of it is derived from small retrospective studies in autoimmune populations [10–12]. In addition, the presence of confounding factors related to underlying disease activity and the use of concurrent medication such as aspirin and heparin limit the assessment of the effectiveness of HCQ in women with RSA. Well-designed studies in a broader high-risk pregnancy population are necessary to elucidate HCQ's effectiveness in complicated pregnancies. Therefore, our study aims to evaluate the real-world effectiveness and safety of HCQ in preventing HPD among high-risk pregnancies with RSA. The findings could offer valuable insights into the repurposing of HCQ as an affordable and readily available intervention to improve outcomes in high-risk pregnancies vulnerable to placental complications.

Materials and methods

Study design and participants

This retrospective cohort study was conducted at Renji Hospital, Shanghai Jiao Tong University School of Medicine, from November 2016 to August 2022.

A total of 666 pregnant women diagnosed with RSA were screened in the study. The inclusion criteria were as follows:

(1) RSA, defined as the loss of two or more pregnancies before the 24th week of gestation according to the criteria established by the American Society for Reproductive Medicine [13].
(2) Singleton pregnancies that extended beyond the 20th week of gestation.

The exclusion criteria included:

(1) Known etiology of previous loss, such as paternal, maternal, or embryo chromosome abnormalities, abnormal uterine anatomy, maternal endocrine dysfunction, vaginal infection, or diagnosis of antiphospholipid antibody syndrome.
(2) Women with infectious diseases, malignancies, severe comorbidities, or major fetal malformations diagnosed between the 11th and 13th weeks of gestation.
(3) Women with existing autoimmune diseases who were prescribed with HCQ as standard treatment (e.g., SLE, rheumatoid arthritis, undifferentiated connective tissue diseases).

The final study cohort consisted of 462 patients after screening by the inclusion and exclusion criteria. In the primary cohort, we aimed to evaluate the effectiveness of HCQ medication compared with non-HCQ patients. Additionally, we generated two sub-cohorts from the original: the aspirin (ASA) cohort ($N=420$, consisting of women who received aspirin) and the combination cohort (i.e., ASA and LMWH) ($N=239$, consisting of women who received both aspirin and LMWH), aiming at further assessing HCQ's effectiveness in the presence of two clinically relevant medications (aspirin and LMWH) (Fig. 1).

Screening and treatment diagram

HCQ treatment was based on undiagnosable abnormal immunological test results. Routine screening encompasses a comprehensive antinuclear antibody profile, antiphospholipid antibody profile, anti-dsDNA antibody, anti-Ro (SSA) antibodies, anti-La (SSB) antibodies, and other relevant autoimmune antibodies.

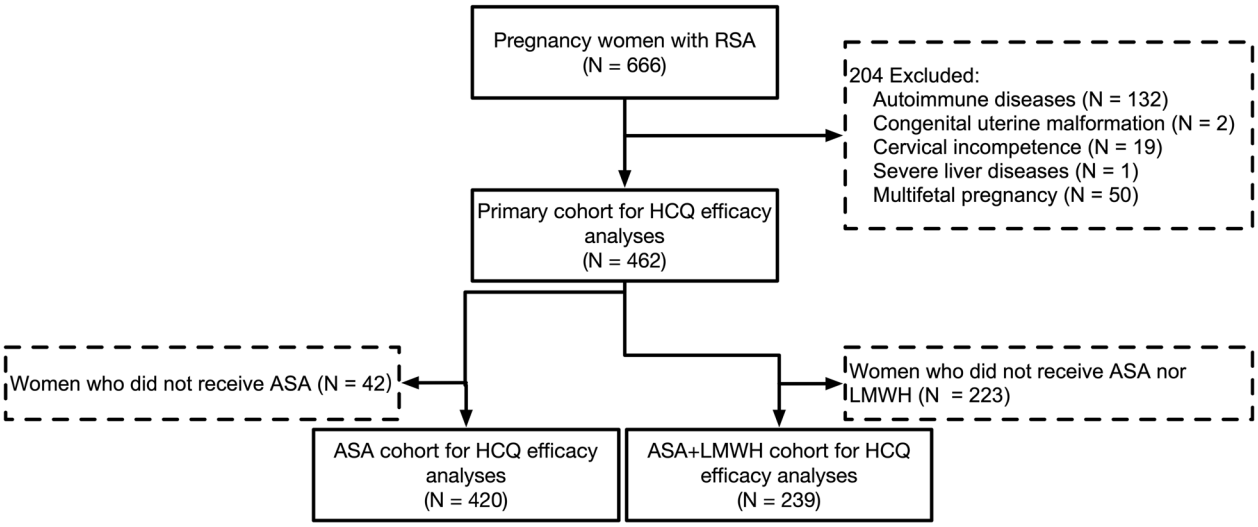

Fig. 1 Flow diagram for study participants

Patients with a history of RSA undergo testing for these indicators before their next pregnancy and receive targeted treatment accordingly. Obstetricians and rheumatologists collaborate closely, engaging in multidisciplinary discussions to develop tailored treatment plans for patients, specifically involving the application of LMWH and aspirin. Once pregnancy is confirmed, patients will continue to have their abnormal indicators monitored throughout the first and second trimesters based on their individual conditions, with treatment plans dynamically adjusted as needed.

