Efficacy of Hydroxychloroquine use on placental mediated diseases in Pregnancies with Lupus and/or Antiphospholipid Autoimmunity: A Systematic Review and Meta-Analysis

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Abstract

Background: Although hydroxychloroquine (HCQ) has been utilized for the therapy of antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE), it is unknown how HCQ affects lupus activation throughout gestation, preeclampsia, and fetal growth restriction (FGR).

Methods: Until September 11, 2024, the databases of PubMed, Embase, and Cochrane were scanned for observational research or randomized clinical trials (RCTs) including extra HCQ therapy and pregnant patients with APS/positive antiphospholipid antibodies (aPLs) and/or SLE. Preeclampsia, IUGR, and high lupus activity risks were investigated.

Results: Thirteen cohort studies and one RCT were selected. The pooled meta-analysis comprised 1764 pregnancies (709 in the HCQ group vs. 1055 in the placebo group). The likelihood of elevated lupus activity dropped following the extra utilization of HCQ (RR: 0.74, 95% CI: 0.57–0.97, p = 0.03). The overall prevalence of preeclampsia dropped (RR: 0.54, 95% CI: 0.37–0.78, p = 0.001). The SLE subgroup (RR: 0.51, 95% CI: 0.34–0.78, p = 0.002) and the APS/aPLs subgroup (RR: 0.66, 95% CI: 0.29–1.54, p = 0.34) did not exhibit statistical significance, according to the subgroup evaluation. Neither the SLE subgroup (RR: 0.74, 95% CI: 0.40–1.36, p = 0.33) nor the APS/aPLs subgroup (RR: 1.26, 95% CI: 0.34–4.61, p = 0.73) showed a statistically significant reduction in the prevalence for IUGR (RR: 0.80, 95% CI: 0.47–1.35, p = 0.46).

Conclusion: The results refute the notion that HCQ reduces the risk of FGR for SLE and/or APS/aPLs or the likelihood of preeclampsia for APS/aPLs participants. Nonetheless, additional administration of HCQ may reduce the likelihood of preeclampsia in those with SLE as well as the probability of elevated lupus activity during pregnancy.

Keywords: SLE ; antiphospholipid syndrome; hydroxychloroquine; preeclampsia; FGR.

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Introduction

Antiphospholipid syndrome and SLE are both of the most significant systemic autoimmune conditions affecting women who are fertile. Antinuclear antibodies and the formation of immunological compounds, which result in the inflammation of several systems, are characteristics of systemic lupus erythematosus (1). Antiphospholipid antibodies (aPLs) and clinical signs of thrombus or worse pregnancy complications are the two main characteristics of APS. While the majority of APS are linked to SLE and are referred to as secondary APS, primary APS happens on its own without any additional autoimmune symptoms (2).

Based on scientific research, adverse pregnancy results are strongly associated with SLE, APS, and high aPLs. For women of childbearing age with SLE and/or APS, reproductive health is crucial since these conditions raise the risk of premature birth, loss of pregnancy, preeclampsia, and fetal growth restriction (FGR) (3-5). In the last century, these conditions were also thought to be prohibitions to conception. Additionally, SLE and/or APS progression is triggered by pregnancy. Nonetheless, the development and application of novel medications during the last several decades has raised the potential and security of conception for females suffering with SLE and/or APS.

One type of synthetic 4-aminoquinoline antimalarial medication is hydroxychloroquine (HCQ). More research has been done lately on the therapeutic effects of HCQ, aside from its antimalarial action. These effects include immunomodulation and anti-inflammatory properties, vascular defense and thrombosis mitigation (6,7). The transition of HCQ from an antimalarial to a rheumatic medication was made easier by the identification of these adverse effects. Due to its comparatively high safety, HCQ is currently frequently used in the management of SLE and is given to pregnant SLE and/or APS patients (8).

The precise advantages of HCQ for expectant mothers with APS or SLE are still unknown, though. It is plausible to suppose that the effectiveness of HCQ for immune-related disorders could vary from that of the general condition given the intricate immunological modifications that occur during gestation. Pregnancy-related lupus activation has not been well studied, and opinions on how HCQ affects pregnancy problems are still divided.

As of right now, only a few meta-analyses have been performed (9–11) discussing the effectiveness of HCQ in pregnancies with SLE or APS. On the other hand, high-quality data regarding the function of HCQ in preeclampsia, IUGR, and lupus activity during pregnancy in individuals with SLE and/or APS is currently lacking. The influence of HCQ on lupus manifestations in pregnant SLE patients as well as placental mediated diseases (e.g: preeclampsia and FGR) in SLE pregnant women are the main topics of this study.

