Low incidence of intrauterine growth restriction in pregnant patients with systemic lupus erythematosus taking hydroxychloroquine

Valentina Canti, Margherita Scarrone, Rebecca De Lorenzo, Giuseppe A. Ramirez, Roberta Erra, Sara Bordoli, Sara Celli, Elena Schmit, Susanna Rosa, Maria T. Castiglioni and Patrizia Rovere-Querini

ABSTRACT
Systemic lupus erythematosus (SLE) preferentially affects women of childbearing age. Miscarriages or fetal death, intrauterine growth restriction (IUGR), preterm delivery, preeclampsia and disease flares complicate pregnancy in SLE patients. Treatment is challenging due to the need to prevent disease exacerbations and limit obstetrical complications, while showing an acceptable safety profile for both the mother and the fetus. We collected data from 74 pregnancies in 53 SLE patients prospectively followed in a dedicated ‘Pregnancy at risk’ outpatient clinic from 2003 to 2019. Out of 74, 45 pregnancies patients were treated with hydroxychloroquine (HCQ). Mothers under HCQ therapy (HCQ+ patients) and those who did not receive HCQ (HCQ− patients) were homogeneous in terms of age and comorbidities. Disease activity prior to conception was slightly higher in HCQ+ patients. No significant difference was observed in terms of obstetrical history. In patients achieving a viable pregnancy, the rate of IUGR (4/39, 10% in HCQ+ vs 8/25, 32%, in HCQ− patients, p < .05) was significantly lower in HCQ+ patients. Conversely, HCQ+ patients displayed a significantly longer time to delivery (37.8 ± 1.72 vs. 36.3 ± 4.11 in HCQ− patients, p < .05). HCQ is safe in pregnant patients with SLE and protects against obstetrical complications.

1. Introduction
Systemic lupus erythematosus (SLE) preferentially affects women of childbearing age. Pregnancy in patients with SLE may have detrimental effects for the mother and the fetus. Adverse pregnancy outcomes (APOs) occur in up to 19% of patients with SLE and encompass fetal death (4%), neonatal death (1%), preterm delivery (9%), small fetus for gestational age (10%) and preeclampsia (2%). The frequency of APOs is higher in patients with SLE and antiphospholipid antibodies (aPL Abs) [1].

Active lupus nephritis, decreased complement levels, thrombocytopenia, positive aPL Abs and anti-SSA/SSB antibodies are risk factors for APOs [2–6]. Pregnant SLE patients with lupus nephritis suffer higher rates of APOs [7,8]. A history of nephritis predispose to lupus flares during pregnancy [9], especially in case of active disease at conception [10]. SLE flares contribute to morbidity and mortality [11–14] and associate with higher rates of APOs [1]. Conversely, quiescent disease at conception does not associate with increased APOs despite a history of lupus nephritis [15].

The management of SLE during pregnancy is challenging. Pregnancy per se influences several laboratory and clinical parameters used to measure disease activity. Obstetric complications mimic lupus flares, making the distinction challenging [16]. Accordingly, modified scales to assess SLE activity have been developed [17]. Adapting the need for pharmacological disease control to pregnancy safety is of importance to minimize pregnancy risks [18] and warrants the implementation of a comprehensive follow up plan, from preconception counseling [19] to post-partum monitoring.

Drugs compatible with pregnancy in SLE include hydroxychloroquine (HCQ) [20]. HCQ anti-inflammatory effect stems from interference with intracellular Toll-like receptors [21], with phospholipase activity and with the inflammatory cytokines production, thus promoting the TH2 shift typical of a
normal pregnancy [22]. Moreover, the agent inhibits platelet aggregation and secretion of arachidonic acid by activated platelets [23,24], decreases the risk of thrombosis and increases overall survival in patients with SLE [25,26]. HCQ has a protective effect on placenta and trophoblast damage in anti-phospholipid syndrome (APS). It reverses aPL-mediated inhibition of trophoblast IL-6 secretion and limit inhibition of cell migration [27]. HCQ restores the trophoblastic differentiation [28], limits complement activation, prevents the binding of antibodies to phospholipids [24,29], decreases aPL titers [30] and inhibits endothelial cell activation and TNFz production [31].