All patients discontinued HCQ treatment after delivery, and the prescribed dosage of HCQ during the study period ranged from 200 to 400 mg per day. The dosage of HCQ is determined based on its safe usage guidelines. The initial dose is typically set at 5–6.5 mg per kilogram of body weight. For patients with higher abnormal antibody titers, the dose may be appropriately increased. This dosing regimen ensures both efficacy and safety in clinical use. Heparin therapy is prescribed based on a comprehensive assessment of coagulation risk factors, including body weight, age, and uterine artery blood flow. Additionally, prednisone is considered for patients with abnormal erythrocyte sedimentation rates or positive double-stranded DNA antibodies.

Ethical approval

Ethical approval for the study was obtained from the Medical Ethical Committee of Renji Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (LY2023-045-B).

Data collection

Medical records of all enrolled patients were independently reviewed and relevant data were collected. Baseline characteristics included age, pre-pregnancy body mass index (BMI), smoking status, the number of prior miscarriages, in vitro fertilization (IVF) history, and a history of preeclampsia, chronic hypertension, and pregestational diabetes mellitus (PGDM). Age categories were defined as <35, 35–39, and ≥ 40 years, while BMI categories were classified as normal (BMI <24), overweight (BMI 24–28), and obese (BMI ≥ 28) based on Chinese classification [14].

Variables related to treatment included the use of HCQ, prednisone, aspirin, LMWH, and the chosen anticoagulation strategy, which was categorized as none, aspirin only, LMWH only, or ASA plus LMWH.

Study outcomes

The primary outcome was the occurrence of HPD, a composite endpoint including preeclampsia/eclampsia, gestational hypertension or preeclampsia superimposed on chronic hypertension [15]. Preeclampsia was defined as new-onset hypertension accompanied by new-onset proteinuria exceeding 2+on dipstick or exceeding 300 mg in a 24-h urine collection. In cases where proteinuria was absent, preeclampsia was diagnosed based on clinical signs and symptoms, which included thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, or cerebral or visual symptoms, by the guidelines of the International Society for the Study of Hypertension in Pregnancy [16]. Early-onset preeclampsia was defined as preeclampsia that

developed before 34 weeks of gestation [17]. The other maternal and neonatal outcomes were considered as secondary outcomes.

In addition to the primary outcomes, the study also investigated a wide range of pregnancy outcomes, which included: gestational diabetes mellitus (GDM), stillbirth, antepartum hemorrhage, postpartum hemorrhage, placenta previa, placental abruption, gestational week at delivery, and delivery mode. Furthermore, neonatal outcomes were meticulously examined, which included small for gestational age (SGA), preterm birth, birth weight, Apgar scores at 1-min and 5-min intervals, need for neonatal intensive care unit (NICU) admission, and neonatal asphyxia. SGA was defined as an estimated fetal weight or fetal abdominal circumference below the 10th percentile for gestational age [18]. Gestational week at delivery was classified as <28, $28\sim34$, $34\sim37$, and ≥37 weeks. Neonatal birth weight can be further categorized into low birth weight (LBW, <2500 g), very low birth weight (VLBW, <1500 g), and extremely low birth weight (ELBW, ≤1000 g) [19].

Statistical analysis

To address selection bias related to HCQ treatment, we used propensity score matching to account for potential confounders in baseline characteristics. These scores were estimated by fitting confounding variables into a multivariable logistic regression model to quantify the probability of prescribing HCQ. Candidate variables were initially screened through univariable analysis with a threshold of $P<0.2$.

Subsequently, stepwise regression was used to select variables with a threshold of $P<0.1$. The use of LMWH and ASA was also included in propensity score estimation due to their clinical significance. Finally, the logistic model included the number of prior miscarriages, the use of prednisone, ASA, and LMWH.

