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Original Research Article

Role of hydroxychloroquine in preconception period of recurrent miscarriage patients

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ABSTRACT

Background: Three or more times of embryonic or fetal losses is termed as recurrent pregnancy loss (RPL). 1-2% women globally suffer from RPL which in turn causes physical and emotional devastation in such women. A deregulation of immune cells and cytokines is observed in women with RPL. Immunomodulatory drugs like hydroxychloroquine (HCQ) could thus be a justifiable line of therapy for normal conceiving in women who encountered RPL. Thus, the objective of current study was to evaluate whether oral administration of HCQ 200 mg twice a day in preconception period would improve conception and pregnancy outcome in RPL patients or not.
Methods: Total 50 women with history of RPL and difficulty in conception were given 200 mg bd of HCQ orally twice a day along with once a day 5 mg dose of folic acid. To the above treatment protocol low dose ecosprin was added immediately after positive pregnancy test. After 20 weeks, HCQ dose was terminated while ecosprin was continued. Iron, calcium and protein supplements were continued in all patients.
Results: 36 patients out of 50 who received HCQ conceived easily. Majority of patients who received the treatment protocol remained asymptomatic and exhibited no severe adverse effects. Out of 36 patients who conceived total 15 patients had normal delivery while 8 patients underwent lower segment caesarean section (LSCS) at term end and 5 patients had to undergo preterm delivery.
Conclusions: HCQS use in preconception period facilitate conception and prevent miscarriage in refractory cases of RPL.

Keywords: Recurrent pregnancy loss, Immune systems, Immunomodulatory drugs, Hydroxychloroquine, Preconception period

INTRODUCTION

According to world health organization (WHO) the term miscarriage is referred as baby who dies before 28 weeks of pregnancy, and if the babies die at or after 28 weeks than the condition is referred as stillbirths.[1] Recurrent pregnancy loss (RPL) is defined as failure of three or more pregnancies including embryonic and fetal losses before 20 to 24 weeks of gestation.[2] The prevalence rate of RPL is approximately 1% to 2% globally and is considered as reproductive health burden causing not only physical distress but also emotional devastation.[3]

Although standard investigations fail to reveal any apparent cause of RPL in more than 50% of couples, it is observed and reported that common underlying mechanisms of RM includes; immunological (20 to 50%), endocrine or hormonal (17 to 20%), anatomical (12 to 16%), genetic or choromosomal (5%), infections (0.5 to 1.5%) and blood coagulation/platelet defects.[4,5] A vital role is played by endometrial environment in placental development and embryo implantation.[6] Survival of the semi-allogeneic fetus in normal pregnancy is dependent on maternal immune tolerance. It has been observed and reported in several literatures that there exist a

deregulation of immune cells and cytokines in women with RPL.[7-9] Thus, it can be hypothesized that immunomodulatory drugs like hydroxychloroquine (HCQ) could be a relevant therapy for normal conceiving in women who encountered RPL.

The main therapeutic uses of HCQ includes: rheumatoid athritis (RA), malaria profylaxis and treatment, systemic and discoid lupus erythematosus (SLE).[10] Hydroxychloroquine is considered safe to be used in pregnant women and is widely used during pregnancy, specifically in patients with systemic lupus erythematous.[11] The therapeutic properties of HCQ like; anti thrombotic, vascular protective, immunomodulatory, improved glucose intolerance, lipid lowering and anti-infectious, could be beneficial and effective against some mechanisms of RPL with unidentified cause.[10-14] Additionally, convenient oral administration since the preconception period, low cost and minimal adverse event makes HCQ a possible treatment strategy for women with RPL.

METHODS

Study type, design, duration and sample size

Current study was a clinical interventional; cross over design conducted on 50 patients for a duration of twenty-two months from 01 March 2021 to 30 December 2022.

Inclusion criteria

Inclusion criteria for current study were; females of age group between 18 to 35 years, women with at least 3 earlier consecutive miscarriages in the first trimester of unknown origin, women with no uterine abnormalities and patients who did receive standard treatment with low dose ecosrpin and low molecular heparin (0.5 mg per kg body weight) in their earlier failed pregnancies.

Exclusion criteria

Exclusion criteria for current study were; earlier history of venous thrombosis and known contraindications to treatment by HCQ (retinopathy, hypersensitivity to HCQ, G6PD deficiency, intermittent acute porphyria chronic liver or renal insufficiency, extensive cutaneous psoriasis not controlled by local treatment).