Other effects include protection from endothelial dysfunction via activation of the ERK5 protein kinase [32], prevention from generation of reactive oxygen species [33], lipid lowering and anti-diabetic actions [34]. HCQ crosses the placenta [35] but no significant risk of congenital malformations, retinopathy or ototoxicity has been demonstrated [36–40]. Its discontinuation during pregnancy increases the risk of disease flares [37] and therapeutic HCQ blood range protects from flares [41]. Current EULAR recommendations are to start HCQ preconceptionally and to continue it throughout pregnancy [42]. Substantial effort is being devoted to verify whether HCQ might effectively protect the mother and the infant, without undue toxicity [43–46]. Little is known about the role of HCQ in pregnant patients with SLE without aPL Abs. The objective of this study is to compare the rate and characteristics of pregnancy complications in patients with SLE treated or not with HCQ.

2. Materials and methods

2.1. Study design and population

We performed a monocentric prospective observational study of pregnant women with SLE classified according to the revised American College of Rheumatology criteria [47]. All patients also satisfied the 2019 EULAR/American College of Rheumatology criteria [48]. We collected data from 74 pregnancies carried by 53 patients with SLE followed at the ‘Pregnancy at risk’ multidisciplinary outpatient clinic of San Raffaele Hospital, Milan, Italy from 2003 to 2019. Approval was obtained from the Comitato Etico Ospedale San Raffaele, Milan, Italy (protocol ‘Autoimmuno-mol’, PI Angelo Manfredi, no. 2/2013INT). This study was conducted in accordance with the Declaration of Helsinki. Forty-five out of 74 (61%) pregnancies were carried by SLE patients receiving HCQ therapy (HCQ+ group) and 29/74 (39%) by SLE patients who were not treated with HCQ during pregnancy (HCQ− group). The dosage of HCQ/day was standard and equivalent to 300 mg/day throughout pregnancy.

Data regarding demographics and disease history were collected at enrollment. Patients were then monitored with regular visits every month from pre-conception counseling to delivery and post-partum. At each visit the following information was recorded: disease activity (by using the SLE disease activity index, SLEDAI-2K [49]) and findings at physical examination, laboratory tests including complete blood count, C reactive protein (CRP), complement levels and serology (anti-dsDNA, anti-SSA/Ro, anti-SSB/La antibodies). All patients were also screened for the presence of aPL [50], namely anticardiolipin antibodies (aCL IgG and IgM), anti-beta2-glycoprotein I antibodies (aβ2GPI IgG and IgM) assessed by ELISA (QUANTA Lite) and lupus anticoagulant (LAC). Serial obstetric ultrasound to monitor fetal growth and uterine arteries doppler were also performed at each visit and associated findings recorded.

2.2. Statistical analysis

Statistical analysis was performed with SPSS 15.0. Groups were retrospectively defined based on the use of HCQ during pregnancy. We first compared the baseline characteristics of the two groups (HCQ+ and HCQ−) to account for possible confounding factors. We then tested for bivariate or multivariate associations among APOs, aPL Abs profile and HCQ status by using chi-square test or Fisher exact test and Anova, as appropriate. We considered differences to be statistically significant at p < .05.

3. Results

3.1. Baseline demographics, general medical and obstetric history

HCQ+ and HCQ− patients did not differ at baseline in terms of demographic data except for year of delivery that was more recent in HCQ+ than HCQ− patients. This could reflect the increased confidence that we acquired during the last 20 years in HCQ use for the treatment of SLE patients during pregnancy. Moreover, also general clinical history and obstetrical history did not differ except for previous thromboembolic events, which were more frequent in the HCQ− group (p < .05). APS was equally represented in the two groups (Table 1). HCQ+ and HCQ− patients were homogeneous in terms of early (first trimester miscarriages) and late pregnancy complications (preeclampsia, gestational
hypertension, IUGR, stillbirth and preterm delivery) (Table 1).

