

# Mechanisms and roles of hydroxychloroquine in pregnancy in rheumatic diseases

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## ABSTRACT

**Introduction:** Hydroxychloroquine (HCQ), originally an antimalarial drug, is currently used to treat multiple disorders, especially rheumatic diseases. Given its good efficacy and safety, HCQ is widely administered in pregnant patients. However, the safety profile of HCQ during pregnancy remains controversial due to limited research. In addition, HCQ has been reported to reduce preeclampsia in patients with systemic lupus erythematosus (SLE) and could potentially alleviate the symptom of preeclampsia. However, the clinical profile and molecular mechanism of HCQ in preeclampsia is yet to be fully understood.

**Method:** We reviewed the literature on HCQ treatment in pregnancy with rheumatic diseases and preeclampsia in PubMed and Web of Science. We also discussed the safety of long-term therapy with HCQ during pregnancy.

**Results:** HCQ mainly modulates autoimmune response through inhibition of lysosomal function, toll-like receptor (TLR) signalling, nicotinamide adenine dinucleotide phosphate-mediated oxidative stress and autophagy. Benefits of HCQ in treating rheumatic diseases, including antiphospholipid syndrome, rheumatoid arthritis and Sjogren's syndrome during pregnancy, has been demonstrated in clinics. In particular, multiple clinical guidelines recommend HCQ as an indispensable therapeutic drug for pregnant patients with SLE. Additionally, it may potentially function in preeclampsia to improve clinical symptoms.

**Conclusion:** HCQ is effectively used for rheumatic diseases during pregnancy. The benefits of HCQ treatment in rheumatic diseases outweigh the risk of adverse reactions it induces in pregnant women.

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**Keywords:** efficacy and safety, HCQ, preeclampsia, pregnancy, rheumatic diseases

## CLINICAL IMPACT

### What is New

- This presentation summarised the latest advanced role, mechanism, treatment and safety of hydroxychloroquine (HCQ) in rheumatic diseases during pregnancy.
- Meanwhile, we discussed the application prospects of HCQ in preeclampsia.

### Clinical Implications

- To provide the pharmaceutical perspective on the effect and safety of HCQ in pregnancy, aiming to help clinicians use HCQ or any other anti-rheumatic drugs more reasonably and safely in the treatment of pregnant women.

## INTRODUCTION

With the prevalence of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) around the world, hydroxychloroquine (HCQ) has once again come into public attention due to its potential therapeutic role in COVID-19. HCQ is a classic antimalarial drug that belongs to the 4-aminoquinoline phospholipase A2 inhibitors. It was first introduced in 1955 and quickly gained popularity in the treatment of systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS) and other rheumatic diseases. Apart from its immunomodulatory function, the effect of HCQ has extended to antiviral, hypolipidaemic, hypoglycaemic and antithrombosis, as well as anti-malignancies (Fig. 1).<sup>1</sup> Due to its good efficacy,

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safety profile and low cost, HCQ is now commonly administered as a single agent or in combination with other immunosuppressants during pregnancy to treat rheumatic diseases.<sup>2</sup>

Rheumatic diseases occur primarily in females of childbearing years, including SLE, APS, rheumatoid arthritis (RA) and Sjogren's syndrome (SS). HCQ predominantly alleviates the symptoms of typical rheumatic diseases, particularly skin problems and joint pain, by reducing the inflammatory response in patients. Since pregnant women with rheumatic diseases are always considered to be at higher possibility of pregnancy complications and adverse pregnancy outcomes (APOs), they should require more intensive observation and prompt pharmacotherapy. With the development and use of HCQ in clinical therapy, recent research has generally recognised the benefit of HCQ in improving pregnancy outcomes and its safety profile in pregnant women with rheumatic disorders.

Although the application of HCQ in reproductive immunity has become a new research hotspot, the molecular mechanism is not yet entirely understood. This review primarily focused on the mechanism and clinical treatment of HCQ in pregnancy with rheumatic diseases, such as SLE, APS, SS and RA. It also discussed the relevance and potential use of HCQ in preeclampsia. Finally, we further presented our opinion on the safety of pregnant patients taking HCQ for rheumatic disorders. Keywords

such as "rheumatic disease" OR "rheumatism" OR "antiphospholipid antibody syndrome" OR "Sjogren's syndrome" OR "rheumatoid arthritis" OR "systemic lupus erythematosus" OR "preeclampsia" AND "hydroxychloroquine" AND "pregnancy" OR "gestation" were used in the literature search in PubMed and Web of Science. We also checked reference lists for relevant publications, recent reviews and editorials.