Primary and secondary outcomes measured

Primary outcome determined in current study was live birth. Secondary outcomes that were determined in present study were adverse pregnancy outcomes, pre term birth, IUGR, Placental insufficiency and still birth.

Procedure

Study group patients' treatment protocol initiated before conception and at least 6 months after the last abortion. Patients of the study group administered 200 mg bd of HCQ tablet orally; along with once a day 5 mg dose of folic acid. To the above treatment protocol low dose ecosprin was added immediately after positive pregnancy test. After 20 weeks, HCQ dose was terminated while ecosprin was continued. Iron, calcium and protein supplements were continued in all patients.

Women were called after every 15 days for initial one month to ensure the occurrence of any unwanted effects like jaundice, loss of appetite, skin rashes, itchy skin, headache, stomach pain or any eye problems like; blurred vision, sensitivity to light or changes in colour visualization capacity. Muscle weakness, stiffness or spasms, throat/mouth ulcers, bruising and hypoglycaemia like side effect were also carefully observed in patients during their first month of visit post administration of treatment protocol. Skin reactions such as large areas of scaly skin, pus filled spots along with elevated temperature, or sensitization of skin to sun depicted by skin redness, hallucinations, confusion and depression with thoughts of self-harm were some other observation parameters that were investigated in patients post administration of treatment protocol.

Investigations done during follow-up

During follow up patients were investigated for complete blood count (CBC), renal function test, liver function test and other routine antenatal tests.

RESULTS

It was observed form the current study findings that most of the women patients (72%) who received the treatment protocol remained asymptomatic and exhibited no severe adverse effects (Table 1 and Figure 1). Total nine patients (18%) exhibited nominal side effects like headache, nausea, vomiting and abdominal pain (Table 1 and Figure 1). Three patients (6%) developed deranged liver functions, and two patients (4%) exhibited severe nausea and vomiting and could not tolerate the dose of HCQ; thus, these two patients were given exit from the current investigation by terminating the treatment protocol followed by liver and other supportive treatment for recovery.

Total 36 out of 50 patients conceived easily within 3 to 4 months of following treatment protocol, whereas 9 patients did not conceive even after following treatment protocol for 6 months (Table 2 and Figure 2). Total 8 of 36 patients aborted in first trimester while the rest of patients continued with pregnancy till delivery. Total 15 patients had normal delivery while 8 patients underwent LSCS at term end to deliver healthy babies. Total 5 patients had to undergo preterm delivery between 34 to 36 weeks, due to premature rupture of membranes (Table 3 and Figure 3).

Table 1: Distribution of patients according to adverse events observed after following the treatment protocol.

Observation	N (%)
Asymptomatic	36 (72)
Headache/nausea/vomiting/abdominal pain	9 (18)
Deranged liver functions	3 (6)
Severe nausea, vomiting/non-tolerance of HCQ	2 (4)

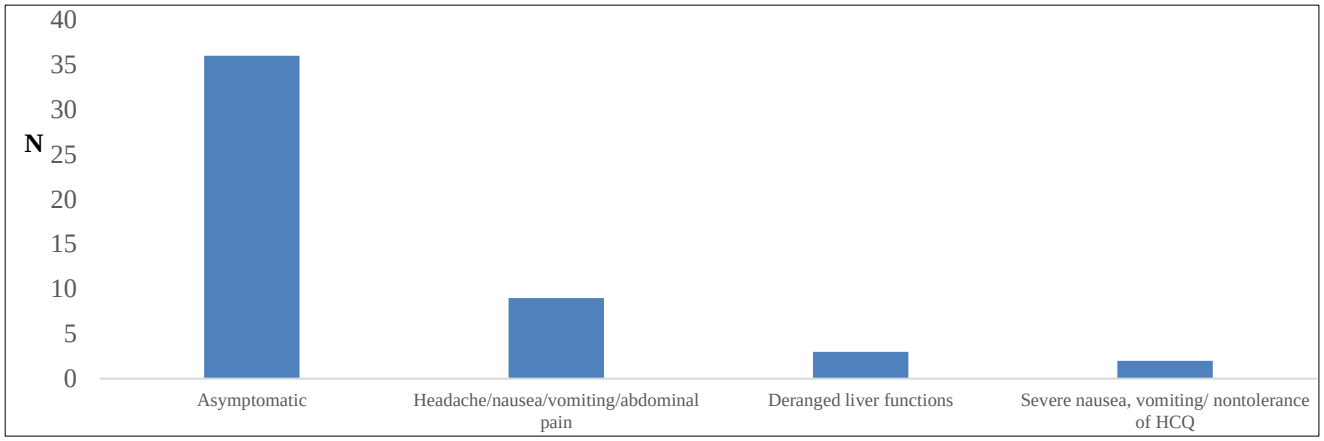

Figure 1: Number of patients with observed events post treatment protocol administration.