Inverse probability of treatment weighting (IPTW) was then applied to evaluate the efficacy of HCQ in preventing HPD, with participants weighted by the inverse of the predicted probability of using HCQ at baseline (Table S1). Additionally, propensity score matching analyses were performed. Patients treated with HCQ were matched 1:1 using the nearest neighbor approach with the "Match" R package. The efficacy of HCQ in preventing HPD was determined using weighted hazard ratio (HR) in the IPTW population via Cox regression, supplemented by a log-rank test. The cumulative incidence of HPD at 34 weeks was also estimated. Differences in secondary outcomes between women in the HCQ and non-HCQ groups were examined through univariate analyses. HR estimates were also derived for the PSM population and the original population. Subgroup analyses were subsequently conducted, stratified by age, body mass index (BMI), smoking status, number of prior miscarriages, and IVF treatment. Cumulative incidence was also depicted among the two treatment arms.

In the ASA cohort, given that prednisone usage was the only associated variable with HCQ use (Table S2), an adjustment strategy was preferred when analyzing HCQ effectiveness. Age, BMI, and pregestational hypertension disease (PGHD) were found to be significantly associated with the primary outcome in univariate analysis (Table S3). Considering that prednisone and LMWH are drugs commonly used in combination with HCQ, three models were constructed to examine the effectiveness of HCQ in preventing HPD: (1) model 1: adjusted by age, (2) model 2: additionally adjusted by BMI and PGHD, (3) model 3: additionally adjusted by prednisone and LMWH.

The full adjustment model was employed for further subgroup analyses. Parallel sub-analyses were conducted in the ASA + LMWH cohort, mirroring the methodology employed in the ASA cohort. Three models were generated accordingly: (1) model 1: adjusted by PGHD, (2) model 2: additionally adjusted by BMI, (3) model 3: additionally adjusted by prednisone. The screening process is shown in Table S4 and S5.

A two-sided significance level of $P<0.05$ was deemed statistically relevant for all analyses. Data analysis was performed using the R statistical software package (version 4.2.2).

Results

Characteristics of study participants

A total of 462 eligible women were included in the primary cohort (Fig. 1). Of the 462 women, 148 (32.8%) received HCQ during pregnancy. To comprehensively evaluate the homogeneity of the study groups, baseline characteristics stratified by HCQ utilization are summarized in Table 1. Notably, minimal disparities were observed between the HCQ and non-HCQ cohorts. There were no statistically significant differences between groups in regard to age, BMI, smoking status, number of prior miscarriages, IVF, history of preeclampsia, chronic hypertension, or history of diabetes mellitus.

Noteworthy variations were identified in the concurrent medication regimens between the groups. Specifically, aspirin (97.3% vs. 87.9%, $P<0.001$), LMWH (67.6% vs. 47.1%, $P=0.002$), and prednisone (75.7% vs. 16.6%, $P<0.001$) were significantly more prevalent among the HCQ-treated group. After the application of inverse probability treatment weighting and propensity score matching, Table 2 and Table S6 present the harmonized

Table 1 Participant characteristics stratified by HCQ use

	Non-HCQ (*N* = 314)	HCQ (*N* = 148)	*P* value
Demographic characteristics and comorbidity			
Age (yrs), no. (%)			> 0.99
< 35	203 (64.6%)	96 (64.9%)	
35–39	87 (27.7%)	41 (27.7%)	
≥ 40	24 (7.6%)	11 (7.4%)	
BMI (kg/m^2), no. (%)			0.43
< 24.0	232 (73.9%)	117 (79.1%)	
24.0–27.9	62 (19.7%)	22 (14.9%)	
≥ 28.0	20 (6.4%)	9 (6.1%)	
Smoking, no. (%)	18 (5.7%)	11 (7.4%)	0.62
No. of miscarriage, no. (%)			0.27
2	173 (55.1%)	71 (48.0%)	
3	92 (29.3%)	54 (36.5%)	
> 3	49 (15.6%)	23 (15.5%)	
IVF, no. (%)	57 (18.2%)	29 (19.6%)	0.81
PE history, no. (%)	1 (0.3%)	0 (0.0%)	> 0.99
PGHD, no. (%)	23 (7.4%)	4 (2.7%)	0.08
PGDM, no. (%)	9 (2.9%)	2 (1.4%)	0.52
Treatment			
Prednisone, no. (%)	52 (16.6%)	112 (75.7%)	< 0.001
ASA, no. (%)	276 (87.9%)	144 (97.3%)	0.002
LMWH, no. (%)	148 (47.1%)	100 (67.6%)	< 0.001
Anticoagulation, no. (%)			< 0.001*
None	31 (9.9%)	2 (1.4%)	
ASA	135 (43.0%)	46 (31.1%)	
LMWH	7 (2.2%)	2 (1.4%)	
ASA + LMWH	141 (44.9%)	98 (66.2%)	

HCQ hydroxychloroquine, *BMI* body mass index, *IVF* in vitro fertilization, *PE* preeclampsia, *PGHD* pregestational hypertension disease, *PGDM* pregestational diabetes mellitus, *ASA* aspirin, *LMWH* low-molecular-weight heparin