Methods

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) criteria were followed in the submission of reports of this investigation, which was conducted in compliance with the PICO concepts and standardised protocol (12). This investigation did not include any new data regarding the human or animal subjects; instead, it was based on earlier research that had been released.

Literature Search

Before any material was retrieved, each author decided on the approach for searching the current literature. Any research released between the creation of the databases and May, 2024, was included in a proper search of the scientific literature carried out by the databases PubMed , Embase , and the Cochrane Register of Controlled Trials . Pregnancy and "hydroxychloroquine" were among the search phrases utilized. There was only En-

glish spoken. After conducting the search on their own, the two authors combined all of the material they had found and eliminated any duplicates.

Research Selection

We investigated the connection between lupus activity, preeclampsia occurrence, and IUGR prevalence and the extra usage of HCQ during gestation. Prior to the choice of studies, the standards for inclusion and exclusion were established. In order to decide if these papers meet the inclusion characteristics, two writers independently and methodically went over the title, abstract, and entire text. In case of a dispute, the additional writer would confer with them and make conclusions until the desired outcome was achieved.

The following characteristics were used to choose the research articles for this analysis: (1) study design: Observational researches or randomized controlled trials (RCTs) comparing the additive administration of hydroquin in pregnant cases with the control group treated with hydroquin (including placebo); (2) pregnant cases with SLE, APS, or positive aPLs; (3) excessive lupus activity during pregnancy, IUGR, and preeclampsia. The SLE Disease Activity Index (SLEDAI) was used to define elevated lupus activation. A fetal weight or abdominal circumference below the 10th percentile for gestational age was referred to as an IUGR. After 20 weeks of pregnancy, hypertension along with proteinuria or other organ damage was referred to as preeclampsia. It was permitted to use particular diagnostic requirements that referenced national or international standards.

Data Extraction and Quality Assessment

Based on every investigation, we obtained the following information: author, year of publication, methodology, and final results of significance . The quality of every investigation included was assessed separately by a couple of the researchers, and all conflicts were settled through conversation. Using the Cochrane Collaboration's tool for the risk of bias (13), the reliability of RCT was assessed. The Newcastle–Ottawa Scale (NOS) was used to evaluate observational cohort study quality (14). By providing answers to eight questions, a maximum of nine points can be earned in each of all three types of bias (selection, comparability, and outcome).

Statistical Analysis

With the use of Cochrane Collaboration Review Manager 5.4.1 software (Nordic Cochrane Center), data for every dichotomous outcome were combined and examined. The hydroquin group and the control group (placebo or therapy other than hydroquin) were compared. For every dichotomous outcome, we conducted a normal pairwise meta-analysis and calculated the relative risk (RR) and 95% confidence intervals (CI).

The Cochran Q test and the I2 statistic were used to measure the heterogeneity between the studies. A fixed-effect model was employed when heterogeneity was acceptable and $I2 < 50\%$ or $p < 0.1$, when heterogeneity was deemed high and warranted the employment of a random-effect model. When significant heterogeneity emerged, the cause of the heterogeneity was confirmed using a sensitivity study that involved either altering the analysis model or carefully reviewing each article individually. To evaluate the publication bias, funnel plots were created if a group or subgroup contained ten investigations or more. The funnel plot's symmetrical point distribution suggested little to no bias.

Results

Upon eliminating replications, 427 of the 465 records that were found through the search process, were retained. A total of 393 entries were eliminated based on their title and abstract, primarily due to unrelated research and study population. After the 34 papers underwent full-text assessment, 20 further research were deemed ineligible due to insufficient contrast or treatment group and uninteresting outcomes. After being found to

meet the enrollment criteria, fourteen research were approved for collecting data and quality evaluation. In Figure 1, the PRISMA flow chart is displayed.

