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Hydroxychloroquine in Obstetrics: Newer Perspectives

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Abstract

Hydroxychloroquine (HCQ) was developed during World War II to treat malaria. It has been extensively used to treat a diverse range of autoimmune diseases including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) during pregnancy for many decades. Additionally, HCQ was also used in cases with refractory antiphospholipid syndrome. The drug's exact mechanism of action in individual diseases is not clear and multiple possible explanations have been proposed for its immunomodulatory and anti-inflammatory actions. The safety of HCQ during pregnancy and lactation is well established by evidence of no major congenital malformation. There is no increased risk of adverse perinatal outcomes at a daily dose of 400 mg or less. It is also safe to use while breastfeeding. In recent years, HCQ has received significant attention because of its possible role in treatment for the highly infectious respiratory disease, COVID-19. Its role was also studied in preeclampsia, chronic placental inflammation, and repeated implantation failure during In Vitro Fertilisation (IVF). The most common adverse effects after long-term exposure include retinopathy and cardiotoxicity. HCQ is not indicated for patients having pre-existing retinopathy or other retinal diseases; conduction block or other arrhythmias; and/or severe liver or kidney disease. The recent updates for HCQ use in various conditions in obstetrics have been highlighted.

Key words: Pregnancy; hydroxychloroquine; preeclampsia; antiphospholipid syndrome.

Introduction

Hydroxychloroquine sulfate (HCQ) and Chloroquine phosphate (CQ) are derived from quinacrine. HCQ is an antimalarial medication, first approved by the FDA in 1955. HCQ has been used in the treatment of SLE in pregnancy since the early 1990s. Owing to its multiple immune modulatory and anti-inflammatory effects, HCQ has become an established therapeutic agent for pregnant patients at a dose of 200 - 400 mg/day for the treatment of autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), and undifferentiated connective tissue disease (UCTD). It also has a role in the regulation of glucose and lipid metabolism[1]. HCQ has been shown to have antiviral effects against several viruses.

Pharmacokinetics in pregnancy

The pharmacokinetics of HCQ are complex and not completely understood. This is because of its large volume of distribution, significant tissue binding, and long elimination half-life. Historically, terminal elimination half-life of HCQ was considered very long, (40 - 50 days), but more recent studies suggest a shorter half-life of about 5 days[2]. It has a high volume of distribution of 44,000 L and extensive tissue uptake[3]. HCQ can be detected in plasma for more than 42 days and takes around 6 - 8 weeks for complete elimination from the body. The drug takes at least 6 months of therapy, to reach a steady-state concentration of 95%, hence a shorter duration of therapy may not provide the full therapeutic results. The efficacy is further affected by variable pharmacokinetics among individuals[4]. Dose adjustments are not needed during pregnancy[5]. HCQ is available as 200 mg HCQ sulfate tablets, which contain 155 mg HCQ base. The daily dosage of HCQ may vary according to indication; however, the American Academy of Ophthalmology (2016-AAO) recommends no more than 5 mg/kg/day of real body weight in SLE to decrease retinopathy occurrence[6]. The complete remission of disease is related to higher blood concentrations, while lower blood levels may result in treatment failure. It is metabolised by cytochrome P450 enzyme in the liver, is predominantly excreted by the kidneys, and a small fraction is excreted in faeces, skin, and breast milk.

Mechanism of action

HCQ ($C_{18}H_{26}ClN_3O$) is a derivative of chloroquine. Though the exact mechanism of action is not fully understood, it has well-known anti-inflammatory and immunomodulatory effects as shown in Fig. 1.

Inhibition of TLR-7 and TLR-9: HCQ causes suppression of endosomal Toll Like Receptors (TLR) activation by direct binding to nucleic acids rather than inhibition of endosomal

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acidification. This results in inhibition of Interferon (IFN)-I production by plasmacytoid dendritic cells[7]. Inhibition of IFN-I production is also caused by inhibition of cyclic GMP-AMP synthase (cGAS) activity and STING (stimulator of interferon genes) pathway[8].