* Fisher's exact test used

Table 2 Participant characteristics stratified by HCQ use after inverse probability treatment weighting

	Non-HCQ (*N* = 462.8)	HCQ (*N* = 453.9)	*P* value
Demographic characteristics and comorbidity			
Age (yrs), no. (%)			0.53
< 35	313.2 (67.7%)	283.1 (62.4%)	
35–39	117.5 (25.4%)	121.4 (26.7%)	
≥ 40	32.0 (6.9%)	49.4 (10.9%)	
BMI (kg/m^2), no. (%)			0.88
< 24.0	346.3 (74.8%)	331.1 (73.0%)	
24.0–27.9	87.3 (18.9%)	97.4 (21.5%)	
≥ 28.0	29.1 (6.3%)	25.4 (5.6%)	
Smoking, no. (%)	26.3 (5.7%)	27.7 (6.1%)	0.88
No. of miscarriage, no. (%)			0.66
2	241.8 (52.3%)	234.9 (51.8%)	
3	150.9 (32.6%)	166.2 (36.6%)	
> 3	70.1 (15.1%)	52.7 (11.6%)	
IVF, no. (%)	86.2 (18.6%)	94.1 (20.7%)	0.69
PE history, no. (%)	1.1 (0.2%)	0.0 (0.0%)	0.32
PGHD, no. (%)	32.8 (7.1%)	23.9 (5.3%)	0.66
PGDM, no. (%)	12.6 (2.7%)	3.0 (0.7%)	0.06
Treatment			
Prednisone, no. (%)	164.8 (35.6%)	164.4 (36.2%)	0.92
ASA, no. (%)	421.3 (91.0%)	420.7 (92.7%)	0.74
LMWH, no. (%)	254.2 (54.9%)	261.0 (57.5%)	0.70
Anticoagulation, no. (%)			0.85
None	33.1 (7.1%)	29.4 (6.5%)	
ASA	175.5 (37.9%)	163.5 (36.0%)	
LMWH	8.4 (1.8%)	3.8 (0.8%)	
ASA + LMWH	245.8 (53.1%)	257.2 (56.7%)	

HCQ hydroxychloroquine, *BMI* body mass index, *IVF* in vitro fertilization, *PE* preeclampsia, *PGHD* pregestational hypertension disease, *PGDM* pregestational diabetes mellitus, *ASA* aspirin, *LMWH* low-molecular-weight heparin

baseline characteristics in both study arms, signifying the successful mitigation of potential confounding factors.

Primary outcome

Maternal and neonatal outcomes analyzed using IPTW, are presented in Table 3, with outcomes in the primary and PSM cohort shown in Table S7. The IPTW analysis unequivocally revealed that the risk of HPD was significantly lower in the HCQ-treated group compared to the non-HCQ group (weighted hazard ratio [HR] = 0.38, 95% confidence interval [CI] 0.16–0.94; $P < 0.001$), as illustrated in Fig. 2A. This protective effect of HCQ remained consistent within the original cohort (HR = 0.42, 95% CI 0.23–0.77; $P = 0.003$; Fig. 2B) and the PSM-derived cohort (HR = 0.29, 95% CI 0.12–0.72; $P = 0.004$; Fig. 2C).

The data further highlighted a stark difference in the incidence of HPD at the critical 34-week gestational milestone, with notably higher rates observed in the non-HCQ group compared to the HCQ group (IPTW adjusted: 0.14 vs. 0.05; unadjusted: 0.13 vs. 0.04; PSM: 0.17 vs. 0.03; Fig. 2).

The risk of gestational hypertension was reduced by HCQ administration after IPTW (weighted HR 0.17, 95% CI 0.06–0.53, $P < 0.001$). The risk of preeclampsia differed with HCQ treatment (weighted HR 0.51, 95% CI 0.18–1.46, log-rank $P = 0.002$, Wald test $P = 0.209$). The protective effect of early preeclampsia was however not

Table 3 Outcomes stratified by HCQ Use after inverse probability treatment weighting