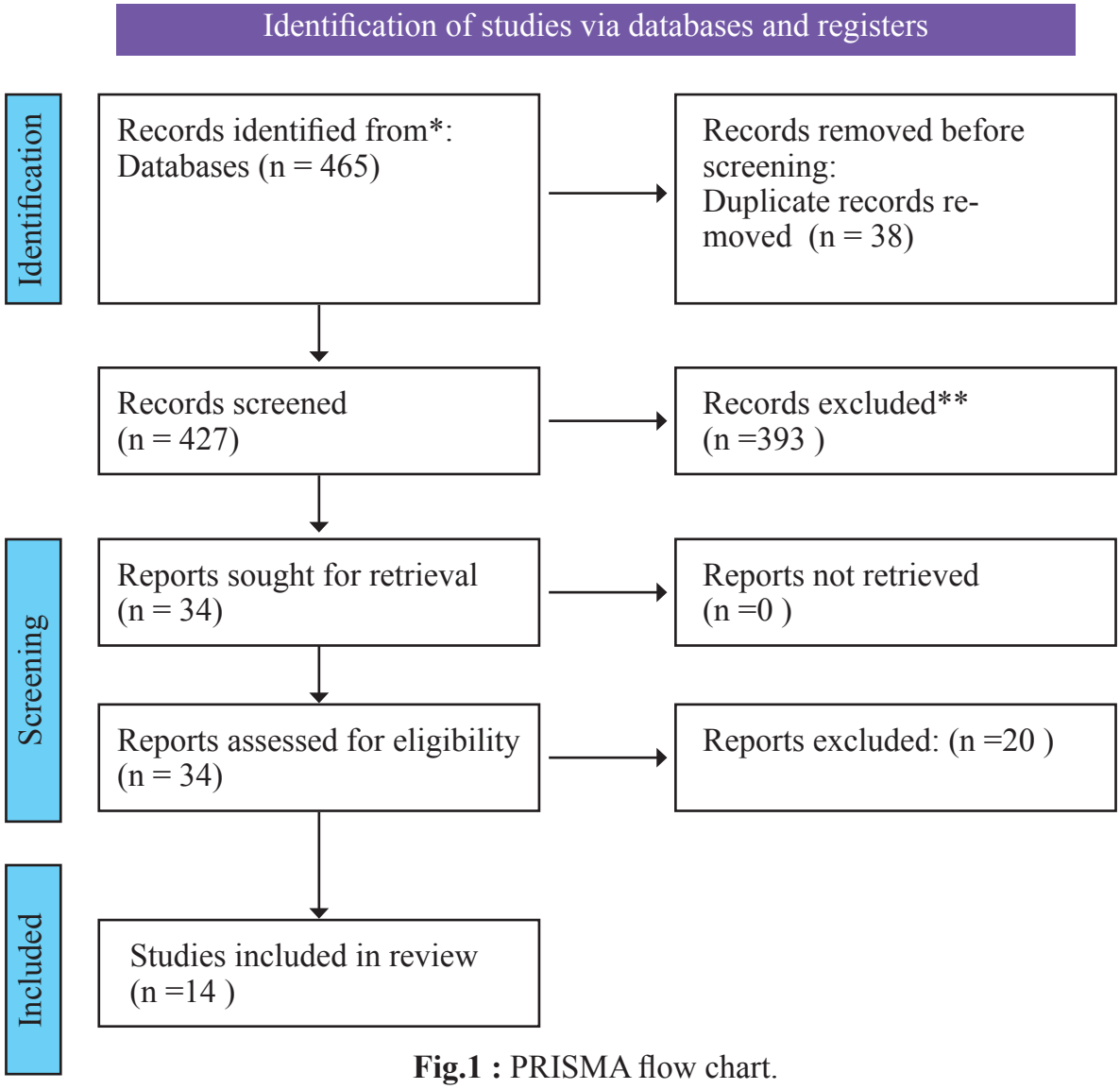

Fig.1 : PRISMA flow chart.

This meta-analysis and comprehensive review included Thirteen observational cohort investigations alongside a single RCT. The years of publishing were 2001–2022. SLE (11 studies) and APS or positive aPLs (three studies) were among the research participants. There were 1856 conceptions in all, of which 1764 were accounted for in the meta-analysis that was pooled (709 in the HCQ group and 1055 in the untreated group).

In the Cochrane risk of bias analysis, one RCT (15) was present. Table 2 presents the evaluation outcome. Although selection bias and detection bias were thought to be unknown, the likelihood of bias was mainly minimal.

The NOS quality assessment comprised thirteen observational investigations (16–28). Six research received a score of nine points, while seven investigations received an eight. We identified pregnancy as the primary factor and disease condition as the secondary factor for the comparison area.

Because seven investigations (16–19,23,26,27) did not account for or identify the second significant variable, they received a score of one point, indicating the possibility of variations in the two cohorts' disease conditions. The last six studies (20–22, 24–25, 28) received a maximum score of two points. In conclusion, every study received the highest possible score of three points for the result category, signifying the reliability of the outcome data. Regarding ancillary medications, azathioprine, aspirin, heparin, and/or corticosteroids were given to a number of SLE patients. Low-molecular-weight heparin (LMWH) and low-dose aspirin (LDA) were administered to every patient with APS/aPLs.

