Published in final edited form as:

Clin Pharmacokinet. 2019 April ; 58(4): 525–533. doi:10.1007/s40262-018-0712-z.

Pharmacokinetics of Hydroxychloroquine in Pregnancies with Rheumatic Diseases

Stephen J. Balevic, MD, MHS^{1,2,3}, Thomas P. Green, MD⁴, Megan E.B. Clowse, MD, MPH³, Amanda M. Eudy, PhD³, Laura E. Schanberg, MD^{1,2}, and Michael Cohen-Wolkowicz, MD, PhD^{1,2}

¹Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina

²Department of Pediatrics, Duke University School of Medicine, Durham, North Carolina

³Department of Medicine, Duke University School of Medicine, Durham, North Carolina

⁴Department of Pediatrics, Northwestern University/Ann and Robert H. Lurie Children's Hospital, Chicago, Illinois

Abstract

Background: Hydroxychloroquine (HCQ) is an oral drug prescribed to pregnant women with rheumatic disease to reduce disease activity and prevent flares. Physiologic changes during pregnancy may substantially alter drug pharmacokinetics (PK). However, the effect of pregnancy on HCQ disposition and potential need for dose adjustment remains virtually unknown.

Methods: We performed a population PK analysis using samples from the Duke Autoimmunity in Pregnancy Registry from 2013–2016. We measured HCQ concentration using HPLC-MS/MS and analyzed data using nonlinear mixed effect modeling. We calculated differences between pregnancy and postpartum Empirical Bayesian Estimates (EBEs) using paired t-tests. We computed steady state concentration profiles for HCQ during pregnancy and postpartum using individual clinical data and EBEs developed from the final PK model.

Results: 145 serum samples were obtained from 50 patients, 25 of whom had paired pregnancy and postpartum specimens. Five subjects had average concentrations (pregnancy and postpartum) <100 ng/mL, consistent with medication non-adherence, and were excluded. The population estimated apparent volume of distribution (V_d/F) was 1850 L/70kg and estimated apparent clearance (CL/F) was 51 L/hr. Compared with postpartum, median V_d/F increased significantly

Corresponding Author: Stephen J. Balevic, MD, Duke University Medical Center, Divisions of Adult and Pediatric Rheumatology, 2301 Erwin Road, Durham, NC 27710, Phone: 919-684-6575, Fax: 919-684-6616, Stephen.balevic@duke.edu, TGreen@luriechildrens.org, megan.clowse@duke.edu, amanda.eudy@duke.edu, laura.schanberg@duke.edu, michael.cohenwolkowicz@duke.edu.

Compliance with Ethical Standards

Conflicts of Interest:

T.P.G. has no relevant disclosures.

Ethical Approval:

We conducted the study in compliance with the Declaration of Helsinki and the Duke Institutional Review Board approved the protocol.

Informed Consent:

All subjects included in the study provided informed consent.

during pregnancy ($p < 0.001$), whereas CL/F and 24-hour area under the curve ($AUC_{24/F}$) did not change.

Conclusion: A one-compartment population PK model was developed for HCQ in pregnant women with rheumatic disease. Estimates for serum clearance were within the expected range for plasma in non-pregnant adults. Because clearance and $AUC_{24/F}$ did not change during pregnancy compared with postpartum, our modeling in this small cohort does not support adjusting HCQ dose during pregnancy.

1. Introduction

Active rheumatic disease during pregnancy can result in devastating neonatal outcomes, with up to two-third of mothers with active systemic lupus erythematosus (SLE) delivering preterm (1). Because hydroxychloroquine (HCQ) is considered safe during pregnancy and breastfeeding (2), many rheumatologists prescribe HCQ to pregnant mothers to control maternal disease activity and prevent flares. Pregnant women with SLE who discontinue HCQ are twice as likely to have active systemic disease and have more disease flares (3, 4). Further, pregnant women with rheumatic disease who demonstrate persistent disease activity often receive adjuvant corticosteroid therapy. Corticosteroids are independently associated with poor neonatal outcomes (5), underscoring the critical need to optimize HCQ dosing during pregnancy.

Changes in drug pharmacokinetics (PK) during pregnancy may include alterations in the volume of distribution (V_d) secondary to increasing adipose mass and total body water and decreased concentrations of albumin and alpha(1)-acid glycoprotein, as well as changes in clearance (CL) secondary to increased glomerular filtration and alterations in drug metabolizing enzymes (6, 7). HCQ PK is characterized by a high V_d and elimination through the kidneys (8); therefore, the changes in physiology that occur during pregnancy may alter HCQ concentrations (6). In addition, aminoquinolines such as HCQ are metabolized by multiple hepatic enzymes including CYP2C8, CYP3A4, and CYP2D6 (8, 9). The activity of CYP3A4 and CYP2D6 increase in pregnancy and may cause more rapid metabolic clearance of parent HCQ to the active metabolites (6, 7).