	Non-HCQ (*N* = 462.8)	HCQ (*N* = 453.9)	*P* value
Maternal outcomes			
HPD, no. (%)	99.8 (21.6%)	37.5 (8.3%)	0.02
PE, no. (%)	66.6 (14.4%)	31.9 (7.0%)	0.15
Early PE, no. (%)	27.5 (5.9%)	21.0 (4.6%)	0.73
GH, no. (%)	33.2 (7.2%)	5.6 (1.2%)	< 0.001
GDM, no. (%)	128.9 (27.9%)	118.0 (26.0%)	0.74
Live births, no. (%)	459.5 (99.3%)	452.2 (99.6%)	0.60
Antepartum hemorrhage, no. (%)	15.4 (3.4%)	10.3 (2.3%)	0.65
Postpartum hemorrhage, no. (%)	12.6 (2.7%)	27.5 (6.1%)	0.18
Placenta previa, no. (%)	2.2 (0.5%)	0.0 (0.0%)	0.16
Placenta abruption, no. (%)	35.0 (7.6%)	45.4 (10.0%)	0.50
GW at delivery, week, no. (%)			0.90
≥ 37 w	361.6 (78.1%)	348.8 (76.8%)	
34–37 w	73.5 (15.9%)	71.0 (15.6%)	
28–34 w	24.4 (5.3%)	32.3 (7.1%)	
< 28 w	3.3 (0.7%)	1.8 (0.4%)	
Route of delivery, no. (%)			0.35
Vaginal delivery	94.7 (20.6%)	116.9 (25.9%)	
Cesarean section	364.7 (79.4%)	335.2 (74.1%)	
Neonatal outcomes			
SGA, no. (%)	53.0 (11.5%)	46.6 (10.3%)	0.80
LBW, no. (%)	70.7 (15.4%)	73.0 (16.1%)	0.88
VLBW, no. (%)	13.3 (2.9%)	17.8 (3.9%)	0.72
ELBW, no. (%)	4.4 (1.0%)	2.0 (0.4%)	0.49
Apgar, mean (SD)			
1 min	9.9 (0.4%)	9.9 (0.6%)	0.30
5 min	10.0 (0.1%)	10.0 (0.1%)	0.92
NICU admission, no. (%)	27.6 (6.0%)	28.5 (6.3%)	0.94
Neonatal asphyxia, no. (%)	2.2 (0.5%)	3.4 (0.8%)	0.64

HCQ hydroxychloroquine, *HPD* hypertensive pregnancy disorder, *PE* preeclampsia, *GH* gestational hypertension, *GDM* gestational diabetes mellitus, *GW* gestational week, *SGA* small for gestational age, *LBW* low birth weight, *VLBW* very low birth weight, *ELBW* extremely low birth weight, *NICU* neonatal intensive care unit

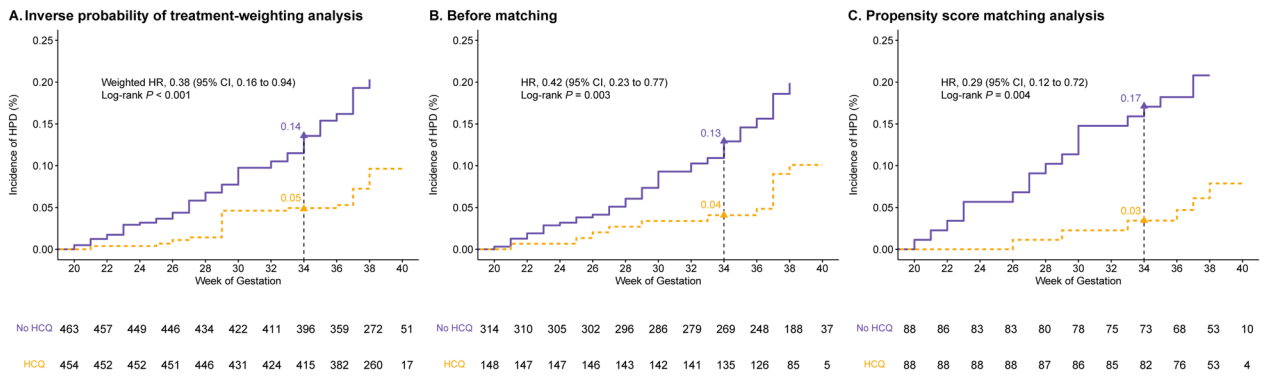

Fig. 2 Cumulative incidence of delivery with HPD. **A** Cumulative incidence of delivery with HPD after IPTW. **B** Cumulative incidence of delivery with HPD in the unadjusted model. **C** Cumulative incidence of delivery with HPD after PSM. *HPD* hypertensive pregnancy disorder, *IPTW* inverse probability treatment weighing, *PSM* propensity score matching, *HR* hazard ratio, *CI* confidence interval, *HCQ* hydroxychloroquine

