

Original Research Article

The role of hydroxychloroquine during the periconception period for recurrent miscarriage – a prospective observational study

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Received: 22 May 2025

Revised: 07 September 2025

Accepted: 12 September 2025

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ABSTRACT

Background: Recurrent miscarriage (RM) remains a significant clinical challenge with multifactorial etiologies, many of which are immunological or unexplained. Hydroxychloroquine (HCQ), an antimalarial with immunomodulatory properties, has shown promise in improving pregnancy outcomes in autoimmune conditions. However, its role in RM, particularly during the periconception period, has not been extensively explored. Objective was to evaluate the safety and efficacy of hydroxychloroquine administered during the periconception period in women with a history of recurrent miscarriage.

Methods: A prospective observational study was conducted on 160 women with a history of ≥ 3 miscarriages. Participants were administered 200 mg of HCQ daily for three months prior to attempting conception. Comprehensive clinical, hematological, and biochemical assessments were performed at baseline and during follow-up. Adverse events and pregnancy outcomes were recorded.

Results: A total of 115 women (71.9%) conceived following periconception HCQ therapy. Among them, 45.2% had full-term normal vaginal deliveries, 26.1% underwent cesarean sections, and 15.7% experienced preterm deliveries, while 13.0% had first-trimester losses. Most participants (75%) were asymptomatic during therapy, with 12.5% reporting mild gastrointestinal symptoms and 6.25% experiencing transient hepatic enzyme elevations. Laboratory parameters remained stable, with no significant deterioration. HCQ was well-tolerated overall, and no new infections or seroconversions were observed.

Conclusions: Periconception use of HCQ appears to be a safe and potentially effective therapeutic option in improving conception and pregnancy outcomes in women with recurrent miscarriage. Further randomised controlled trials are recommended to validate these findings.

Keywords: Hydroxychloroquine, Immunomodulation, Maternal health, Periconception care, Pregnancy outcome, Recurrent miscarriage

INTRODUCTION

Worldwide, around 1% and 2% of women during their reproductive age experience recurrent miscarriages (RM). RM is the loss of two or more successive pregnancies before 20 weeks of gestation.¹ It is often multifactorial, where several factors contribute to its aetiology, including genetic, anatomical, endocrine, infectious, and

immunological reasons. However, in almost half of the cases, the aetiology is still unknown, which makes management and treatment plans extremely difficult.² Immunological dysregulation is a significant contributing factor to unexplained RM. The pathophysiology of RM has been linked to abnormal maternal immunological responses, such as the presence of antiphospholipid antibodies, increased natural killer (NK) cell activity, and

an imbalance between pro- and anti-inflammatory cytokines. These immunological changes can result from defective placentation, poor trophoblast invasion, and ultimately, pregnancy loss.^{3,4}

A 4-aminoquinoline derivative, hydroxychloroquine (HCQ), is often utilised as an antimalarial drug to treat autoimmune conditions like rheumatoid arthritis and systemic lupus erythematosus (SLE).⁵ Research has now indicated that this could be a potential treatment option for immune-mediated pregnancy complications owing to its immunomodulatory properties, such as stabilizing lysosomal membranes, reducing the synthesis of pro-inflammatory cytokines, and inhibiting toll-like receptor signaling.⁶ The possible advantages of HCQ in enhancing pregnancy outcomes for women with RM have been investigated in several recent studies.^{7,8} For example, Singh et al studied women with a history of RM by administering 200 mg of HCQ twice daily during the preconception phase. According to the study findings, 72% of the participants could conceive, and a sizable percentage of them went on to have full-term pregnancies. The study concluded that HCQ use in the preconception period could facilitate conception and prevent miscarriage in refractory cases of RM.⁹

Additionally, Mirzaei et al assessed the effects of HCQ on the outcomes of infertility in a systematic review and meta-analysis. Although there was no discernible difference in the abortion rate across the groups, the study showed that the combination of HCQ and prednisone increased fertilization and live birth rates when compared to prednisone alone. According to these results, HCQ may improve several elements of reproductive success, especially in cases of immune-mediated infertility.¹⁰ HCQ has shown vasculoprotective and antithrombotic qualities in addition to its immunomodulatory actions, which may be helpful in diseases like RM and preeclampsia. Regardless of the mother's autoimmune state, HCQ may provide therapeutic benefits in controlling RM due to its capacity to reduce vascular endothelial dysfunction and immunological impairment, according to a review by de Moreuil et al. The evidence is still equivocal.¹¹

One hundred pregnant women with a history of RM were started on HCQ in prospective multicenter registry research conducted in France. According to the study, the only significant predictor of pregnancy continuation was the number of previous miscarriages, with only 38% of pregnancies continuing past 12 weeks of gestation.¹² This implies that although HCQ might have advantages, variables like the number of prior pregnancy losses may restrict how effective it is. Given the promising yet mixed evidence, further research is warranted to elucidate the role of HCQ in the periconception management of RM. This study aimed to evaluate the efficacy of HCQ administered during the periconception period in improving pregnancy outcomes among women with a history of RM.