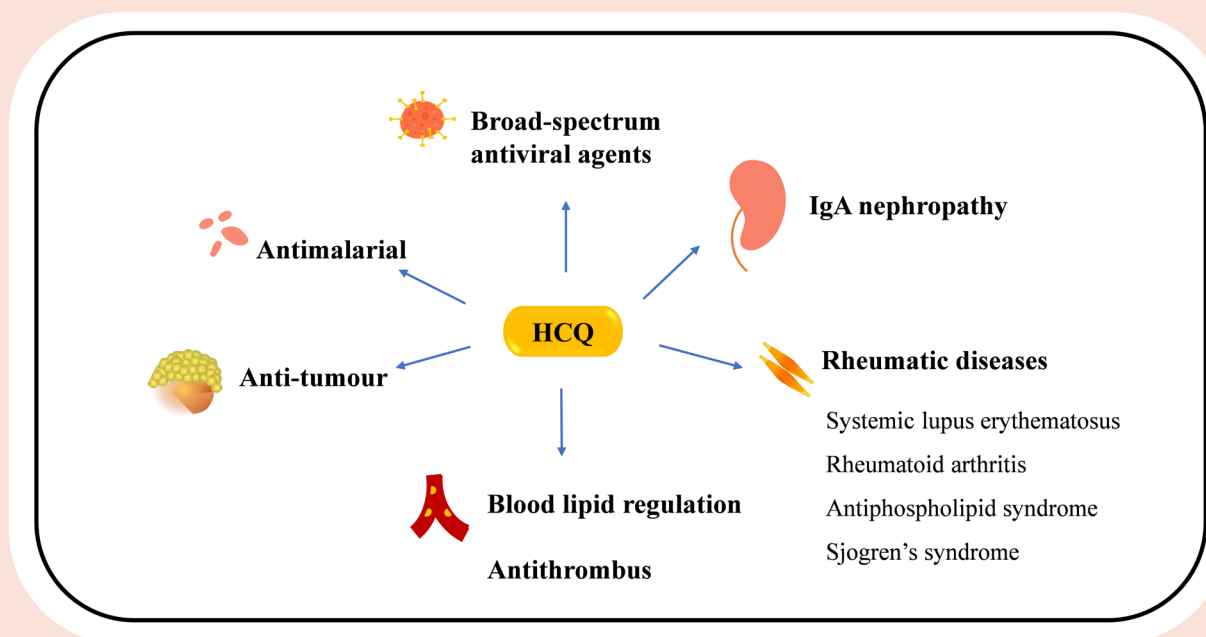
### Mechanism of action of HCQ

The exact mechanism of how HCQ regulates immune function has not been entirely delineated. HCQ has been reported to function mainly in rheumatic diseases through versatile immunomodulatory and anti-inflammatory responses, with additional roles such as antiplatelet and antioxidant effects.<sup>3</sup> In general, HCQ could exert therapeutic effects via modulating different cellular signals, especially the inhibition of endolysosomal activities, innate inflammatory signalling pathways, oxidative stress and thrombosis (Fig. 2).

### Inhibition of lysosomal function

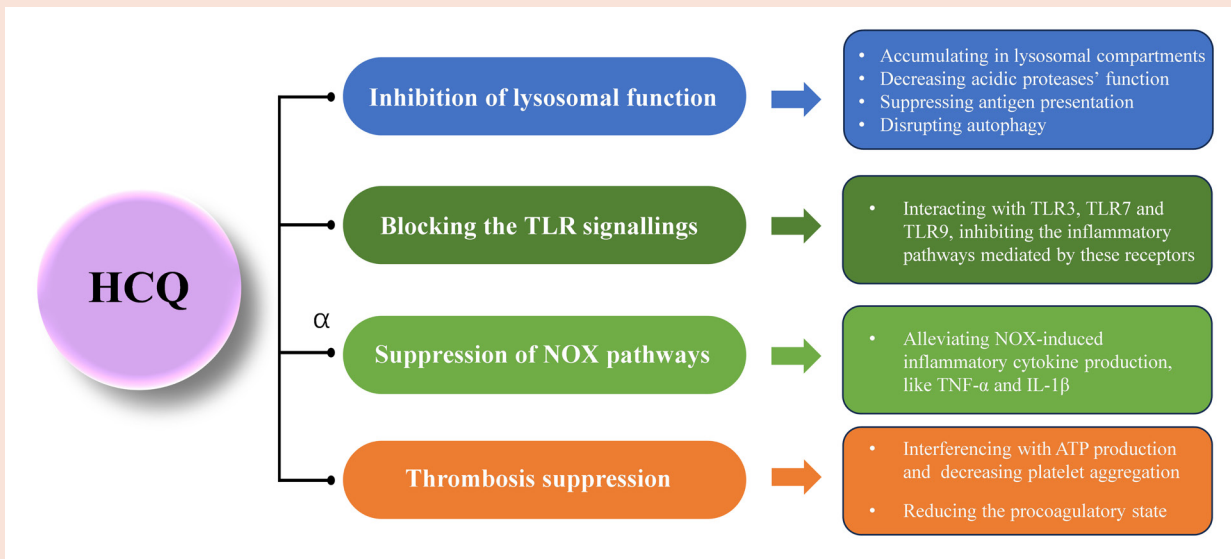
Due to its hydrophobicity and alkalescence, HCQ disperses quickly into acidic lysosomes across cell membranes. It accumulates in lysosomal compartments, stabilises cell membrane and decreases the functions of acidic proteases, thereby increasing the pH of acidic subcellular

Fig. 1. Benefits of HCQ in various diseases.



HCQ: hydroxychloroquine; IgA: immunoglobulin A

Fig. 2. Major mechanisms of HCQ.



ATP: adenosine triphosphate; HCQ: hydroxychloroquine; IL-1 $\beta$ : interleukin-1 beta; NOX: nicotinamide adenine dinucleotide phosphate (NADPH) oxidase; TLR: toll-like receptor; TNF- $\alpha$ : tumour necrosis factor-alpha

compartments. Meanwhile, alteration in acid enzyme activity reduces the formation and transport of major histocompatibility class II complex molecules, leading to suppression of antigen presentation and autoimmune responses. Furthermore, HCQ disrupts autophagy, a lysosomal-dependent degradation process that degrades damaged cytoplasmic materials and organelles to maintain cell homeostasis.<sup>1</sup>