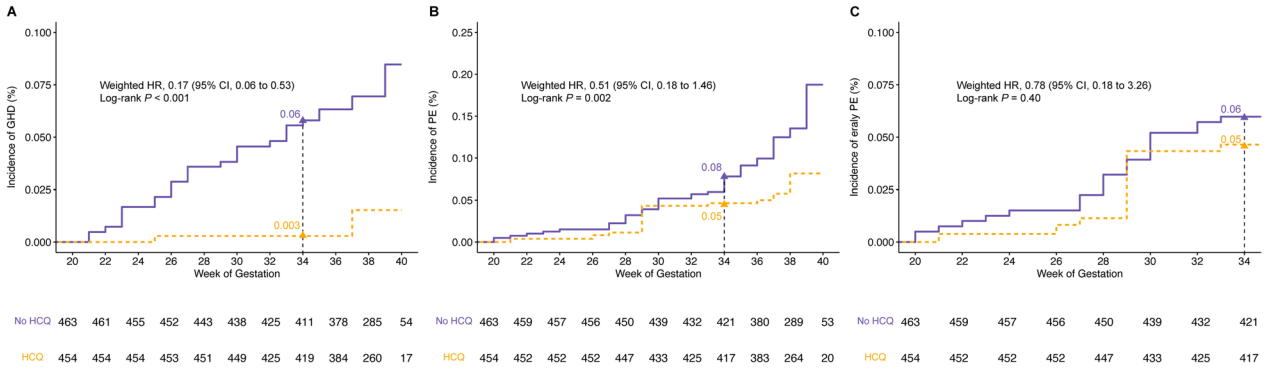

Fig. 3 Cumulative incidence of delivery with GH, early PE and PE after IPTW. **A** Cumulative incidence of delivery with GH. **B** Cumulative incidence of delivery with early PE. **C** Cumulative incidence of delivery with PE. *IPTW* inverse probability treatment weighing, *GH* gestational hypertension, *PE* preeclampsia, *HR* hazard ratio, *CI* confidence interval, *HCQ* hydroxychloroquine

statistically significant (weighted HR 0.78, 95% CI 0.18–3.26, $P=0.40$) (Fig. 3). Meanwhile, we did not observe significant improvement after HCQ medication in other maternal outcomes (Table S8).

To delineate the optimal clinical setting for HCQ medication, we conducted a subgroup analysis of HPD risk post-IPTW. Notable subgroups included patients with age < 35 years (weighted HR = 0.25, 95% CI 0.12–0.55), BMI exceeding 28 (weighted HR = 0.07, 95% CI 0.01–0.63), a history of no more than three prior miscarriages (two prior miscarriages: weighted HR = 0.20, 95% CI 0.05–0.77; three prior miscarriages: weighted HR = 0.32, 95% CI 0.12–0.83), and those with non-IVF pregnancies (weighted HR = 0.17, 95% CI 0.08–0.37), as illustrated in Figure S1.

Effectiveness of HCQ in ASA cohort

Despite widespread aspirin administration (87.9% in the non-HCQ group and 97.3% in the HCQ group), the incremental benefit of HCQ remained a subject of inquiry. Accordingly, we established the aspirin cohort ($N=420$) by excluding non-aspirin users. The baseline characteristics of the aspirin cohort are detailed in Table 4.

Within this cohort, HCQ exhibited a notable reduction in the occurrence of HPD and preeclampsia when compared to the non-HCQ group (HPD: 8.3% vs. 18.8%, $P=0.007$; preeclampsia: 5.56% vs. 12.32%, $P=0.04$), as outlined in Table S9.

Subsequent investigation into mitigating factors within the aspirin cohort (details in Statistical section) yielded a six-variable model encompassing HCQ, age, BMI, PGHD, prednisone and LMWH. The cumulative incidence plot further underscored the protective effect of HCQ in patients receiving aspirin (unadjusted HR = 0.44, 95% CI

Table 4 Participant characteristics stratified by HCQ use in ASA cohort

	Non-HCQ ($N=276$)	HCQ ($N=144$)	*P* value
Demographic characteristics and comorbidity			
Age (yrs), no. (%)			0.77
< 35	175 (63.4%)	94 (65.3%)	
35–39	83 (30.1%)	39 (27.1%)	
≥ 40	18 (6.5%)	11 (7.6%)	
BMI (kg/m^2), no. (%)			0.48
< 24.0	205 (74.3%)	114 (79.2%)	
24.0–27.9	53 (19.2%)	21 (14.6%)	
≥ 28.0	18 (6.52%)	9 (6.25%)	
Smoking, no. (%)	16 (5.80%)	11 (7.64%)	0.60
No. of miscarriage, no. (%)			0.34
2	152 (55.1%)	69 (47.9%)	
3	82 (29.7%)	52 (36.1%)	
> 3	42 (15.2%)	23 (16.0%)	
IVF, no. (%)	51 (18.5%)	28 (19.4%)	0.91
PE history, no. (%)	1 (0.4%)	0 (0.0%)	> 0.99
PGHD, no. (%)	22 (8.0%)	4 (2.8%)	0.06
PGDM, no. (%)	7 (2.5%)	2 (1.4%)	0.72
Treatment			
Prednisone, no. (%)	51 (18.5%)	110 (76.4%)	< 0.001
LMWH, no. (%)	141 (51.1%)	98 (68.1%)	0.001
Anticoagulation, no. (%)			0.001
None			
ASA	135 (48.9%)	46 (31.9%)	
LMWH			
ASA + LMWH	141 (51.1%)	98 (68.1%)	