**Disease activity and therapy before conception and during pregnancy**

Disease duration calculated at the time of delivery was similar between HCQ\(^+\) and HCQ\(^-\) patients (Table 1). Concerning disease history prior to conception, the rate of organ involvement in the two groups was similar, while anti-dsDNA antibodies and hypocomplementemia were more frequent in HCQ\(^+\) patients compared with HCQ\(^-\) patients (67 vs. 34%, \(p = .004\) and 75 vs. 52%, respectively; \(p = .04\)) (Table 2).

At the preconception counselling, disease activity evaluated using the SLEDAI index, was higher in HCQ\(^+\) patients compared with HCQ\(^-\) patients (3.56 ± 2.56 vs. 2.15 ± 2.24, respectively; \(p = .02\)) (Table 3). During pregnancy, disease activity evaluated for each trimester was similar between the two groups. Complement levels were comparable between the groups, both at preconception counselling and during pregnancy (Table 3).

During the 6 months before conception, the two groups received similar pharmacological treatment. In the HCQ\(^+\) group 40% of patients used azathioprine and 56% of patients were treated with corticosteroids. Similarly, in the HCQ\(^-\) group, 21% of women assumed azathioprine and 48% used corticosteroids (Table 4). During pregnancy, only 4 out of 29 patients (4%) in the HCQ\(^-\) group used azathioprine, compared to 16 out of 45 patients (36%) in the HCQ\(^+\) group. Treatment with corticosteroids during pregnancy was similar in the two groups but the mean equivalent daily dose of prednisone was higher in HCQ\(^-\) then in HCQ\(^+\) (2.4 ± 1.7 vs. 0.9 ± 1.2 mg, \(p < .007\)). By contrast, treatment with low dose aspirin (LDA), low molecular weight heparin (LMWH) and their association were equally distributed between the two groups (Table 4).

**Pregnancy outcome: APO and delivery**

The rate of first and second trimester miscarriages was comparable between the two groups. A viable pregnancy was achieved in 39/45 (87%) patients in the HCQ\(^+\) group and in 25/29 (86%) patients in the HCQ\(^-\) group. Bilateral notches at Uterine Artery doppler were detected during mid-second trimester ultrasound in 1/39 (3%) patients in the HCQ\(^+\) group and in 4/25 (16%) of the HCQ\(^-\) group (\(p = .07\)). 1/39 (3%) patients in the HCQ\(^+\) group

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**Table 1.** Baseline demographic characteristics, general clinical and obstetric history of the study population. IUGR: intrauterine growth restriction.

| Past medical history                  | HCQ\(^+\) (n = 29) | HCQ\(^-\) (n = 45) | \(p\) Value |
|---------------------------------------|-------------------|-------------------|-------------|
| Antiphospholipid syndrome             | 6 (21)            | 6 (13)            | n.s.        |
| Connective tissue disease             | 23 (79)           | 39 (87)           | n.s.        |
| Arterial hypertension                 | 4 (14)            | 6 (13)            | n.s.        |
| Thyroid disease                       | 7 (24)            | 11 (24)           | n.s.        |
| Thrombophilia                         | 6 (21)            | 7 (16)            | n.s.        |
| Congenital thrombophilia              | 3 (10)            | 1 (2)             | n.s.        |
| History of thromboembolism            | 7 (24)            | 2 (4)             | .02         |
| Nephropathy                           | 6 (21)            | 7 (16)            | n.s.        |

**Table 2.** History of organ involvement and biomarkers of disease activity.

| Organ involvement                      | HCQ\(^-\) (n = 29) | HCQ\(^+\) (n = 45) | \(p\) Value |
|----------------------------------------|-------------------|-------------------|-------------|
| Nephritis                              | 7 (24)            | 18 (40)           | n.s.        |
| Neurologic manifestations              | 4 (14)            | 8 (18)            | n.s.        |
| Hematologic manifestations             | 12 (41)           | 25 (56)           | n.s.        |
| Cutaneous manifestations               | 15 (52)           | 28 (64)           | n.s.        |
| Muskolo-skeletal manifestations        | 14 (48)           | 29 (64)           | n.s.        |
| Serositis                              | 4 (14)            | 8 (18)            | n.s.        |
| Constitutional symptoms                | 10 (34)           | 32 (71)           | n.s.        |
| Serological biomarkers                 |                   |                   |             |
| Anti-dsDNA antibodies                  | 10 (34)           | 30 (67)           | .004        |
| Anti-Ro/SSA antibodies                 | 7 (24)            | 16 (36)           | n.s.        |
| Hypocomplementemia                     | 15 (52)           | 34 (75)           | .04         |


The time to delivery was significantly longer in HCQ+ patients (37.8 ± 1.72 vs 36.3 ± 4.11 gestational weeks, \( p < .05 \)). Preterm delivery occurred more frequently in HCQ− patients compared with HCQ+ patients (28 vs 18%), even if this difference did not reach statistical significance.