Inhibition of autophagy: Lysosomes have a main role in generating immune responses by regulating antigen processing. HCQ preferentially accumulates in lysosomes and raises their pH (Fig. 1), which inhibits antigen processing, prevents the alpha and beta chains of the major histocompatibility complex (MHC) class II from dimerizing, inhibits antigen presentation of the cell, and reduces the inflammatory response. By inhibiting lysosomal functions, it leads to inhibition of major histocompatibility complex (MHC) class II-mediated autoantigen presentation by antigen presenting cells to CD4+ T cells[9].

Inhibition of inflammatory cytokine production and angiogenesis: HCQ decreases mRNA expression of various Interleukins, e.g., IL-1α, IL-6, and Tumour Necrosis Factor (TNF-α) in cutaneous lupus erythematosus skin lesions. It also decreases vascular endothelial growth factor (VEGF) expression and results in inhibition of angiogenesis. It reduces local inflammation by decreasing mononuclear cellular infiltrate in the skin[10].

Antithrombotic effects: HCQ reduces blood cells aggregation and blood viscosity, lowers platelet aggregation by inhibition of phospholipase A2 *in vitro*. It decreases antiphospholipid antibodies (aPL) binding to phospholipid bilayers in trophoblast. It has shown a reduction in thromboembolic risk in SLE. The HCQ exposed SLE patients showed an 83% reduction in VTE risk in a case control study of 272 patients with SLE[11].

Effects on endothelial dysfunction: HCQ activates Extracellular signal regulated kinase 5 (ERK5) protein kinase and inhibits Vascular cell adhesion molecule 1 (VCAM-1) expression. ERK5 is a mitogen-activated protein kinase that

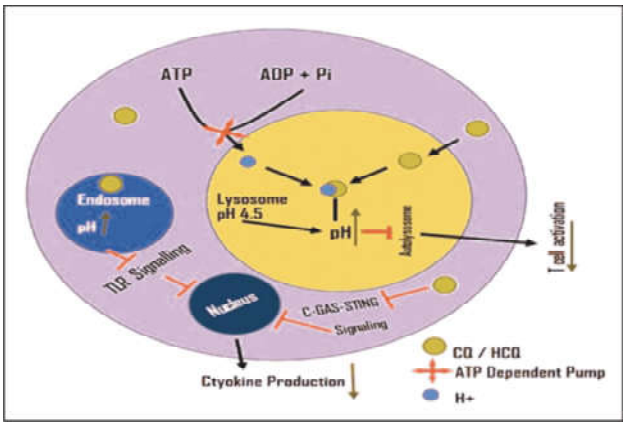

Fig. 1: *Mechanism of action of HCQ in the intracellular space.*

inhibits endothelial inflammation and dysfunction. This mechanism is responsible for anti-diabetic actions, lipid lowering effects and antioxidant actions[12-14] (Fig. 1). It causes reduced phosphorylation of protein kinase C, thus regulating nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase activation on the plasma membrane[15].

Metabolic effects: It has been shown in *in vitro* studies that HCQ improves insulin secretion and peripheral insulin sensitivity. HCQ also lowers glycated haemoglobin levels in patients with type 2 diabetes and rarely can cause hypoglycaemia. The prevalence of diabetes in patients with RA is similar to that of other patients; however, RA patients have sedentary lifestyles and often treated with corticosteroids that induce weight gain. Most of the anti-diabetic and lipid lowering effects of HCQ have been observed in RA patients. In a prospective observational cohort of 4,905 RA patients, 77% of patients had a reduction in relative risk of diabetes[13-14].

Antiviral effects: HCQ decreases the endosomal pH and prevents pH dependent virus-cell interaction. It also interferes with glycosylation of the angiotensin-converting enzyme 2 (ACE2) receptor, resulting in inhibition of SARS-CoV-2 S protein – ACE2 interaction[16].

Safety of HCQ in pregnancy and lactation

HCQ is a pregnancy category C drug and its use during pregnancy and breastfeeding is considered safe[17]. HCQ crosses the placental barrier and has foetal serum concentrations equal to those measured in maternal blood. HCQ is also excreted in breast milk, in a very small fraction of around 2% of maternal dose, which is considered safe[18]. The safety of HCQ in pregnancy has been established by various studies as shown in Table I. No adverse perinatal outcomes were reported with daily maternal doses of HCQ ≤400 mg. There was no increased risk of pre-term labour as shown by Bérard *et al* in a large cohort study involving 2,33,748 pregnant women exposed to HCQ[19]. There has been an increased use of HCQ use during pregnancy in the past 13 years (from 6.3% in 2005 to 60.9% in 2017), based on the reported safety profile of HCQ in pregnancy[20].