HCQ hydroxychloroquine, *ASA* aspirin, *BMI* body mass index, *IVF* in vitro fertilization, *PE* preeclampsia, *PGHD* pregestational hypertension disease, *PGDM* pregestational diabetes mellitus, *LMWH* low-molecular-weight heparin

0.24–0.83; $P=0.01$), as demonstrated in Figure S2. Subgroup analysis illuminated a substantially diminished risk of HPD among patients aged 35–39 (adjusted HR = 0.06, 95% CI 0.01–0.44), as presented in Figure S3.

Effectiveness of HCQ in ASA + LMWH cohort

The usage of LMWH was prevalent in over half of the participants in both the non-HCQ (51.5%) and HCQ (68.1%) cohorts. Consequently, we established a distinct cohort of patients who received both aspirin and LMWH medication ($N=239$). The baseline characteristics of this cohort are presented in Table S10.

Within this cohort, early-onset preeclampsia and gestational hypertension were more frequently observed in the non-HCQ group, although neither reached statistical significance (early-onset preeclampsia: 4.96% vs. 4.08%, $P>0.99$; gestational hypertension: 9.2% vs. 3.1%, $P=0.07$), as outlined in Table S11.

In univariate and multivariate stepwise logistic regression analysis, prednisone was identified as the sole independent risk factor pertinent to HCQ modality, rendering methods like PSM or IPTW impractical (details in Statistical section). Therefore, we devised a clinically relevant model incorporating BMI, PGHD, and prednisone to mitigate selection bias within the aspirin and LMWH cohort. HCQ medication decreased the risk of HPD by 53% (unadjusted HR = 0.47, 95% CI 0.23–0.96, $P=0.04$), as illustrated in Figure S4. The adjustment model we adopted further proved a notably protective effect of HCQ in this context (adjusted HR = 0.42, 95% CI 0.18–0.95; $P=0.04$). Subgroup analysis utilizing this model indicated that HCQ treatment could confer more substantial protective effects on patients aged 35–39 (adjusted HR = 0.02, 95% CI 0.01–0.56), as detailed in Figure S5.

Discussion

Our findings suggest that HCQ exerts a preventive effect on HPD incidence, with a lower cumulative incidence of HPD at 34 weeks in the HCQ group. To our knowledge, our study contained by far the first cohort that evaluated the effectiveness in RSA pregnancies with unknown etiology.

Our study, encompassing a relatively extensive retrospective cohort, provides evidence that HCQ significantly reduces the likelihood of HPD in RSA pregnancies by 62%, compared to the non-HCQ group. Moreover, our study found that HCQ reduced the incidence of preeclampsia (weighted HR 0.51). However, this result should be interpreted with caution, as the Wald test in the Cox model was not significant ($P=0.209$), despite a significant log-rank test ($P=0.002$). Recent meta-analyses pooling data from seven published studies have corroborated a reduction in preeclampsia and gestational hypertension associated with HCQ usage in pregnant patients with autoimmune disorders [20, 21]. Guo et al. demonstrated that HCQ was an independent protective factor of clinical pregnancy rate in patients positive for autoantibodies during frozen embryo transfer cycles [22]. An ongoing open-label randomized controlled trial also aimed at evaluating the efficacy of HCQ on RSA patients with undifferentiated connective tissue disease [23]. However, above-mentioned studies all investigated the prophylactic potential of HCQ in women with autoimmune diseases, leaving RSA with unknown etiology as an unresolved population. Therefore, the protective effect of HCQ in non-autoimmune disorder patients provides intriguing insights into possible mechanisms of HCQ in this context.

Several biological mechanisms likely underpin HCQ's putative protective effects during pregnancy. Aberrant inflammation is strongly implicated in the pathogenesis of both preeclampsia and RSA. By inhibiting lysosomal Toll-like receptor signaling, HCQ is believed to dampen the heightened inflammatory state driving placental dysfunction and vascular abnormalities integral to preeclampsia development [24]. Through its immunomodulatory actions, HCQ may also ameliorate vascular injury by reducing tumor necrosis factor-alpha (TNFα)-induced endothelin-1 secretion and vascular cell adhesion molecule-1 (VCAM-1) expression, thereby impeding inflammatory leukocyte recruitment and preserving the maternal endothelium [12, 25]. The translation of these mechanistic insights into tangible clinical benefits in the current study represents an important advance in corroborating the biological plausibility of HCQ's antenatal protective effects.