Despite the extensive use of HCQ in pregnant patients (3, 4), and the significant impact of potential treatment failure, the effect of pregnancy on HCQ disposition and the potential need for dose adjustments remains virtually unknown. Therefore, the aim of this study was to characterize the population PK of HCQ in pregnancies complicated by rheumatic diseases.

2. Methods

2.1 Study design

We performed a population PK analysis using data and samples collected through the Duke Autoimmunity in Pregnancy (DAP) Registry, which prospectively collects biospecimens and clinical data. We conducted the study in compliance with the Declaration of Helsinki, and the Duke Institutional Review Board approved the protocol. All subjects included in the study provided informed consent.

2.2 Patient population

We identified participants taking HCQ prior to pregnancy from November 2013 to December 2016 from the DAP Registry. We enrolled participants if they were maintained on HCQ longitudinally throughout pregnancy, and had at least one blood sample available for analysis. We excluded subjects with multiple gestations (e.g., twins).

2.3 Drug dosing, sample collection, and data collection

The DAP is an observational registry; participants' own rheumatologists prescribed and dosed oral HCQ according to standard of care (SOC). At each visit, the prescribed HCQ dosing was confirmed with the subject and recorded in the registry and electronic health record (EHR). However, the exact administration time for the last drug dosage was unknown for most participants; therefore, we imputed a time of 8:00 am on the day of the study visit. We collected blood samples at the same time as SOC laboratory studies at each clinic visit, which typically occurred 2–4 times per participant during pregnancy and postpartum. Research blood is spun and aliquoted into serum samples following blood draw and maintained in a freezer between -20°C and -80°C until the time of analysis. We recorded the time of sample collection in the EHR. We also recorded clinical data (e.g., actual weight) at each visit.

2.4 Analytical methods

We quantified concentrations of HCQ in serum at NMS labs (Willow Grove, PA, USA) using a validated high-performance liquid chromatography/tandem mass spectrometry (HPLC-MS/MS) assay. HCQ is stable in serum for at least 12 months frozen at 20°C (10). The assay's lower limit of quantitation (LLOQ) was 10 ng/mL and was linear to 5000 ng/mL. The between-run precision varied as a function of concentration, and ranged from 9.46% at the LLOQ to 4.38% at high concentrations.

2.5 Population PK model evaluation and validation

We analyzed HCQ serum data using nonlinear mixed effects modeling with Phoenix NLME (Certara, Princeton, NJ, USA, v 7.0) to derive population PK models. We used the first-order conditional estimation method with extended least squares. We explored one- and two-compartment structural PK models and proportional, additive, and proportional-plus-additive residual error models. We assumed K_a (the absorption rate constant) to be 1.15/hr and T_{lag} (the lag time of absorption) to be 0.39 hr (11, 12). Since all drug was administered only orally to our patients, we could not estimate bioavailability (F).

During model building, we assessed model performance by successful minimization of the objective function value (OFV), diagnostic plots, and plausibility and precision of parameter estimates. The goodness-of-fit plots included: individual predictions (IPRED) and population predictions (PRED) vs. observations; conditional-weighted residuals (CWRES) vs. time; and individual-weighted residuals (IWRES) vs. IPRED.

We investigated covariates for their influence on PK parameters for the base model. We evaluated the following univariate covariates: disease (SLE vs. other), race (white vs. other), maternal age, postmenstrual age (PMA), postnatal age (PNA), and weight in kg. We used

forward inclusion ($p < 0.01$) and backward elimination ($p < 0.001$) to determine inclusion of the covariates. We defined PMA as the time elapsed since the last menstrual cycle and PNA as the time elapsed since birth.

We used nonparametric bootstrapping with 1000 replicates to evaluate the analysis and to generate the 95% confidence intervals for parameter estimates. We used the final model to generate Monte Carlo simulation replicates per time point; and we used visual predictive checks (VPCs) to compare simulated results with those observed in the study. We used the same dosing and covariate values in the study population to generate the simulations in the VPC.

Based on previous literature, we defined medication non-adherence as HCQ concentrations < 100 ng/mL (13–15). Therefore, we excluded patients with average concentrations < 100 ng/mL throughout pregnancy and postpartum ($n = 5/50$ subjects). To determine the impact of subject and/or sample exclusion on PK parameter estimates, we performed retrospective analyses comparing two additional models against our primary model: model B (excluding individual samples < 100 ng/mL [$n = 35/145$ samples]), and model C (excluding subjects with any concentration < 100 ng/mL [$n = 13/50$ subjects]). Additional sensitivity analyses explored 1) the impact of volume estimates on estimated apparent clearance (CL/F), and 2) the impact of varying HCQ administration timing on CL/F and apparent volume of distribution (V_d/F) estimates.