Role of HCQ in Obstetrics

Role of HCQ in SLE

SLE is a chronic autoimmune inflammatory disease that can virtually affect any organ or system. It has been seen that nearly 90% of SLE cases develop in women, more common in African-American women. Because of the fear of poor pregnancy outcomes [miscarriage, stillbirth, preterm labour, intrauterine growth restriction (IUGR), and pre-

eclampsia], these women were not advised to conceive in older times. The favourable pregnancy outcomes are seen for most women with quiescent lupus activity for at least 6 months before conception; absent lupus nephritis; neither antiphospholipid syndrome nor lupus anticoagulant are detected; and no superimposed preeclampsia. Pregnant women with SLE are also screened for anti-SS-A (antiRo) and anti-SS-B (anti-La) antibodies in addition to serum complement levels (C3 and C4), dsDNA titres, and antiphospholipid antibodies at the beginning of pregnancy because of associated foetal complications of congenital heart block in foetus.

Table I: Various studies regarding the safety of HCQ in pregnancy

Studies	Number of the study population	Results
Huybrechts *et al* (2020)[21]	HCQ exposed-1867 pregnancies HCQ unexposed-19,080 pregnancies	No substantial rise in significant congenital malformations in newborns exposed to HCQ during the first trimester of pregnancy
Mother To Baby/ Organisation of Teratology Information Specialists Autoimmune Diseases in Pregnancy Cohort study[22]	HCQ exposed-279 HCQ unexposed-279	No increased risk of structural congenital anomalies
Andersson *et al*, in 2021[23]	HCQ/CQ exposed-12,40,875 pregnancies	No increased risk of major birth defects, small for gestational age, preterm birth
PATCH study 2020[24] (Preventive Approach To Congenital Heart Block with HCQ)	54 women with SLE (who have previously had a pregnancy complicated by third degree heart block) HCQ started before the end of the 10th week of pregnancy and was maintained throughout delivery.	reduces the recurrence of CHB in anti-SSA/Ro-exposed pregnancies by more than 50%

Treatment modalities for SLE

There is no cure for SLE at present and complete remission of the disease is rare to achieve. HCQ should be continued during pregnancy because therapy interruption can precipitate a flare. For women not previously using HCQ, it should be initiated in the first trimester because its use is associated with an 85% reduction in the risk of having a small-for-gestational-age neonate, in addition to the reduced risk of foetal congenital heart block by 50% in women with anti-SSA antibodies. Further, the beneficial role of HCQ in SLE in terms of decreased incidence of pre-eclampsia is observed in a recent meta-analysis[25]. The ACOG recommends to start low-dose aspirin in SLE before 16 weeks as a preventive measure of pre-eclampsia. Multiple national and international rheumatology guideline groups recommend use of HCQ to manage SLE during pregnancy for all women with lupus as the standard of care[26-29].

Neonatal Lupus Syndrome

Neonatal lupus is characterised by lupus dermatitis, various haematological manifestations and occasionally congenital heart block. Maternal treatment with HCQ is the only modality which lowers the risk of neonatal lupus. Cutaneous manifestations appear at 4 to 6 weeks of age, present in 30 to 40 per cent of infants. These are usually seen in women with anti-SS-A and SS-B antibodies and nearly 50% of women have these antibodies. The incidence of foetal myocarditis is only 2 to 3 per cent in foetuses of mothers with these antibodies[30,31]. The risk of congenital heart block rises to 20 per cent with a prior affected child. The cardiac lesion is permanent, and a pacemaker is generally necessary. The long-term prognosis is poor[24,32].