### Inhibition of toll-like receptor (TLR)-mediated innate immune response

HCQ inhibits several typical inflammatory pathways, particularly the signalling mediated by TLRs. TLRs expressed primarily by immune cells are significant receptors in the innate immune system, and mediate the induction of inflammatory cytokine genes. TLR3, TLR7 and TLR9 of the innate immune system are present in the intracellular compartments like endosomes. TLR3 mainly induced the expression of type I interferon (IFN) and IFN-inducible genes via TRIF/IRF3. Sensitive to synthetic imidazoquinoline-like molecules, TLR7 triggered the induction of type I IFN and inflammatory cytokines via the myeloid differentiation primary-response protein 88 (MyD88)- and nuclear factor-kappaB (NF- $\kappa$ B)-dependent pathways. TLR9, activated by DNA in the endosome of immune cells, leads to the robust production of IFN. HCQ prefers to interact with TLR3, TLR7 and TLR9, and specifically blocks the activation of these receptors that mediate inflammatory pathways and cytokines. Therefore,

it prevents the activation of these receptors that mediate inflammatory pathways and cytokines.<sup>3</sup>

### Suppression of other signalling pathways

Nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOXs)—exclusive enzyme complexes in the generation of reactive oxygen species (ROS)—are involved in numerous proinflammatory signalling cascades. HCQ has been proven to alleviate NOX-mediated production of TNF- $\alpha$  and IL-1 $\beta$  by directly blocking the translocation of gp91phox.<sup>4</sup> It also protects the endothelium by suppressing NADPH and activating extracellular signal-regulated kinase 5 (ERK5),<sup>4</sup> because overproduction of ROS is the main cause of vascular endothelial dysfunction. With regard to second messenger-mediated signal transduction, HCQ impairs the expression and secretion of immune cytokines and factors in T- and B-cells by interfering with intracellular Ca<sup>2+</sup> mobilisation.<sup>5</sup>

In addition, before low molecular weight heparin was widely applied in clinical practice, HCQ was used to prevent pulmonary embolism after arthroplasty for its potential antithrombotic effect. Its anticoagulant and antithrombotic effects have gradually been recognised with the use of HCQ in treating diverse diseases. Belizna et al. found HCQ dose dependently reduced collagen-induced platelet aggregation and platelet  $\alpha$ -granule release. It suppresses platelet aggregation via adenosine diphosphate (ADP) inhibition and inhibits the release of arachidonic acid caused by activated platelets.<sup>6</sup>

## HCQ treatment in pregnancy with rheumatic diseases

### Systemic lupus erythematosus (SLE)

SLE is an autoimmune rheumatic disease presented with multiple organ injury. Although the pathogenesis of SLE remains incompletely understood, the autoimmune attack theory may be the essential hypothesis so far. Pregnancy with SLE increases the obstetric risk of APOs, such as preterm birth, intrauterine growth restriction and preeclampsia.<sup>2</sup> Generally, therapy for SLE aims to alleviate immune damage in cells, tissues and organs. HCQ benefits SLE from diverse perspectives, particularly through amelioration of systemic symptoms as well as improvement in musculoskeletal and cutaneous mucosal performance. Apart from HCQ-moderate inflammatory response, HCQ obviously decreased the possibility of thrombosis in SLE. Another advantage of HCQ is its potential role in preventing severe complications. It reduces the incidence of diabetes in a dose-dependent manner, as shown in a study of HCQ treatment with 200 mg/day for 1.8 years in SLE patients.<sup>7</sup> HCQ may also be beneficial for osteoporosis, a common complication in SLE patients, by increasing spinal bone mineral density, especially in women receiving prolonged steroid therapy. HCQ-treated group showed a trend towards lower prednisone dosage and reduced the occurrence of preeclampsia and preterm delivery in pregnant women with lupus.<sup>8,9</sup> HCQ treatment during pregnancy also significantly decreased flares during pregnancy and postpartum. Substantial evidence suggests that lupus activity and symptoms in pregnant women could be alleviated by HCQ without any risk to the fetus.<sup>10-12</sup> Significantly, most studies currently indicate that HCQ treatment in SLE women throughout pregnancy remarkably improved birth outcomes, in contrast to pregnant lupus mothers who did not take HCQ.<sup>10,13-15</sup> It also reduced recurrent miscarriages, the occurrence of hypertension, gestational diabetes and pregnancy complications.<sup>16</sup> Based on these findings (Table 1), HCQ should be continued during pregnancy. This is also supported by many clinical guidelines from different countries. A Chinese guideline for pregnancy with SLE suggests that HCQ reduces the activity and recurrence of SLE in pregnant women, improves pregnancy outcomes, and even benefits for the prevention of preeclampsia and neonatal heart block, without harmful effects on newborns.<sup>17</sup> HCQ plus low molecular weight heparin plus low-dose aspirin (LDA) is more suitable than HCQ in addition to LDA or glucocorticoid or Ig for pregnant patients undergoing SLE with antiphospholipid antibodies (aPL) and recurrent

pregnancy loss, according to the Latin American group for the study of lupus (GLADEL).<sup>18</sup> Practice guidelines of the British society for rheumatology (BSR) and the British health professionals in rheumatology recommend HCQ for all pregnant SLE patients, with the exception of contraindications.<sup>19,20</sup> The 2020 American College of Rheumatology (ACR) practice guideline strongly advises all SLE women to take HCQ during pregnancy if possible, showing that HCQ is beneficial to the outcomes of both mothers and fetuses.<sup>21</sup> Furthermore, the European League Against Rheumatism (EULAR) suggests that pregnancies with SLE should be treated with HCQ at a maintenance dose to stabilise the condition and improve pregnancy outcomes. However, the dose of HCQ should not exceed 5 mg/kg/real of body weight (BW) (Table 2).<sup>22</sup>