METHODS

Study design, setting and study period

We conducted a prospective observational study over a period of one year, from August 2023 to July 24, in the obstetrics ward in the ILS Hospital Agartala.

Study participants

We recruited all females aged between 18 and 35 years with at least three earlier consecutive miscarriages during their first trimester without any specific reason, women with no abnormalities of the uterus, and who received low-dose Ecosprin or low molecular weight heparin during their earlier miscarriages. We excluded patients who had a history of venous thrombosis, had conditions where HCQ use was contraindicated (such as G6PD deficiency, chronic renal or liver insufficiency, retinopathy, etc.)

Sample size

The sample size was calculated using a previous study by Singh et al that estimated the conception rate among women treated with HCQ during precondition to be 72%, taking a 95% CI and a 5% alpha error, we calculated the sample size to be estimated as 160 using the OpenEpi version 3.02 software.⁹ We followed a consecutive sampling where all women eligible were included until the same size was reached.

Study procedure

The study started after approval from the institute's ethics committee. We began the study after obtaining informed written consent from all the eligible study participants. The study participants were informed regarding the study's objectives and the benefits and harms of participating in the study. Data was collected using a semi-structured questionnaire. The patient's treatment period before conception upto 6 months after the last abortion was taken into consideration for this study.

The patients who fulfilled the eligibility criteria and consented to the study were administered 200 mg of HCQ twice daily orally before conception and continued for first three months after patient conceived. A 5 mg dose of folic acid was also administered along with it. In addition to the above, all women were started on a low-dose ecosprin immediately following a positive pregnancy test. HCQ was stopped after 20 weeks, and ecosprin was continued. All patients were administered iron, calcium and protein supplements throughout the pregnancy. All women were closely monitored to check for any adverse signs or symptoms such as loss of appetite, jaundice, new skin rashes, itching, stomach pain, headache, or blurred vision. In addition, other side effects such as blurry vision, photosensitivity, muscle weakness or stiffness, throat ulcers, and hypoglycemia were closely monitored

during the first month of starting the protocol. During the follow-up period, investigations such as complete blood count, routine antenatal tests and liver and renal function tests were taken into consideration.

Outcome measures

The primary outcome was live birth at the end of pregnancy. Other outcomes studied included preterm birth, incidence of adverse pregnancy outcomes, IUGR, stillbirth and placental insufficiency

Statistical analysis

All data were extracted from the hospital case records and entered into Microsoft Excel. In our study, continuous variables were expressed as mean±standard deviation. The remaining covariates were categorical, expressed as n (%). The association across categorical variables was assessed using the Chi-square test. A p value <0.05 was considered statistically significant.

RESULTS

We finally recruited 160 women with a history of recurrent miscarriage and who fit the eligibility criteria during our study period. Everyone agreed to participate, making it a response rate of 100%. Table 1 depicts the demographic and clinical characteristics of the study

participants. The study cohort comprised 160 women with a history of recurrent miscarriage. The mean age of participants was 30.4±4.8 years, and the average BMI was 26.1±3.2 kg/m², indicating a predominance of women in the overweight category. A majority of the participants (82.5%) had experienced 3 to 4 previous miscarriages, while the remaining 17.5% had a history of more than 4 miscarriages. Regarding the duration of attempts to conceive, 63.1% had been trying for less than 3 years, whereas 36.9% had been attempting conception for three years or more. These demographic and clinical characteristics reflect a population with significant reproductive challenges and provide a strong foundation for evaluating therapeutic interventions aimed at improving reproductive outcomes.

Table 1: Demographic and clinical characteristics of the study participants (n=160).

Variables	Frequency (%)
Mean Age (± SD) in years	30.4±4.8
BMI (kg/m²), mean±SD	26.1±3.2
Previous number of miscarriages	
3 to 4	132 (82.5)
More than 4	28 (17.5)
Duration trying to conceive	
<3 years	101 (63.1)
3 years and above	59 (36.9)

Table 2: Blood investigations at baseline and during follow-up of the study participants (n=160).