Table 1: Study characteristics

Author , year	Research type	Number of pregnancies	Study population	Intervention (no.)	Outcomes reported
Levy, R. A. 2001	RCT	20	SLE, DLE	a) HCQ (10) b) placebo (10)	lupus activity
Clowse, M. E. 2006	Cohort	257	SLE	a) No HCQ (163) b) HCQ (56) c) HCQ stopped (38)	lupus activity, IUGR
Al Arfaj, A. S. 2010	Retrospective study	383	SLE	a) Prednisolone (222) b) Prednisolone + HCQ (69) c) Prednisolone + azathioprine (30) d) Prednisolone + azathioprine + HCQ (8) e) None (54)	IUGR
Leroux, M. 2015	Retrospective cohort	118	SLE	a)HCQ (41) b) no HCQ (77)	lupus activity, IUGR, preeclampsia
Sciascia, S. 2016	Retrospective cohort	170	aPLs	a) HCQ (51) b) no HCQ (119)	preeclampsia, IUGR
Kroese, S. J. 2017	Retrospective cohort	110	SLE	a) HCQ (30) b) no HCQ (80)	lupus activity, preeclampsia
Seo, M. R. 2019	Retrospective cohort	151	SLE	a) HCQ (80) b) no HCQ (71)	preeclampsia
Abd Rahman, R. 2020	Retrospective cohort	82	SLE	a) HCQ (47) b) no HCQ (35)	IUGR, preeclampsia
Baalbaki, S. 2020	Retrospective cohort	77	SLE	a) HCQ (47) b) no HCQ (30)	IUGR
Do, S. C. 2020	Retrospective cohort	129	SLE	a) HCQ (53) b) no HCQ (76)	preeclampsia, IUGR
Canti, V. 2021	Retrospective cohort	74	SLE	a) HCQ (45) b) no HCQ (29)	preeclampsia, IUGR

Gerde, M. 2021	Retrospective cohort	101	APS	a) HCQ + LDA + LMWH (69) b) LDA + LMWH (32)	IUGR, preeclampsia
Liu, Y 2021	Retrospective cohort	88	SLE	a) HCQ (44) b) no HCQ (44)	preeclampsia
Liu, J 2022	Retrospective cohort	96	APS	a) HCQ (59) b) no HCQ (37)	IUGR, preeclampsia

Table 2: Newcastle-Ottawa Scale for evaluating the validity of cohort/case-control research

Study	Selection				Comparability	Outcome			Final score
	representativeness of the exposed cohort	selection of the non-exposed cohort	ascertainment of exposure	outcome of interest was not present at start of study	comparability of cohorts on the basis of the design or analysis	assessment of outcome	follow-up long enough for outcomes to occur	adequacy of follow up of cohorts	
Clowse, M. E. 2006	*	*	*	*	*	*	*	*	8
Al Arfaj, A. S. 2010	*	*	*	*	*	*	*	*	8
Leroux, M. 2015	*	*	*	*	* *	*	*	*	9
Sciascia, S. 2016	*	*	*	*	*	*	*	*	8
Kroese, S. J. 2017	*	*	*	*	* *	*	*	*	9
Seo, M. R. 2019	*	*	*	*	*	*	*	*	8
Abd Rahman, R. 2020	*	*	*	*	* *	*	*	*	9
Baalbaki, S. 2020	*	*	*	*	* *	*	*	*	9
Do, S. C. 2020	*	*	*	*	*	*	*	*	8
Canti, V. 2021	*	*	*	*	* *	*	*	*	9
Gerde,M. 2021	*	*	*	*	* *	*	*	*	9
Liu, Y 2021	*	*	*	*	*	*	*	*	8
Liu, J 2022	*	*	*	*	*	*	*	*	8

Excess Lupus Activity during Pregnancy

Figure 2 displays the outcome of the pooled meta-analysis for elevated lupus activity in gestation. Four research investigations (one RCT and three cohorts) (15, 18, 20, 22, 33) documented lupus involvement or flare-ups. In all four trials, lupus activity was described using the SLEDAI. Elevated lupus activation is defined as an SLEDAI score of 4 or an SLEDAI-based lupus flare (an increase in 3 scores). There were 137 pregnancies in the HCQ group and 330 pregnancies in the untreated group. Using HCQ resulted in a 26% lower risk of high lupus activity as opposed to the untreated group; this difference was significantly different (RR: 0.74, 95% CI: 0.57–0.97, p = 0.03). Since there was no statistically significant variation among these four investigations (I2 = 0%, p = 0.40), RR and 95% CI were determined using a fixed-effect model. Sensitivity analyses were carried out by eliminating the one RCT or the single trial with a different set of diagnostic parameters, taking into account the variations in the study design and criteria for high lupus activity. Furthermore, one of these investigations (18) found that individuals who had ceased taking HCQ had higher rates of lupus activity and flare-ups during pregnancy when compared to the non-exposed cohort or the continuous-HCQ-use cohort. The lack of assessment of publication bias was due to the smaller number of analyzed papers.