### Antiphospholipid syndrome (APS)

APS, characterised by thrombotic events and pathological pregnancies, is an autoimmune disorder that is more likely to lead to unfavourable pregnancy outcomes. Although low-dose aspirin and heparin treatment for pregnant women with APS has increased the live birth rate by approximately 70%, HCQ has commonly been administered as an adjunctive medication for the treatment of APS-related thrombosis.<sup>23</sup> It decreases the combination of aPL- $\beta$ 2GP1 complex and platelet aggregation by suppressing aPL-activated overexpression of GPIIb/IIIa on the platelet membrane.<sup>23</sup> Treatment of HCQ in patients with aPL during pregnancy increased the live birth rate (67% HCQ group versus [vs] 57% control group,  $P=0.05$ ) and decreased the prevalence of aPL-related pregnancy morbidity and complication (2% vs 10.9%,  $P=0.05$ ).<sup>24</sup> Emerging clinical studies also showed that treatment with 200–400 mg HCQ in refractory APS pregnant women could improve the pregnancy outcome, like lower rates of pregnancy loss, live birth and pregnancy complications (Table 3).<sup>25-27</sup> A retrospective study of 194 pregnant primary APS patients revealed that high dose HCQ (400 mg) and initiation prior to pregnancy were linked to a higher live birth rate in contrast to a low dose (200 mg) and treatment only during pregnancy.<sup>27</sup> To our knowledge, HCQ is currently not included in the standard therapy of primary APS, but it definitely benefits the refractory cases, involving refractory obstetrical APS. EULAR recommends the addition of HCQ in the first trimester may be conducive to APS patients with pregnancy, despite receiving a combination of LDA and heparin.<sup>28</sup> The other compelling clinical guideline has recommended HCQ used routinely

Table 1. Clinical studies on HCQ treatment in pregnant women suffering from SLE.

| Author or committee                | Year | No. of pregnancies                                                      | HCQ dosage                                                     | HCQ duration                                                                | Results and conclusion                                                                                                                                                                                                                                                         |
|------------------------------------|------|-------------------------------------------------------------------------|----------------------------------------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kroese SJ, et al. <sup>7</sup>     | 2017 | 110 pregnancies, 30 of which were treated with HCQ                      | 200 mg or 400 mg per day                                       | Throughout pregnancy                                                        | HCQ decreased the occurrence of flares (non-HCQ group: 6.4% mild and 2.6 severe; HCQ group: 2.6.7% mild and 0 severe) and the dosage of prednisone (OR 0.2, 95% CI 0.0–1.4; <i>P</i> =0.10), as well as increased the duration of pregnancy (95% CI 1.0–3.8; <i>P</i> ≤0.001). |
| Alle G, et al. <sup>10</sup>       | 2024 | 174 pregnant women with SLE                                             | 200 mg daily (6.9%), 400 mg daily (85.1%), different dose (8%) | Throughout pregnancy                                                        | SLE patients with subtherapeutic (HCQ ≤500 ng/mL: 8.8% versus [vs] 0.7%) and non-adherent HCQ levels (≤200 ng/mL: 13.3% vs 1.3%) had more severe flares during pregnancy.                                                                                                      |
| Levy RA, et al. <sup>11</sup>      | 2001 | 20 consecutive pregnant patients, 10 treated with HCQ                   | Not available                                                  | Beginning between 8 and 18 weeks of pregnancy until 12 weeks after delivery | HCQ group lowered prednisone dosage and improved pregnancy duration and Apgar scores compared to the placebo group.                                                                                                                                                            |
| Braga A, et al. <sup>12</sup>      | 2021 | 215 pregnancies from 143 patients, 63.7% with HCQ                       | Not available                                                  | During gestation                                                            | HCQ reduced the risk of flare in SLE patients during pregnancy.                                                                                                                                                                                                                |
| Leroux M, et al. <sup>13</sup>     | 2015 | 118 SLE patients totally, HCQ group (n=41) and no HCQ group (n=77)      | 400 mg daily                                                   | Before pregnancy or during the first 8 weeks                                | The HCQ group has a lower rate of preterm birth (15.8% vs 44.2%) and IUGR (10.5% vs 28.6%).                                                                                                                                                                                    |
| Balevic SJ, et al. <sup>14</sup>   | 2019 | 145 serum samples from 50 patients with RD, 56% of whom had SLE         | 400 mg per day commonly                                        | Throughout pregnancy                                                        | Of patients with SLE, more pregnancies (83%) with average HCQ levels ≤100 ng/mL delivered prematurely than 21% with average levels >100 ng/mL.                                                                                                                                 |
| Canti V, et al. <sup>15</sup>      | 2021 | 74 pregnancies in 53 SLE patients, 45 pregnancies were treated with HCQ | 300 mg/day                                                     | Throughout pregnancy                                                        | SLE patients with HCQ treatment reduced the IUGR rate (10% vs 32%) and showed significantly longer time to delivery (37.8 ± 1.72 vs 36.3 ± 4.11).                                                                                                                              |
| Abd Rahman R, et al. <sup>16</sup> | 2020 | 82 SLE pregnancies included 47 treatments with HCQ                      | Not available                                                  | Not available                                                               | Recurrent miscarriages (17.1% vs 0%, <i>P</i> =0.003), occurrence of hypertension (42.9% vs 6.4%, <i>P</i> =0.01), gestational diabetes mellitus (14.3% vs 0%, <i>P</i> =0.01) and concurrent medical illness (42.9% vs 14.9%, <i>P</i> =0.005) were reduced in HCQ group.     |

For superscript numbers, please see REFERENCES.