Role of HCQ in pre-eclampsia

Pre-eclampsia has a complex pathogenesis, especially the early onset pre-eclpmsia. This syndrome is characterised by inflammation and oxidative stress resulting in cellular dysfunction, apoptosis, and hypoxia. The activation of NADPH oxidase leads to the formation of reactive oxygen species, which leads to activation of the Nuclear factor kappa-light-chain-enhancer of activated B cells (NEκB) controlled pathways, resulting in cell death by apoptosis[33-35]. The combination of ischaemia, NFκB activation and apoptosis is a trigger for the expression of TLR 7and 9, which further causes release of interferon α (IFNα) and the production of pro-inflammatory cytokines, such as interleukin 6 (IL6) and tumour necrosis factor α (TNFα). The sFlt-1 levels start rising with high TNFα and IL6 levels.

Since HCQ has anti-inflammatory, anti-oxidant and anti-thrombotic effects, it acts by inhibiting the production and release of specific cytokines and prostaglandins and decreasing NADPH oxidase activity and TLR activation; it may also reduce the production of reactive oxygen species. Moreover, HCQ safety in pregnancy is well established; hence many authors have proposed HCQ as a promising adjuvant treatment for preeclampsia.

Rahman *et al* reported that HCQ could reduce the oxidative stress-induced placental and endothelial dysfunction based on its antioxidant and anti-inflammatory action along with a positive effect on angiogenesis[33]. HCQ along with low-dose aspirin may be beneficial in the treatment of women with SLE along with Antiphospholipid syndrome (APS), by reducing the risk of thrombosis. The results showed increased rate of live births and a reduction of placenta-mediated complications (pre-eclampsia, IUGR and placental abruption)[36]. Mekinian *et al* studied the role of HCQ in patients with APS or asymptomatic carriers of antiphospholipid antibodies. The addition of HCQ to conventional treatment (aspirin and heparin) resulted in a

decreased rate of pre-eclampsia and/or HELLP (haemolysis, elevated liver enzymes, and low platelets) syndrome and fall in pregnancy losses from 81 to 19% in the group receiving HCQ[37].

Based on these promising results, HCQ may be a new preventive and therapeutic modality for patients with definite risk factors for pre-eclampsia and prior to the onset of severe complications. However, further research is still needed to prove the efficacy of HCQ in prevention and treatment of pre-eclampsia, and more results in this aspect are expected in future.

Role of HCQ in Antiphospholipid Syndrome (APS)

Antiphospholipid syndrome (APS) is a condition of autoantibody-mediated acquired thrombophilia that predisposes to recurrent thrombosis or pregnancy morbidity. This is characterised by persistently positive serum tests for antiphospholipid antibodies (aPLs) plus arterial and/or venous thromboses or pregnancy morbidity. Lupus anticoagulant is the only APA that has been consistently associated with adverse pregnancy outcomes. Around 30% of patients with SLE have aPLs. APS can have three different types of presentations: Thrombotic APS, Obstetric APS and Asymptomatic aPL Carriers.

HCQ in thrombotic APS: HCQ was used as an orphan medicinal product, licensed by European Medicines Agency for the treatment of cases with recurrent and refractory APS, despite adequate anticoagulation. The beneficial role of HCQ is mediated via anti-thrombotic, antiplatelet, and immunomodulatory properties[38,39]. Studies have also suggested that HCQ reduces endothelial dysfunction, improves vascular elasticity and improves blood flow[40]. Moreover, the risk of bleeding associated with HCQ is extremely low.

HCQ in Obstetric APS: The underlying pathology of obstetric APS involves placental thrombosis, inflammation, and complement activation. The use of low dose aspirin (LDA) and heparin is the current standard treatment in obstetric APS with an overall successful pregnancy outcome rate of 70%. However, the remaining 20 - 30% of women with obstetric APS do not respond to heparin and LDA. Better outcomes have been seen in retrospective studies of HCQ as an adjunctive therapy in patients with obstetric APS in addition to the standard treatment[38]. Sciascia *et al* reported higher rate of live births (67% vs 57%; $p = 0.05$) and a lower prevalence of pregnancy morbidity (47% vs 63%; $p = 0.004$)[36]. Gerde *et al* reported better pregnancy outcomes (97.1% (67/69) vs 62.5% (20/32); $p < 0.001$) and lower pregnancy complications in 87 women with refractory primary obstetric APS treated with HCQ compared to standard treatment alone (8.7% (6/69) vs 37.5% (12/32); $p < 0.001$)[41].