Neonatal and placental weight at birth were comparable between the two groups (Table 5). The rate of gestational

| Table 3. Disease activity at the preconception counseling, during pregnancy and in the post-partum. C3 range 0.9–1.6 mg/dL and C4 range 0.1–0.4 mg/dL. |
| --- |
| | HCQ− (\( n = 29 \)) | HCQ+ (\( n = 45 \)) | \( p \) Value |
| Preconception disease activity | | | |
| Preconception SLEDAI | 2.15 ± 2.24 (0, 7) | 3.56 ± 2.56 (0, 12) | .02 |
| Hypocomplementemia | 8/17 (47) | 20/40 (50) | n.s. |
| C3 (mg/dL) | 0.96 ± 0.31 (0.6, 1.54) | 0.91 ± 0.26 (0.47, 1.53) | n.s. |
| C4 (mg/dL) | 0.23 ± 0.15 (0.04, 0.6) | 0.18 ± 0.11 (0.02, 0.42) | n.s. |
| Disease activity during pregnancy | | | |
| Trimester I SLEDAI | 1.72 ± 2.83 (0, 8) | 2.24 ± 2.28 (0.8) | n.s. |
| Trimester II SLEDAI | 1.61 ± 2.48 (0, 10) | 2.00 ± 2.43 (0, 8) | n.s. |
| Trimester III SLEDAI | 1.24 ± 1.70 (0, 5) | 2.03 ± 2.71 (0, 9) | n.s. |
| Hypocomplementemia | 8/26 (31) | 11/44 (25) | n.s. |
| C3 (mg/dL) | 1.06 ± 0.33 (0.32, 1.68) | 1.08 ± 0.33 (0.46, 2.20) | n.s. |
| C4 (mg/dL) | 0.27 ± 0.23 (0.2, 0.9) | 0.21 ± 0.13 (0.07, 0.83) | n.s. |
| Disease activity in the post-partum | | | |
| Post-partum SLEDAI | 3.85 ± 2.81 (0, 14) | 3.68 ± 3.59 (0, 16) | n.s. |

| Table 4. Pharmacological therapy before and during pregnancy. LDA: low dose aspirin; LMWH: low molecular weight heparin. SD: standard deviation. |
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| | HCQ− (\( n = 29 \)) | HCQ+ (\( n = 45 \)) | \( p \) Value |
| Preconception treatment | | | |
| Corticosteroids | 14 (48) | 25 (56) | n.s. |
| Azathioprine | 6 (21) | 18 (40) | n.s. |
| Treatment during pregnancy | | | |
| LDA | 17 (59) | 34 (76) | n.s. |
| LMWH | 9 (31) | 11 (24) | n.s. |
| LDA + LMWH | 8 (28) | 10 (22) | n.s. |
| Azathioprine | 4 (14) | 16 (36) | .06 |
| Corticosteroids | 14 (48) | 27 (60) | n.s. |
| Mean ± SD Mean ± SD | | | |
| Corticosteroids (mean equivalent daily dose) | 2.4 ± 1.7 mg | 0.9 ± 1.2 mg | .007 |
| HCQ daily dose | 0 | 300 mg | / |