CI: confidence interval; HCQ: hydroxychloroquine; IUGR: intrauterine growth retardation; OR: odds ratio; RD: rheumatoid disease; SLE: systemic lupus erythematosus; RD: rheumatoid disease

Table 2. Recommendations of guidelines for HCQ therapy in pregnant women with SLE.

| Committee                  | Year | Recommendation for HCQ treatment in SLE patients with pregnancy                                                         | Grade                     |
|----------------------------|------|-------------------------------------------------------------------------------------------------------------------------|---------------------------|
| CHOPARD <sup>17</sup>      | 2022 | HCQ should be treated throughout pregnancy.                                                                             | Weak                      |
| GLADEL <sup>18</sup>       | 2018 | HCQ plus LMWH plus LDA is advised for pregnant SLE women with antiphospholipid antibodies and recurrent pregnancy loss. | Moderate                  |
| BSR and BHPR <sup>19</sup> | 2016 | HCQ should be treated and continued during pregnancy at a maximum of 400 mg/day.                                        | LOE 1 ++, GOR A, SOA 100% |
| BSR <sup>20</sup>          | 2018 | HCQ can be used at doses of up to 6.5 mg/kg/day, compatible with pregnancy and breastfeeding.                           | LOE 1 ++, GOR A           |
| ACR <sup>21</sup>          | 2020 | All women with SLE should take HCQ during pregnancy if possible.                                                        | Strong                    |
| EULAR <sup>22</sup>        | 2019 | HCQ is suggested for all patients with SLE, at a dose not exceeding 5 mg/kg/real BW.                                    | 1B/A<br>3B/C              |

For superscript numbers, please see REFERENCES.  
ACR: American College of Rheumatology; BHPR: British Health Professionals in Rheumatology; BSR: British Society for Rheumatology; BW: body weight; CHOPARD: Chinese Research Committee of Pregnancy and Reproduction in Autoimmune Rheumatic Diseases; EULAR: European League Against Rheumatism; GLADEL: Grupo Latino Americano de Estudio del Lupus; GOR: grade of recommendation; HCQ: hydroxychloroquine; LDA: low-dose aspirin; LMWH: low molecular weight heparin; LOE: level of evidence; SLE: systemic lupus erythematosus; SOA: strength of agreement

alone or adding to therapeutic schemes for pregnant women with refractory APS or who experience recurrent complications,<sup>29</sup> with a safe dose of 200–400 mg.

**Sjogren’s syndrome (SS)**

SS occurs more predominantly in women than in men, with a female-to-male ratio of about 9:1. Women with SS are likely to experience more complicated pregnancies than healthy women.<sup>29</sup> Although the therapeutic benefit of HCQ in classic SS symptoms remain controversial, there is research illustrating that HCQ alleviates oral domain symptoms and several indicators like unstimulated salivary flow rate (uSFR), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and immunoglobulin M (IgM) as well as immunoglobulin A (IgA) in general patients. Regarding the research on pregnant patients, a retrospective study included 109 pregnant women as control group and 26 pregnancies with SS group showed HCQ were used in 15 patients (57.7%) and may also help ameliorate obstetric outcomes.<sup>30</sup> In 853 autoimmune pregnancies with 49 SS patients, HCQ therapy decreased preeclampsia (19.8% vs 8.91%,  $P<0.001$ ), early-onset preeclampsia (7.78% vs 2.51%,  $P=0.007$ ) and pregnancy loss (2.99% vs 0.56%,  $P=0.036$ ) significantly. Forty-two (85.71%) of 49 SS patients had taken HCQ.<sup>31</sup> On the contrary, Ballester C et al. found there was no premature delivery or low birth weight percentile child in primary SS pregnant patients with HCQ.<sup>32</sup> However, the insufficient number of HCQ group ( $n=6$ ) limited the evaluation of the possible beneficial effects of HCQ. Several

reports also indicated that there is no association between HCQ and a good pregnancy outcome in SS,<sup>33,34</sup> but these findings need to be confirmed in larger sample size studies (Table 4). Furthermore, both EULAR and Sjogren’s Syndrome Foundation suggested that first-line therapy for SS should concentrate on symptom relief, with HCQ (200 mg/day) to treat musculoskeletal pain treatment.<sup>35,36</sup> They also recommended assessing the benefits and risks for patients during pregnancy. BSR also advised the administration of HCQ (6 mg/kg) in SS, especially in patients with skin and joint lesions or fatigue symptoms. Besides, it was mentioned that HCQ might be continued throughout pregnancy and breastfeeding.<sup>37</sup>

**Rheumatoid arthritis (RA)**

RA is a long-term inflammatory joint disorder with a variable progression. Historically, methotrexate (MTX), sulfasalazine, leflunomide, HCQ or chloroquine (CQ) are referred to as disease-modifying anti-rheumatic drugs (DMARDs), generally used in RA. Regrettably, although considerable reviews have established that HCQ is appropriate for pregnant patients with mild and moderate RA, we found few clinical studies on the effectiveness of HCQ treatment in pregnant patients with RA. However, the potential role of HCQ has been widely studied in general patients with RA. Combination of MTX with HCQ in RA treatment was more efficient than MTX alone.<sup>38</sup> According to the 2021 ACR guideline, HCQ is more appropriate than other DMARDs in the therapy of DMARDs-naïve patients with mild RA.<sup>39</sup> EULAR recommends HCQ

Table 3. Clinical studies on HCQ treatment in pregnant women with APS.