HCQ for Asymptomatic aPL Carriers

These individuals have no history of thrombosis (aPL carriers) with aPL, but are also at increased risk of developing thrombosis. In this sub-group, primary prophylaxis with aspirin should be used for prevention of myocardial infarction suggested by the Preventive Services Task Force (USPSTF) report[42]. The reduced risk of a thrombotic event was seen in a cross-sectional study of aPL positive patients with connective tissue disease and APS treated with aspirin and/or HCQ[43].

Role of HCQ in unexplained recurrent early miscarriage (RM)

Recurrent miscarriages have an incidence of 1 - 3%, and an aetiology is never established in approximately 50% of those. As demonstrated by the HEPASA study[44], there is no effective treatment to date, even if RM is associated with risk factors, such as aPL positive status, which is detected in 5 - 15% of women with RM. Mekinian *et al* (2016) found that there was currently no data on the clinical efficacy of HCQ in women with recurrent unexplained miscarriages[37].

Role of HCQ in COVID-19

The US Food and Drug Administration issued an Emergency Use Authorisation (EUA) on March 28, 2020, allowing HCQ and CQ to be used for certain hospitalised patients with COVID-19. HCQ was widely used for SARS-CoV-2 infections during the Coronavirus pandaemic, although data does not support its efficacy in the treatment of COVID-19[45].

Role of HCQ in Artificial Reproductive Therapy

Recent studies showed the association between various autoantibodies (antinuclear antibody, anti-RO/SSA antibody, and anti-dsDNA antibody) with poor reproductive outcomes by affecting embryo implantation, maternal pregnancy, the placenta, and the foetus[46]. In a recent retrospective study, a total of 128 patients who were positive for autoantibodies were included. The study was conducted between October 2017 and December 2022 in patients undergoing Frozen Embryo Transfer (FET) for 65 cycles. HCQ was administered 2 months before embryo transfer and continued till the end of the first trimester while a control group consisted of 63 cycles without HCQ. There were improved clinical pregnancy outcomes and a reduced rate of first-trimester abortion with HCQ use in patients who were positive for autoantibodies during Frozen Embryo Transfer (FET) cycles[47]. There were significantly higher implantation rates (IR), CPR, and ongoing pregnancy rates (OPR) in the treatment group than those in the control group. The results showed clinical pregnancy rate (CPR) OR: 3.106; 95% confidence interval (CI):1.458 - 6.616; P = 0.003. The biochemical pregnancy rate (BPR) and early

miscarriage rate (EMR) were also significantly lower in the treatment group than in the control group ($p = .029$, $p < .001$).

Role of HCQ in Rheumatoid Arthritis

Rheumatoid Arthritis is an immune system disorder just like SLE, Systemic Sclerosis. In nearly 50 - 70% of women with rheumatoid arthritis (RA), the disease improves during pregnancy and half of them will have moderate-to-severe RA activity through pregnancy. HCQ is a disease-modifying anti-rheumatic drug[5], and it is widely used as an anti-rheumatic agent in RA. HCQ interferes with immunological reactions through antigen-related biological events and the cytokines as mentioned earlier. It is thought to suppress and inhibit rheumatoid factor and acute-phase reactants in RA[13].

The use of HCQ in pregnant women with RA is a safe and effective therapy for early and mild to moderate RA, but it is used as an effective component of combination therapy for aggressive RA. Additional benefits of HCQ in patients with RA are the reduced risk of diabetes mellitus and its favourable effects on lipids[48].

Role of HCQ in chronic placental inflammation

Chronic placental inflammation is characterised by disrupted healthy placental tissue, which can only be confirmed by a post-delivery histopathological examination. It has been linked to severe complications of pregnancy, such as foetal growth restriction, premature labour, and miscarriage[49]. The value of adding HCQ to pregnant women with a positive history of chronic placental inflammation was studied by Brady *et al*, showing a decrease in disease severity and a trend for a higher live birth rate[50]. Hence, HCQ is a potential therapeutic option for such cases with chronic placental inflammation. Currently, there is no prospective controlled trials on the efficacy of HCQs in these settings, which emphasizes the need for further investigations to verify HCQ's efficacy in chronic placental inflammation.