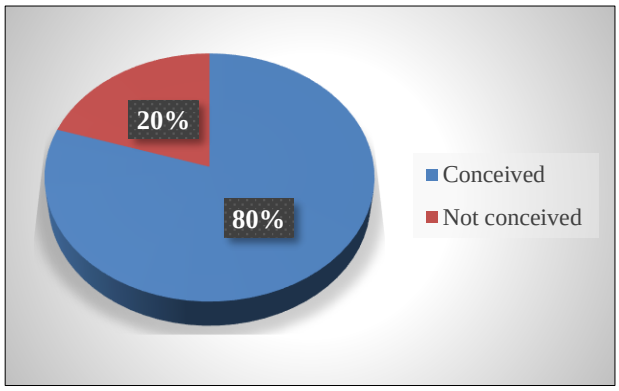

Figure 2: Conceiving rate in study participants.

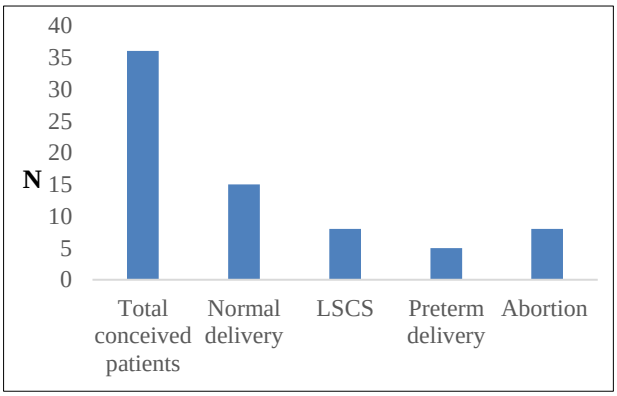

Figure 3: Distribution of conceived patients based on type of delivery.

Table 2: Distribution of patients according to success in conceiving.

Total number of patients	Conceived, N (%)	Not conceived, N (%)
50	36 (72)	9 (18)

Table 3: Distribution of conceived patients based on type of delivery.

Total conceived patients	Normal delivery	LSCS	Preterm delivery	Abortion
36	15	8	5	8

DISCUSSION

In the present investigation study group patients administered 200 mg bd of HCQ tablet orally for 20 weeks, along with once a day 5 mg dose of folic acid, low dose of ecosprin and supplements of iron, calcium and protein. Current study finding revealed that majority of patients either showed no adverse events or exhibited mild adverse events like headache, nausea, vomiting or abdominal pain post administration of agents mentioned in treatment protocol. Only 6% of patients exhibited deranged liver functions and 4% exhibited severe nausea, vomiting and were nontolerant to HCQ so, for such patients' treatment protocol was terminated and liver and other supportive

treatments were given for recovery. The current study findings were similar to reports published by Chakrabarti et al and Huybrechts et al.[10,11]

It was observed from current study findings that out of 45 study participants who continued treatment protocol, 72% patients conceived, while remaining 18% patients did not conceive even after following treatment protocol for 6 months. Out of the 36 patients who conceived, 8 patients aborted in first trimester while the rest of patients continued with pregnancy till delivery. The observed study findings closely related to the findings reported by Pasquier et al and de Moreuil et al.[12,13]

It was observed in current study that out of total 28 patients who continued delivery after following the treatment protocol; 53.57% patients delivered the baby through normal delivery, while 28.57 delivered the baby through LSCS. Total 17.85% of the patients had to undergo preterm delivery between 34 to 36 weeks, due to premature rupture of membranes. The current study findings thus revealed that majority of the patients who followed treatment protocol delivered the baby normally, these findings resembled to findings reported by Pasquier et al, de Moreuil et al and Mekinian et al.[13,14]

Limitations

A relatively small sample size of the investigated study participants could be a considerable limitation of current study and further studies and large trials are needed for better corelation of role of HCQ in patients of recurrent miscarriage.

CONCLUSION

It was concluded from current study findings that HCQ can be used in preconception period not only to ease conception but also to prevent early miscarriage in patients of recurrent miscarriage.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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