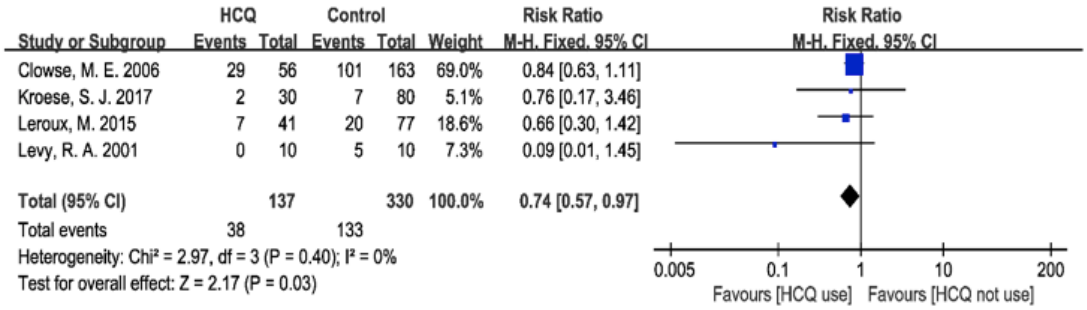

Figure 2: Forest plot for RR with high activity of lupus. When comparing patients using HCQ to either placebo or those who skipped HCQ

Intrauterine Growth Restriction

The prevalence of IUGR has been determined by ten cohort investigations (16, 18, 21, 28), of which seven involved SLE and three involved APS/aPLs. There were 538 pregnancies in the HCQ group and 844 pregnancies in the placebo group. As seen in Figure 3, overall, the HCQ group's risk of IUGR was 20% lower than that of the untreated group; however, the difference was not considered significantly different (RR: 0.80, 95% CI: 0.47–1.35, p = 0.46). The random-effect model was utilized to determine the RR and 95% CI, and the heterogeneity was moderate (I2 = 52%, p = 0.03). The research's subject constituted the basis for a subgroup analysis. Utilizing HCQ in along with the untreated group (n = 656) decreased the incidence of IUGR in the SLE subset by 26% (n = 359); however, this difference was not considered significantly different (RR: 0.74, 95% CI: 0.40–1.36, p = 0.33). I2 = 66%, p = 0.007 indicates a comparatively high level of heterogeneity. To determine whether a single investigation may significantly alter the outcome, a sensitivity analysis was conducted, eliminating each study one at a time and evaluating the remaining ones. A single investigation (16) significantly impacted the meta-analysis's findings during the sensitivity analysis. A finding that was statistically significant (RR: 0.70, 95% CI: 0.50–0.96, p = 0.03) emerged after the investigation was removed, although the heterogeneity maintained moderate (I2 = 54%, p = 0.05). The impact could be explained by possible publication bias as

well as the various baseline features of disease conditions in the study subjects. Nonetheless, in the APS subgroup, employing HCQ along with to the standard control group (n = 188) raised the likelihood of IUGR by 26% (n = 179); however, this difference in risk did not prove significantly different (RR: 1.26, 95% CI: 0.34–4.61, p = 0.73). Between these three investigations, there was no heterogeneity (I2 = 0%, p = 0.84). In each subgroup, there were less than ten studies enrolled, so publication bias was not evaluated.

Preeclampsia

Preeclampsia prevalence has been documented by ten cohort analyses (16,17,19–25,27), comprising three APS/aPLs studies and seven SLE investigations. There were 519 conceptions in the HCQ group and 600 conceptions in the untreated group. Using HCQ in conjunction with the untreated group decreased the overall probability of preeclampsia by 46%, as indicated in Figure 4. This difference in risk was statistically significant (RR: 0.54, 95% CI: 0.37–0.78, p = 0.001). Since there was no heterogeneity across the ten trials (I2 = 0%, p = 0.76), the RR and 95% CI were determined using a fixed-effect model. The research's subject constituted the basis for a subgroup analysis. The HCQ group (n = 340) had a 49 percent reduced likelihood of preeclampsia in the SLE subset when contrasted with the untreated group (n = 412). This difference in risk was of statistical significance (RR: 0.51, 95% CI: 0.34–0.78, p = 0.002) and there was no heterogeneity (I2 = 0%, p = 0.64). In contrast, the HCQ group (n = 179) in the APS/aPLs subgroup had a 34% lower chance of preeclampsia than the untreated group (n = 188); however, this difference in risk did not prove significantly different (RR: 0.66, 95% CI: 0.29–1.54, p = 0.34) and there was no heterogeneity (I2 = 0%, p = 0.59). In every subgroup, there were less than ten studies enrolled, so publication bias was not evaluated.