Investigation	Baseline (mean±SD)	Post 3 months of HCQ (mean±SD)	P value
Hemoglobin (gm/dl)	11.8±1.1	12.1±1.0	0.08
Total leukocyte Count (×10⁹/l)	6.4±1.5	6.2±1.4	0.21
Platelet count (×10⁹/l)	250±40	255±35	0.36
Serum creatinine (mg/dl)	0.82±0.13	0.84±0.12	0.41
Blood urea (mg/dl)	21.5±4.3	22.0±4.0	0.52
AST (U/l)	28±6	30±8	0.09
ALT (U/l)	27±7	31±10	0.07
Fasting blood sugar (mg/dl)	82±12	84±11	0.45
VDRL, HIV, HBsAg, HCV	All non-reactive	No new seroconversions	—
Hemoglobin electrophoresis	Normal in 100%	No changes observed	—
Urinalysis (routine + microscopy)	Normal in 97%	No deterioration	—

Table 2 describes the investigation profile of the study participants. We observed that after three months of hydroxychloroquine (HCQ) treatment, routine laboratory monitoring showed no statistically significant changes in hepatic, renal, or hematological parameters. Liver enzymes (AST and ALT) displayed small elevations within physiological limits (p=0.09 and 0.07, respectively), and hemoglobin levels increased slightly from 11.8±1.1 gm/dl to 12.1±1.0 gm/dl (p=0.08). Blood urea and serum creatinine levels did not change, indicating constant renal function. Likewise, there was no discernible difference in platelet counts or fasting blood

glucose levels. At both time points, none of the subjects had seroconversions and tested negative for VDRL, HIV, HBsAg, and HCV. In 97% of instances, the urinalysis was unremarkable, and hemoglobin electrophoresis was normal across the group. These findings support the systemic safety of HCQ in the periconception period among women with recurrent miscarriage.

The outcomes that the study participants reported are shown in Table 3. Most subjects tolerated hydroxychloroquine well; 75% of them remained asymptomatic during treatment. Twelve percent reported

mild gastrointestinal symptoms such as nausea and abdominal pain, and six and a half reported a brief rise of grade I liver enzymes. Of those who stopped treatment because of intolerance (severe nausea), only 6.25% did so. Regarding reproductive outcomes, 28.1% of women did not become pregnant during the research period, whereas 71.9% (n=115) were pregnant. Of those who became pregnant, 15.7% had preterm births, 26.1% had cesarean sections, and 45.2% had full-term regular vaginal deliveries. 13 percent of the pregnancies had recurrent first-trimester loss. Overall, the data indicate a favorable tolerability profile for HCQ and a promising conception and live birth rate in this high-risk population.

Table 3: Reported outcomes among the study participants (n=160).

Variable	Frequency (%)
Adverse events observed during HCQ periconception therapy	
Asymptomatic	120 (75.0)
Mild GI disturbance (nausea, abdominal pain)	20 (12.5)
Transient hepatic enzyme elevation (grade I)	10 (6.25)
Discontinued due to side effects (severe nausea)	10 (6.25)
Pregnancy outcomes	
Conceived after treatment	115 (71.9)
Did not conceive	45 (28.1)
Outcomes of pregnancies post-conception	
Full-term normal vaginal delivery (FTNVD)	52 (45.2)
Cesarean section (elective or emergency)	30 (26.1)
Preterm delivery (<37 weeks)	18 (15.7)
First trimester loss (recurrent)	15 (13.0)

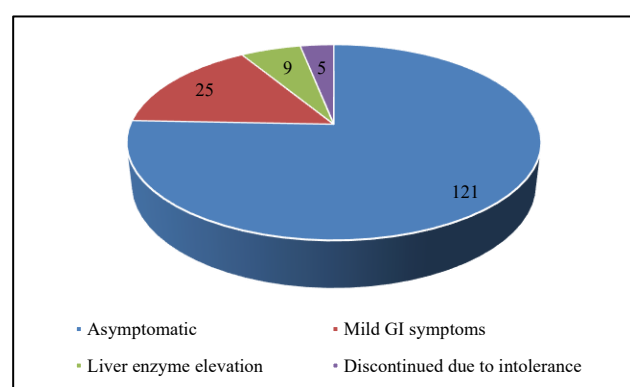


Figure 1: Adverse post-treatment protocol, n=160.