| Table 5. Pregnancy outcomes. |
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| Pregnancy outcomes | HCQ− (\( n = 29 \)) | HCQ+ (\( n = 45 \)) | \( p \) Value |
| Early adverse pregnancy outcomes n = 29 | n = 45 | | |
| Early miscarriage < 10 gw | 3 (10) | 4 (9) | n.s. |
| Late miscarriage > 10 gw < 24 gw | 1 (3) | 2 (4) | n.s. |
| Late adverse pregnancy outcomes n = 25 | n = 39 | | |
| Intrauterine death | 1 (4) | 0 (0) | n.s. |
| Preeclampsia | 4 (16) | 1 (3) | .07 |
| Hypertension | 5 (20) | 5 (13) | n.s. |
| Placental abruption | 0 (0) | 1 (3) | n.s. |
| Bilateral notch | 4 (16) | 1 (3) | .07 |
| IUGR | 8 (32) | 4 (10) | .047 |
| Fetal distress | 3 (12) | 1 (3) | n.s. |
| Stillbirth | 0 (0) | 0 (0) | n.s. |
| Preterm delivery | 7 (28) | 7 (18) | n.s. |
| Delivery outcome Mean ± SD (min, max) Mean ± SD (min, max) | | | |
| Week of delivery | 36.3 ± 4.11 (27, 40) | 37.8 ± 1.72 (34, 40) | .04 |
| Neonatal weight (g) | 2614 ± 977 (225, 3710) | 2859 ± 439 (1620, 3715) | n.s. |
| Placental weight (g) | 460 ± 176 (80, 680) | 454 ± 119 (260, 680) | n.s. |

| Table 6. Multivariate analysis of predictors of IUGR in pregnant patients with SLE. |
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| OR (95%CI) | \( p \) Value |
| aPL Abs | 1.541 (0.268–8.860) | n.s. |
| AZA | 2.450 (0.387–15.506) | n.s. |
| HCQ | 0.151 (0.031–0.727) | .018 |

**Intrauterine death at 27 weeks of gestation.**
hypertension, stillbirth and placental abruption as well as the delivery outcome did not differ between the two groups (Table 5).

**Discussion**

Considerable efforts have been made to evaluate HCQ effects on adverse obstetric complications [43–45]. Based on these reports supporting HCQ efficacy and relative safety, the agent has been used more frequently in the last years in pregnant patients with SLE. This applies also to our cohort, as can be evinced by the years of delivery reported in Table 1. Thus, patients in HCQ group might have benefited from other advances in the treatment of the disease as well that have emerged in most recent years. In our study, we have indeed observed a significantly lower rate of complications in patients treated with HCQ. The gestational week at delivery was significantly higher in the HCQ group, revealing a possible effect also on the incidence of prematurity. This is relevant, since these patients at the preconception counseling had a significantly higher disease activity. A statistically significant protection of HCQ against pregnancy complications (and in particular IUGR) could be demonstrated in SLE patients regardless of the presence of aPL Abs, suggesting that the agent is effective on events associated or not to aPL Abs.

The impact of HCQ may be higher on complications related to placental function, because of its vascular-prootive effects [32,33]. For example, IUGR was shown to be related to placental dysfunction, even in the absence of APS [51] and placental vasculopathy and hypoxic damage independent of aPL Abs have been described in SLE [52]. The antithrombotic action of HCQ [25] may increase placental perfusion and fetal growth. However, HCQ efficacy on very early stages of pregnancy—and possibly in the preconceptional phase—suggests that other mechanisms are involved, including the regulation of complement activity [53], the maintenance of the action of physiological anticoagulants, such as Annexin 5 [29] and modulation of the inflammatory response which is fundamental for successful pregnancy [22]. Further studies are needed to define the mechanisms involved in the protective action of HCQ in pregnant patients. Meanwhile, the observations reported in this study strongly suggest that the agent is a safe and effective complement to the treatment of pregnant patients with systemic autoimmune diseases, SLE in particular.

**Conclusion**

Taking into consideration the excellent safety profile of HCQ and its numerous beneficial effects on obstetrical outcomes, it should be given preconceptionally and continued throughout pregnancy in SLE patients, independently of disease activity with possible beneficial effects both for the mother and the newborn.

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**Disclosure statement**

No potential conflict of interest was reported by the author(s).

**ORCID**

Patrizia Rovere-Querini http://orcid.org/0000-0003-2615-3649

**Data availability statement**

The data that support the findings of this study are available from the corresponding author, [VC], upon reasonable request.

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