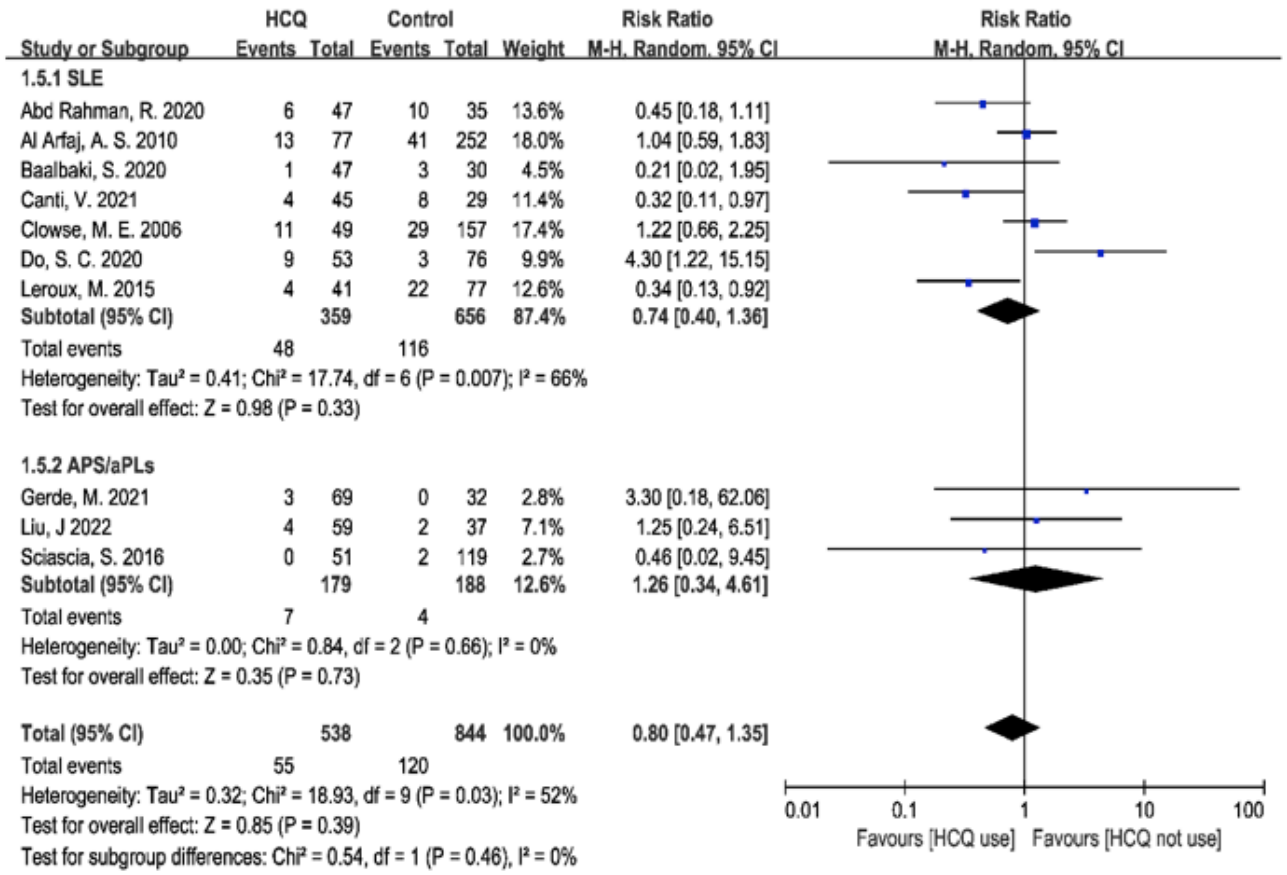

Figure 3: Forest plot of the RR of IUGR in the intervention & control groups

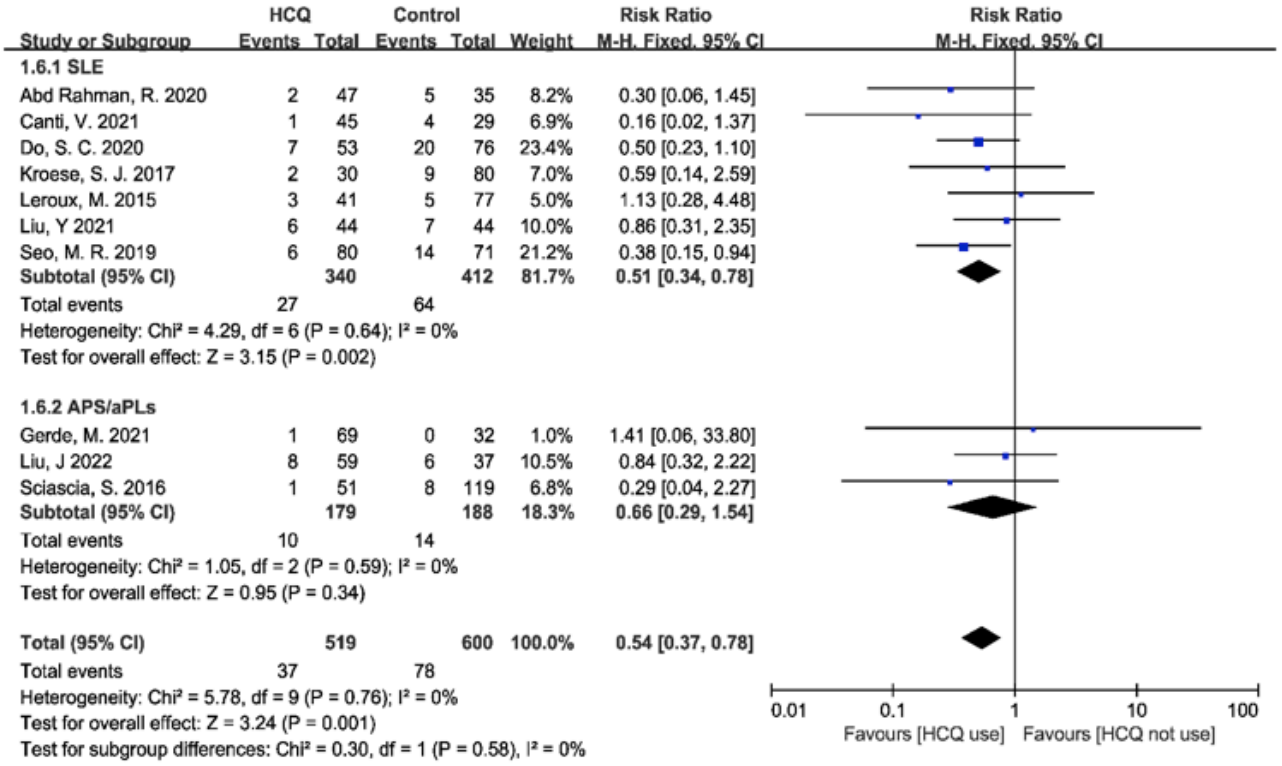

Figure 4: The pre-eclampsia RR's forest plot. To obtain the pooled estimate of the RR of IUGR, those on HCQ were compared to those who were not taking on HCQ.

Discussion

In order to deliver scientific proof on the impact of increased HCQ use on lupus activity, FGR and preeclampsia prevalence in pregnant women with SLE and/or APS/aPLs, a systematic review and meta-analysis were performed. According to our findings, extra HCQ administration during gestation may reduce the possibility of preeclampsia in SLE patients and the likelihood of elevated lupus activity during gestation, but not in APS/aPLs people. HCQ does not appear to lower the probability of FGR among individuals with APS/aPLs or SLE, though.

Research on HCQ's effectiveness in limiting lupus flares has been conducted extensively in the overall patient population (29), but there are a few investigations, particularly high-quality RCTs or cohorts, specifically focused on pregnant women. As a result, meta-analysis is deficient. To the best of our knowledge, this is one of the first study to compile existing research on the efficacy of extra HCQ use on lupus activity control during pregnancy. According to our findings, using HCQ continuously during pregnancy may help lower the chance of having high lupus activation. Nevertheless, no such decline was found in the findings of the sensitivity studies. Furthermore, the low number of research may account for this outcome. Thus, there ought to be more excellent research done with this goal as the emphasis. Furthermore, the limited number of research suggests that there are negative effects associated with stopping HCQ during gestation, despite one study reporting these consequences.