Figure 1 illustrates the distribution of adverse events observed among the study participants (n=160) following hydroxychloroquine (HCQ) administration during the periconception period. Most patients (n=121) remained asymptomatic, indicating good tolerability to the drug.

Mild gastrointestinal symptoms, such as nausea and abdominal discomfort, were reported in 25 participants, representing the most common side effect among those experiencing any adverse events. Liver enzyme elevation- characterized as transient and within grade I toxicity limits- was documented in 9 patients. Notably, 5 participants discontinued HCQ therapy due to severe intolerance, primarily persistent nausea and vomiting. Overall, the figure underscores the relatively safe and well-tolerated profile of HCQ in a periconception setting among women with a history of recurrent miscarriage.

DISCUSSION

We performed a prospective observational study that showcased the utility of HCQ among women with recurrent miscarriages. The patients started on the HCQ protocol had minimal adverse effects, improved conception rates and tolerability. Our study results showed that 75% of women remained asymptomatic over the three months of periconception HCQ therapy, while only 12.5% of patients had mild gastrointestinal issues. Around 72% of the women were able to conceive after treatment.

According to our research, over three-quarters of the women who began HCQ therapy became pregnant. Additionally, majority of pregnancies resulted in favorable outcomes, including full-term normal vaginal deliveries and cesarean sections. Interestingly, the rate of first-trimester pregnancy loss dropped to 13.0%, indicating that HCQ may help increase the survivability of pregnancies. Our findings are consistent with other research that examined the effect of HCQ on the outcomes of pregnancies in women with RM. For example, a French multicenter registry found that women with RM who were exposed to HCQ had a higher likelihood of pregnancies progressing beyond the first trimester.¹³ Similar to this, a pilot trial showed that the group treated with HCQ had a reduced miscarriage rate compared to the placebo group; however, the difference was not statistically significant, possibly because of the small sample size.¹⁴

In our study, 75.0% of individuals remained asymptomatic, indicating that HCQ was well tolerated. Most adverse effects were modest and temporary, such as slight increases in liver enzymes and gastrointestinal problems. Crucially, throughout the follow-up period, no appreciable changes were seen in hematological, renal, or hepatic markers, supporting the safety profile of HCQ documented in prior research. These results were consistent with earlier studies that evaluated HCQ's safety profile during pregnancy.^{15,16} Additionally, Singh et al's study from India revealed a similar pattern of HCQ adverse event profiles among patients throughout the preconception phase. Consideration of HCQ as a therapeutic option in controlling RM is supported by the positive safety and efficacy results seen, especially when immunological variables are involved.⁹

An antimalarial medication with immunomodulatory qualities, hydroxychloroquine (HCQ), has been used to treat autoimmune conditions such as rheumatoid arthritis and systemic lupus erythematosus (SLE). Recent studies have focused on its possible contribution to better pregnancy outcomes for women with RM, especially those who have underlying immunological problems.^{17,18} It is thought that HCQ's immunomodulatory properties support its potential as a treatment for RM. It has been demonstrated that HCQ inhibits toll-like receptor signaling, lowers pro-inflammatory cytokine production, and alters immune cell activity, all of which support an environment that is favorable for embryo implantation and maintenance. The antithrombotic qualities of HCQ may also lessen the chance of placental thrombosis, which is known to contribute to pregnancy loss.

This study possesses several strengths, including a prospective study design, clearly defined inclusion criteria, and comprehensive follow-up of participants through both the preconception and pregnancy periods. The relatively large sample size of 160 women adds to the robustness of the findings. However, limitations include the absence of a randomized control group, which restricts causal inference, and potential selection bias due to the single-centre design. Furthermore, longer-term neonatal outcomes were not assessed. Future studies with larger, more diverse populations are necessary to confirm these findings.

CONCLUSION

In conclusion, our study showed that HCQ during the periconception period improved pregnancy outcomes among women with RM, and it also appears to be safe. Its immunomodulatory and antithrombotic properties may address underlying pathophysiological mechanisms contributing to pregnancy loss. Future research should focus on identifying specific patient populations that may benefit most from HCQ therapy and delineating optimal dosing regimens to maximise therapeutic efficacy while minimising potential risks.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Singh M, Tripura NG. The role of hydroxychloroquine during the periconception period for recurrent miscarriage – a prospective observational study. *Int J Community Med Public Health* 2025;12:4500-5.