Side-effects of HCQ

HCQ has multiple adverse effects, which require vigilance as mentioned in Table II. The common side-effects are nausea, vomiting, diarrhoea, and abdominal pain, which generally subside after a few days of treatment. Other adverse effects include retinopathy, hyperpigmentation, myopathy, and skin reactions[51]. Haemolysis has been reported in individuals with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. The most discussed and studied HCQ side-effect in SLE is retinopathy. The important risk factors for HCQ-related retinopathy are the duration of treatment, chronic kidney disease, and pre-existent retinal disease.

Table II: Side-effects of hydroxychloroquine[51].

System	HCQ's side-effects Short-term	HCQ's side-effects Long-term
Cardiovascular	Hours-days: prolonged QT (attention to the association with other drugs that affect the QT interval) Overdose: cardiovascular shock, collapse	Weeks-months: Conduction troubles, cardiomyopathy, vacuolar myopathy, valvular disorders
Dermatologic	Days-weeks: pruritus, rashes, urticaria exanthematous pustulosis, toxic epidermal necrolysis, Stevens-Johnson syndrome	Years: hyperpigmentation
Digestive intolerance	Days: nausea, vomiting, diarrhoea, bloating	
Haematological	Days to weeks: bone marrow toxicity, cytopenia (neutropenia)	Weeks-months: bone marrow toxicity, cytopenia (neutropenia)
Metabolic	Days: hypoglycaemia	
Neuromuscular	Days: increase of creatine kinase	Months: myositis, muscle weakness
Otorhinolaryngology	Days-weeks: ototoxicity, tinnitus	
Ophthalmologic	Days-weeks: eye accommodation troubles	Months-years (5-20 years): retinopathy (maculopathy)
Only case reports	Fulminant hepatic failure; toxic myopathy with respiratory failure; podocytopathy mimicking Fabry disease; rare cutaneous side-effects (erythroderma, dark rash, gray skin, erythema multiforme)	

Ophthalmologic screening is mandatory. In cases with pre-existing risk factors, yearly screening starting from baseline is required. In cases without retinopathy risk factors, the first screening at 5 years on HCQ, and yearly thereafter[52,53]. The current 2020 Joint Statement on HCQ recommended using sensitive testing modalities such as optical coherence tomography (OCT) and automated visual fields that could detect early retinal toxicity.

The most common long-term adverse effects (use over five years) include retinopathy, which can lead to retinal damage and permanent loss of sight, and cardiotoxicity, which results in damage of the heart and potentially lethal cardiac arrhythmias[54]. The risk of HCQ-induced retinopathy is 0.3% among patients on standard dosage[55], while cardiomyopathy is rare. Irreversible retinopathy with retinal pigmentation changes (bull's eye appearance), visual field defects (paracentral scotomas) and visual disturbances (visual acuity), maculopathies (macular degeneration), decreased dark adaptation, and colour vision abnormalities have been reported.

HCQ is not indicated in patients who have pre-existing retinopathy or other retinal diseases; conduction block or other arrhythmias; and/or severe liver or kidney disease. The

recommended dose limit is reduced from 6.5 mg/kg of ideal body weight to no more than 5.0 mg/kg of actual body weight.

Ongoing trials on the role of HCQ in recurrent miscarriage and pre-eclampsia

Two phase-3 multicentre double-blind randomised clinical trials are ongoing and are investigating the preventive effect of HCQ on foetal loss in women with a history of Recurrent Miscarriage[56]. One trial is "HCQ for prevention of RM or BBQ" (ClinicalTrials.gov: NCT03165136; estimated study completion date: February 2023). It is a French study, which is comparing HCQ to a placebo in women with RM (three or more losses in the first trimester of pregnancy) regardless of their thrombophilia status. HCQ was started before conception in a daily dose of 400 mg till the end of 10 weeks gestation, with the primary outcome of a live and viable birth. The other trial is "HCQ for Recurrent Pregnancy Loss", of women with RM without APL antibody positivity (ClinicalTrials.gov: NCT03305263; estimated study completion date: January 2023). It is a Danish study. Research is ongoing in three upcoming trials (not yet recruiting) on women with autoimmune diseases, with the aim to evaluate the impact of HCQ in addition to conventional therapy in the prevention of obstetrical complications (ILIFE trial: NCT03671174; HYDROSAPL[57]; and HYPATIA[58] as mentioned earlier.

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