There aren't many APS/aPLs research and conflicting outcomes from earlier SLE studies when it comes to pregnancy problems. Furthermore, no research has combined and contrasted APS and SLE investigations. Our findings vary across patients with SLE and APS/aPLs as well as preeclampsia and IUGR. The interplay of their mechanisms should be connected to the implications of HCQ on IUGR and preeclampsia. Prior research have

shown that HCQ can maintain the placenta's integrity and lower the risk of placenta-mediated problems by acting through several mechanisms in immune effect, endothelial preservation, and metabolic regulation. Regarding immunological and anti-inflammatory effects, HCQ may influence innate immunity through inhibition of an immune reaction to auto-antigenic peptides; and preserving the balance between helper T cells (Th)1/Th2 by lowering the release of pro-inflammatory cytokines (30). Furthermore, HCQ can maintain the lysosomal membrane by creating a condition that is alkaline, which also prevents phagocytosis, chemotaxis, and antigen presentation (7). Regarding endothelial safeguards, HCQ may avert damaged endothelial cells by suppressing the increase of ERK5 kinase activity, which in turn inhibits the development of vascular cellular adhesion molecule-1 (VCAM). Additionally, it might prevent platelets from clumping together and from releasing arachidonic acid when triggered (32). Furthermore, it was noted that HCQ could inhibit APS-related pathways and lower plasma levels of aPL, which would stop thrombogenesis (30). Regarding metabolic control, a meta-analysis (33) found that HCQ can reduce the likelihood of diabetes and enhance lipid levels through the molecular pathways under investigation.

While IUGR and preeclampsia share many pathogenic mechanisms, there are notable distinctions as well. Preeclampsia and IUGR are characterized by rapid endothelial dysfunction, hypoxia of the placenta, and inappropriate increasing the activity of inflammation. Nevertheless, compared to FGR, preeclampsia appears to have greater amounts of endothelial stimulants, more substantial alterations in placenta-derived growth factor (PlGF), and more advanced inflammatory conditions. Furthermore, compared to FGR, metabolic irregularities appear to be more prevalent in preeclampsia (34). These variations could result in various medication reactions.

There are parallels and distinctions between SLE and APS individuals. Persons with APS and SLE experience thrombocytopenia and complement system stimulation (35, 36). Pregnancy-related difficulties in those with SLE are frequently linked to immune complex-induced local tissue inflammation (37), with lupus nephritis (35) and flare-ups of the disease during gestation being two specific risk variables. Reproductive difficulties in APS patients are largely related to thrombogenesis and placental malfunction brought on by aPLs (38, 36). It is possible in principle that the molecular mechanisms associated with both APS and SLE are impacted by the pharmacological effects of HCQ. Distinct baseline therapies for the two diseases, yet, can have various results. However, it appears that those with SLE are likely will profit more than APS/aPLs individuals from the added usage of HCQ in reducing pregnancy problems, even in the absence of statistical differences. This might have to do with the fact that most individuals respond well to normal APS therapy (LDA + LMWH), yet baseline SLE medication (e.g: glucocorticoids) has very little effect. However, it is impossible to draw firm conclusions from the limited number of research investigations on APS and HCQ. These findings are in accordance with the recommendations made by the American College of Rheumatology (ACR) and EULAR, which state that HCQ should be administered to SLE patients both before and during pregnancy, and that HCQ should only be considered in conjunction with conventional therapy for resistant APS individuals (8, 39–41).

There are certain restrictions on this research. Initially the restricted number of research may have an impact on certain findings. The assessment of publication bias was not conducted since there were never more than 10 studies in any given group or subdivision. Secondly, even though we performed sensitivity analyses and found a few components, there are still a few potential drivers of het-

erogeneity that need to be looked at. Thirdly, due to a shortage of information in some initial investigations, we did not concentrate on the application and dose of HCQ and the health condition of the general population (refractoriness of APS, SLE association with lupus nephritis). Finally, aspirin was given to some SLE individuals in addition to various basic therapies; this helped mitigate preeclampsia. There may be variations even though the intervention group and the control group in each study had similar characteristics.

Conclusion

In summary, those suffering from SLE may benefit from increased HCQ administration in hindering lupus flare-ups or elevated lupus activation during gestation. While HCQ has been linked to a decreased incidence of preeclampsia in sufferers of SLE, this effect was not shown in individuals with APS/aPLs on conventional therapy. We were unable to demonstrate that HCQ effectively prevents IUGR among individuals with APS/aPLs or SLE. According to our findings, HCQ should be taken as usual in conceptions involving SLE; however, further use in pregnancies involving APS/aPL without concomitant problems is not recommended at this time.

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