| Author or committee              | Year | No. of pregnancies                                  | HCQ dosage                                         | HCQ duration                                                                                                 | Results and conclusion                                                                                                                                                                                                                                            |
|----------------------------------|------|-----------------------------------------------------|----------------------------------------------------|--------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sciascia S, et al. <sup>24</sup> | 2016 | 170 pregnancies in 96 women                         | 400 mg (200 mg twice daily) or 200 mg (once daily) | At least 6 months prior to pregnancy and continued throughout pregnancy                                      | HCQ group has a higher live birth rate (67% vs 57%, $P=0.05$ ), prolonged pregnancy (27.6 weeks vs 21.5 weeks, $P=0.03$ ) and lower occurrence of aPL-related pregnancy morbidity and complication (2% vs 10.9%, $P=0.05$ ).                                      |
| Mekinian A, et al. <sup>25</sup> | 2015 | 35 pregnancies from 30 APS patients                 | 200–400 mg                                         | 80% started before pregnancy                                                                                 | HCQ decreased pregnancy losses from 81% to 19% and improved the rate of live born babies to 78% in patients with refractory obstetrical APS.                                                                                                                      |
| Gerde M, et al. <sup>26</sup>    | 2021 | 101 pregnancies of 87 refractory primary OAPS women | 200 mg per day or 200 mg twice daily               | At least 2 months before pregnancy (200 mg) or initiation of pregnancy, both throughout the entire pregnancy | The live birth rates were obviously higher in the group receiving with HCQ (97.1%, 67/69) with regard to the control group (62.5%, 20/32) ( $P<0.001$ ). The occurrence of pregnancy complications was also reduced in the HCQ group (8.7% vs 37.5%, $P<0.001$ ). |
| Ruffatti A, et al. <sup>27</sup> | 2018 | 194 pregnant PAPS patients                          | 200–400 mg daily                                   | 112 patients (57.7%) before pregnancy and 82 (42.3%) during pregnancy                                        | Treatment with HCQ markedly increased the live birth rate ( $P=0.027$ ). A higher dosage (400 mg vs 200 mg, $P=0.036$ ) and treatment before pregnancy (before vs during pregnancy, $P=0.027$ ) contributed to a higher live birth rate.                          |

For superscript numbers, please see REFERENCES.

aPL: antiphospholipid antibodies; APS: antiphospholipid syndrome; HCQ: hydroxychloroquine; OAPS: obstetric APS; PAPS: primary APS

to be considered only in a particular circumstance when the other DMARDs failed or with MTX and sulfasalazine.<sup>40</sup> Furthermore, the Asia Pacific League of Associations for Rheumatology notes HCQ can only be used in combination with other DMARDs in patients with RA, primarily considering its possible metabolic and cardiovascular benefits.<sup>41</sup> Thus, reviews summarise and conclude that HCQ is beneficial for RA patients with a mild or moderate disease during pregnancy and suggest continuing treatment in these patients who were willing to conceive. Regarding the guideline recommendation for RA pregnant patients, recommendations for medication therapy in pregnancy just points out HCQ did not increase the occurrence of congenital malformations and can be used throughout pregnancy with rheumatic diseases.<sup>19</sup> HCQ efficiency on pregnant women with RA should be further studied.

### Potential use of HCQ in preeclampsia

Preeclampsia (PE) is an obstetric complication leading to high neonatal and maternal morbidity and mortality. Rheumatic diseases tend to increase the incidence of preeclampsia. Since HCQ is generally used for thrombosis prevention, anti-inflammation and anti-oxidation in rheumatic diseases, the researchers investigated whether HCQ directly plays a preventive role in preeclampsia, which has similar standard features and pathophysiology to SLE.<sup>8,42</sup> In terms of molecule mechanism,

endothelial dysfunction is one of the most persuasive opinions on preeclampsia development. Researchers preliminarily speculate that HCQ may benefit PE by suppressing oxidative stress and inflammatory mediators like cytokines, chemokines and cell adhesion molecules (i.e. intercellular adhesion molecule 1 [ICAM-1], vascular cell adhesion molecule 1 [VCAM-1]), which could result in endothelial damage.<sup>42</sup> Generally, HCQ restores NOX availability and disrupts vascular ROS overproduction induced by NADPH oxidase. HCQ also mitigated endothelial injury of PE by inhibiting the release of TNF- $\alpha$  and VCAM-1 as well as ICAM-1 to keep monocyte from adhering to the endothelium.<sup>42</sup> Despite HCQ being the major medication in the treatment of pregnancy with SLE, no randomised controlled trials (RCTs) and observational studies have been conducted to report the efficiency of HCQ treatment in preeclampsia women without rheumatoid diseases. Previous clinical studies only focused on the treatment of HCQ in preeclampsia induced by rheumatoid disorders. Rector et al. indicated no statistically significant correlation between HCQ and preeclampsia in either nulliparous or multiparous lupus pregnancies.<sup>43</sup> Conversely, it reported that HCQ treatment in pregnant women with autoimmune diseases reduced the occurrence of preeclampsia.<sup>24</sup> A meta-analysis including 709 HCQ-treated pregnancies and 1055 pregnancies without HCQ showed that the additional use of HCQ apparently

Table 4. Clinical studies of HCQ therapy in pregnancy with SS.