Notably, our study demonstrates HCQ's effectiveness even in the context of concurrent aspirin use, which was prevalent in the vast majority of patients. Among the aspirin sub-cohort, HCQ use still conferred a significantly lower risk of HPD, including preeclampsia and early-onset preeclampsia compared to aspirin alone. Similarly, in the subgroup receiving both aspirin and LMWH, HCQ remained to be associated with a decreased risk of developing HPD after adjustment for confounders. Regarding the impact of aspirin or/and LMWH on the incidence of HPD in RSA, a randomized trial of 364 women showed no significant difference in the incidence of preeclampsia between the aspirin-only group and the combination group receiving aspirin plus nadroparin [26]. Similar results were also observed in most other studies [27]. A meta-analysis concluded no substantial influence on the occurrence of preeclampsia (LMWH: risk ratio [RR] = 1.1, 95% CI 0.53–2.31, $P=0.792$; LMWH + aspirin: RR = 1.49, 95% CI 0.25–8.79, $P=0.662$) after analysis of 7

studies involving 1849 patients [28]. Our study suggests that HCQ may offer incremental value above existing preventative therapies like low-dose aspirin. The combination of HCQ and aspirin may allow a more comprehensive targeting on the multifactorial pathogenesis of preeclampsia.

Interestingly, our study found no significant impact of HCQ in preventing placenta-derived complications, including low birth weight, SGA, preterm delivery and placenta abruption. These findings contrast with studies suggesting a lower rate of adverse pregnancy outcomes with HCQ, such as pregnancy loss, fetal growth restriction, preterm delivery, and fetal distress [29].

The significant clinical potential of HCQ lies not only in its efficacy, but also in its safety profile for pregnant women. HCQ is associated with minimal side effects for both the pregnant patients themselves and their newborns, making it a promising treatment option in this context. Maternal outcomes such as GDM, hemorrhage and placenta complications along with neonatal outcomes such as Apgar scores, NICU admission rate and neonatal asphyxia did not differ between the HCQ and control groups, indicating minimal side effects (Table 3). Patients discontinued the use of HCQ after delivery. Due to the relatively short duration of use and the controlled, safe dosage, no severe adverse reactions—such as retinal pigmentation, corneal opacity, significant gastrointestinal disturbances, or central nervous system effects—were observed in our cohort. Furthermore, recent studies support the safety of HCQ during pregnancy, and it is recommended for women with SLE or RA during pregnancy [30–32].

The principal strength of this study lies in its large sample size. Furthermore, we managed to control the risk of bias by using IPTW and PSM, generating robust conclusions regarding the effectiveness of HCQ in patients with RSA.

Despite these promising findings, it is imperative to acknowledge the limitations of this study. Our analysis is based on retrospective data, which inherently carries the risk of selection bias and unmeasured confounders, despite attempts to mitigate these through propensity score matching and inverse probability treatment weighting. As a single-center study, the results may not be fully generalizable to broader populations. The optimal HCQ dosing regimen and timing of treatment initiation remain unclear. Prospective randomized controlled trials are warranted to further validate these findings by addressing potential bias, and hopefully experimental investigations will elucidate the precise mechanisms underlying HCQ's protective effects. Moreover, only SGA but not FGR was evaluated in our cohort, which could underestimate the rate of newborns with true pathological condition who had a higher risk of adverse perinatal outcome. Further studies are warranted to accurately estimate FGR by Delphi's consensus [33]. The long-term side effects of HCQ on newborns could be an important consideration in clinical settings. Further research could benefit from incorporating this aspect to provide a more comprehensive understanding of its use in pregnancy.

Our study provides important real-world evidence that hydroxychloroquine may prevent hypertensive pregnancy disorders in patients with recurrent spontaneous abortion of unknown etiology. It highlights the potential benefits of combined use of HCQ with current therapies in a high-risk population. Further research is warranted to confirm these findings and elucidate the underlying mechanisms driving HCQ's potential preventive role in HPD.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-025-02549-9.

Additional file 1.

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Author contributions
Conceived and designed the study: XK, YW, NZ, WD; Collected data: XK, WTC; Analyzed the data: XK, WTC, SBH, JYW, NZ, WD; Made the figures: XK, WTC, SBH, HTS, JYW, YW; Interpreted the results: XK, NZ, SBH, HTS, NZ, WD; Wrote the first draft of the manuscript: XK, WTC, SBH, KUL, YW; Revised and refined the manuscript: XK, SBH, KUL, YW, NZ, WD. The author(s) read and approved the final manuscript.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Ethical approval for the study was obtained from the Medical Ethical Committee of Renji Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (LY2023-045-B).

Consents for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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