| Author or committee               | Year | No. of pregnancies                                                                         | HCQ dose            | HCQ duration                                                                        | Results and conclusion                                                                                                                                                 |
|-----------------------------------|------|--------------------------------------------------------------------------------------------|---------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Barros T, et al. <sup>30</sup>    | 2022 | 109 normal pregnant women and 26 SS pregnancies, 15 pregnancies with HCQ therapy           | Not reported        | Not reported                                                                        | Treatment with HCQ might benefit the obstetric results in SS patients.                                                                                                 |
| Ye S, et al. <sup>31</sup>        | 2023 | Among 853 pregnancies with autoimmune, 49 pregnancies with SS, of whom 42 treated with HCQ | ≤400 mg/day         | 32 initiated before pregnancy, 5 from early pregnancy, 5 from mid or late pregnancy | HCQ treatment significantly reduced preeclampsia, early-onset preeclampsia and pregnancy loss in 853 pregnancies with autoimmune abnormalities, including 49 SS cases. |
| Ballester C, et al. <sup>32</sup> | 2017 | 54 pregnancies in 19 women with pSS                                                        | At least 200 mg/day | Started before pregnancy and throughout the pregnancy                               | 6 patients treated with HCQ (n=6) did not deliver prematurely or give birth to a child in the LBW percentile.                                                          |
| Fierro JJ, et al. <sup>33</sup>   | 2023 | 48 SLE and 21 pSS pregnancies with 70 fetuses (1 twin)                                     | Not reported        | Not reported                                                                        | No significance of APO in patients with pSS between HCQ use and non-HCQ use.                                                                                           |
| Priori R, et al. <sup>34</sup>    | 2013 | 45 pregnancies in 36 women, 11% of which were treated with HCQ                             | Not reported        | Not reported                                                                        | No differences in pregnancy and fetal outcome no matter whether treated with medications, including HCQ.                                                               |

For superscript numbers, please see REFERENCES.  
APO: adverse pregnancy outcomes; HCQ: hydroxychloroquine; LBW: low birth weight; pSS: primary Sjogren’s syndrome;  
SLE: systemic lupus erythematosus; SS: Sjogren’s syndrome

decreased the total risk of preeclampsia in pregnancies with SLE by 46%, but it had no effect on the incidence of preeclampsia for APS/aPLs patients.<sup>44</sup> In parallel with that conclusion, Liu et al. summarised that treatment with 200–400 mg of HCQ daily significantly lowered the incidence of preeclampsia in autoimmune disorders.<sup>9</sup> Therefore, the clear efficiency of HCQ in preeclampsia induced by rheumatic diseases needs more evidence from further RCTs and large-scale prospective cohort studies. Next, more basic and clinical studies should examine the benefit of HCQ treatment in preeclampsia patients without rheumatic diseases.

Safety of HCQ therapy during pregnancy

Drug safety during pregnancy is a significant consideration for medical treatment. HCQ is an oral medication that is rapidly and completely absorbed from the upper intestinal tract.<sup>3</sup> It is primarily metabolised into N-desethylhydroxychloroquine in the liver via cytochrome P450 enzymes.<sup>3</sup> A large apparent volume of distribution leads to an elimination half-life of approximately 40 to 60 days.<sup>3</sup> Since creatinine clearance is not associated with the response to HCQ bioavailability, dosage adjustment is not necessary in patients with

renal insufficiency. Notably, HCQ readily crosses the placenta with the ratio of fetal concentration to maternal concentration being 1.04.<sup>45</sup> Various adverse reactions of HCQ have been found, of which ocular, skin and cardiac toxicity represent the most potential, especially when long-term therapy and large doses are used.<sup>45</sup> A small number of investigations indicate that HCQ treatment during pregnancy may be associated with ocular damage in fetuses.<sup>46,47</sup> This is debatable because normal newborns are likely to have malformations and these are just a few cases in the control group. A cohort study proposed the risk of malformations in first trimester pregnancy was slightly increased by HCQ, showing an adjusted relative risk (RR) of 1.26.<sup>48</sup> A clinical trial showed 5 of 45 (11%) infants exposed to 400 mg HCQ in utero had a prolonged corrected QT interval of more than 2 standard deviation (SD), without other symptoms.<sup>49</sup> Meanwhile, numerous clinical studies recently consider HCQ has no harmful effect on fetal outcomes (Table 5). In a retrospective study, 14 mothers who received HCQ treatment for an average of 7.2 months during their pregnancies at an average dose of 317 mg reported that their newborns’ visual acuity was normal with no

Table 5. Clinical studies on the safety of HCQ treatment during pregnancy.

| Authors                                     | Type of study       | Year | HCQ duration                                                                         | HCQ dosage                       | No. of pregnancies                                                              | Results and conclusion                                                                                                                          |
|---------------------------------------------|---------------------|------|--------------------------------------------------------------------------------------|----------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| Huybrechts KF, et al. <sup>48</sup>         | Retrospective study | 2021 | During the first trimester versus no use                                             | 371 mg mean daily dose           | 2045 pregnancies exposed to HCQ and 3,198,589 pregnancies without HCQ exposure  | A small increase in the risk of malformations associated with HCQ use in the first trimester, particularly with a daily HCQ dose ≥400 mg.       |
| Friedman DM, et al. <sup>49</sup>           | Clinical trial      | 2020 | Throughout pregnancy                                                                 | 400 mg daily                     | 45 infants exposed to HCQ during gestation                                      | HCQ treatment during pregnancy is associated with a low incidence of infant QTc prolongation.                                                   |
| Klinger G, et al. <sup>50</sup>             | Retrospective study | 2001 | 7.2 months mean duration of HCQ exposure                                             | 317 mg average daily dose        | 14 HCQ-treated cases in 21 pregnancies                                          | No ophthalmic abnormality was found in children exposed to HCQ in uterus.                                                                       |
| Costedoat-Chalumeau N, et al. <sup>51</sup> | Retrospective study | 2003 | At least 6 months prior to pregnancy and throughout gestation                        | 200 mg twice daily or once daily | 133 pregnancies treated with HCQ, 70 pregnancies without HCQ                    | Pregnancy outcomes were not statistically different between 2 groups.                                                                           |
| Reynolds JA, et al. <sup>52</sup>           | Retrospective study | 2023 | Prescribed during pregnancy                                                          | Not recorded                     | 284 live births of 199 mothers, 149/284 (52.5%) exposed to HCQ                  | No obvious negative outcomes in children exposed to HCQ during pregnancy.                                                                       |
| Chambers CD, et al. <sup>2</sup>            | Prospective study   | 2022 | HCQ treatment in the first day of the last menstrual period to the end of pregnancy  | 324.8 mg average daily dose      | 837 pregnancies, of which 279 exposed to HCQ                                    | HCQ exposure showed no abnormality in the rates of structural defects or other adverse outcomes. Risks did not differ at HCQ doses ≥400 mg/day. |
| Andersson NW, et al. <sup>53</sup>          | Retrospective study | 2021 | Women with HCQ prescriptions from 14 days before conception                          | 200 mg (IQR, 200–250)            | 1,240,875 pregnancies, of which 303 exposed to HCQ                              | Pregnancies treated with HCQ have no increased risk of major birth defects, preterm birth or SGA.                                               |
| Bérard A, et al. <sup>54</sup>              | Prospective study   | 2021 | 71.8 days on average                                                                 | 204.3 mg mean daily dose         | 233,748 pregnancies, including 105 HCQ-exposed cases                            | No data showed the increased risk of prematurity, LBW or MCM in HCQ-exposed pregnancy.                                                          |
| Leroux M, et al. <sup>13</sup>              | Retrospective study | 2015 | Before pregnancy or during the first 8 weeks                                         | 400 mg daily                     | 118 SLE patients, containing HCQ group (n=41) and group without HCQ (n=77)      | No malformation was found in fetuses exposed in utero to HCQ.                                                                                   |
| Diav-Citrin O, et al. <sup>55</sup>         | Prospective study   | 2013 | 98.2% of patients were treated with HCQ at least in the first trimester of pregnancy | 300 mg (IQR, 200–400)            | 455 pregnant women without HCQ exposure compared to 114 HCQ-exposed pregnancies | HCQ treatment in pregnancy is not a major malformation.                                                                                         |
| González R, et al. <sup>56</sup>            | Clinical trials     | 2024 | 400 mg/day for 3 days and 200 mg/day for 11 days                                     | 400 mg/day and 200 mg/day        | 55 women in HCQ group and 60 women in control                                   | No differences were in the occurrence of adverse pregnancy outcomes between 2 groups.                                                           |

For superscript numbers, please see REFERENCES  
HCQ: hydroxychloroquine; IQR: interquartile range; LBW: low birth weight; MCM: major congenital malformations; QTc: heart rate-corrected QT interval; SGA: small size for gestational age; SLE: systemic lupus erythematosus

ophthalmological abnormalities.<sup>50</sup> The conclusion was also confirmed by a study that included 90 women and 133 pregnancies treated with 200 mg HCQ per day (11 pregnancies) or twice daily (122 pregnancies).<sup>51</sup> Reynolds et al. showed no significant differences in the incidence of congenital malformations or intrauterine growth restriction, regardless of whether children were exposed to HCQ in utero or not.<sup>52</sup> Additionally, HCQ treatment did not increase the risk of spontaneous abortion or preterm delivery, birth defects and low birth weight, compared to the control group without HCQ.<sup>2,13,53,55</sup> This is consistent with data from an RCT of 115 pregnant women with mild SARS-CoV-2 infection, which found no obvious differences in the occurrence of adverse pregnancy outcomes and newborns with health problems at birth between the HCQ group and the control.<sup>56</sup> A meta-analysis comprising 3948 immune-disordered pregnancies, of which 1617 patients were in the HCQ group and 2331 in the control group, revealed that there was no significant correlation between HCQ and adverse fetal outcomes and congenital malformation.<sup>8</sup> Although the safety evidence of HCQ during pregnancy in clinical studies remains insufficient to evaluate teratogenicity, most researchers insist that the benefits of HCQ treatment in pregnant women could outweigh the potential risks in the clinic.<sup>57</sup> Furthermore, we discover the amount of HCQ in these articles, which showed no effect on fetal safety, varies approximately from 200 to 400 mg during pregnancy. Huybrechts et al. showed that a daily dose of  $\geq 400$  mg HCQ in the first-trimester had a higher risk of malformations than  $< 400$  mg daily (RR 1.33 vs 0.95).<sup>48</sup> Therefore, the possibility of the HCQ side reactions occurring may be dose dependent. This is verified by a consensus from the Netherlands, which states that HCQ treatment at a dose of 200–400 mg/day during pregnancy and lactation may be safe for pregnant women.<sup>58</sup> EULAR also announced that the recommended dose of less than 5 mg/kg carries a low risk of toxicity in pregnant SLE patients.<sup>22</sup>

## CONCLUSION

Undoubtedly, HCQ is extensively used as a safe modulator in pregnant women with rheumatic diseases. Based on previous evidence, there is less risk of adverse fetal outcomes when treated with HCQ at a dose below 400 mg. However, there are insufficient prospective studies and no large-scale RCTs on the efficacy and safety of HCQ in rheumatic diseases. Currently, a multicentre, double-blind, prospective clinical trial called HIBISCUS is ongoing in order to investigate HCQ safety and whether additional treatment with HCQ improves the fetal outcomes in a population of

patients with primary APS.<sup>59</sup> HYPATIA, another international multicentre RCT, is also underway to explore the effectiveness of HCQ in improving pregnancy outcomes in patients with persistently positive aPL, as well as its safety.<sup>60</sup> With its low cost, HCQ might be an extremely valuable adjunct to the treatment of rheumatic diseases during pregnancy.

## Ethics statement

Not applicable

## Declaration

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