2.6 Pregnancy and postpartum comparisons

To investigate the effect of pregnancy progression on HCQ PK, we performed several additional modeling exercises. First, we tested both pregnancy status (categorical) and duration of gestation as potential covariates in the complete PK model. Secondly, we developed a postpartum PK model from subjects who had both pregnancy and postpartum samples. We then used the intrapartum data from these same subjects to develop PK models from the entire pregnancy period. Comparisons of the Empirical Bayesian Estimates (EBEs) of parameter values between pregnancy and the postpartum period were performed using paired t-tests with R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria) and RStudio version 1.0.153 (RStudio, Inc., Boston, MA). The apparent 24-hour area under the curve ($AUC_{24/F}$) was calculated by dividing the dose by the EBE for CL/F.

2.7 Predicted drug concentration profiles

We computed expected steady state drug concentration profiles for the most common dosage of HCQ, 400 mg once daily, using the individual clinical data from the 25 subjects with paired pregnancy and postpartum samples and individual EBEs developed from the final PK model. Concentrations were calculated using the following formula:

$$C = \frac{D}{V_d/F} * \left(\frac{K_a}{K_a - K} \right) * \left(\frac{e^{-k(t - td - Tlag)}}{(1 - e^{k\tau})} - \frac{e^{-ka(t - td - Tlag)}}{(1 - e^{ka\tau})} \right) \quad (1)$$

where C is HCQ serum concentration, D is the dose of HCQ, Vd/F is the EBE parameter estimate for volume of distribution, K is the elimination rate constant (CL/V), t is time in hours, td is the time the subject took the dose, and τ is the dosing interval.

3. Results

3.1 Subject demographics

Fifty subjects met the inclusion criteria. The median age of all participants was 31 years (interquartile range [IQR] 29–35), the median body mass index at the first pregnancy visit was 27.1 kg/m² (IQR 23.9–31.6), and most (64%) were white. Participants had a variety of rheumatic diseases, the most common of which were SLE (56%), rheumatoid arthritis/juvenile arthritis (14%), and undifferentiated connective tissue disease (10%). The maximum observed creatinine was 1 mg/dL during pregnancy and 1.2 mg/dL postpartum. Most subjects took HCQ as 400 mg once daily. During pregnancy, approximately 60% of subjects were taking a concomitant, non-over-the-counter prescription medication, most commonly azathioprine (18%) and prednisone (28%). Postpartum, 70% of mothers were taking at least one prescription concomitant medication. However, none of the concomitant medications taken during pregnancy or postpartum are known to impact HCQ PK. Twenty-five subjects had both pregnancy and postpartum specimens; there were no significant differences in baseline demographics, concomitant medications, and disease activity as measured by the physician global assessment in this subgroup. Postpartum visits occurred at a median of 7 weeks (IQR 5–8) after delivery.

Altogether, 145 serum samples were obtained from the 50 study patients. Six of these samples (4%) were below the LLOQ (<10 ng/mL). Thirteen subjects had a total of 19 concentrations that were very low (<100 ng/mL) during either pregnancy or postpartum. Five subjects had average concentrations (pregnancy and postpartum) <100 ng/mL, consistent with medication non-adherence, and were excluded from further analysis. The highest mean drug levels were observed in the oldest specimens (approximately 3 years of age), suggesting no sample degradation occurred.

3.2 Population PK model development and evaluation

Model-building steps are outlined in Table 1. The base model was a one-compartment model with between-subject variability estimates of V/F and CL/F ; the final model was a 1-compartment model with fixed allometric scaling of weight (WT) on V/F and between-subject variability of CL/F . In univariate analysis, none of the covariates tested, other than WT on V/F , were significant at a threshold of $p < 0.01$. Residual error was best described using a proportional error model.

PK parameters are provided in Table 2. The final population PK model is shown below.

$$ka = tvka \quad (2)$$

$$V = tvV * \left(\frac{WT}{70}\right)^{dVdWT} \quad (3)$$

$$CL = tvCL * \exp(\eta CL) \quad (4)$$

$$Tlag = tvTlag \quad (5)$$

WT denotes an individual's actual weight in kg. *CL* and *V* are a subject's parameter estimates, where *tvV* and *tvCL* represent the typical parameter values in this population. *dVdWT* denotes the exponential, allometric scaling of weight/70 on volume and ETA (η) estimates between-subject variability.

Diagnostic plots suggested a good fit of the observed data to the model; correlation between individual-predicted and observed concentrations was better than the correlation between population-predicted and observed concentrations (Online Resource 1).

3.3 Sensitivity analyses

3.3.1 Importance of low serum HCQ concentrations—The impact of very low concentrations on model performance (final model compared with models B and C) is presented in Online Resource 2. Correlation between observed and predicted concentrations progressively improved with the exclusion of very low concentrations in models B and C. For model B, the V/F was 2000 L/70 kg (% coefficient of variation [CV] 2) and the CL/F was 47 L/hr (%CV 7). For model C, the V/F was 1842 L/70 kg (%CV 45) and the CL/F was 44 L/hr (%CV 8). Histograms illustrating the EBEs for CL/F estimates for all models are provided in Online Resource 3. Progressive exclusion of very low concentrations resulted in a normal distribution of CL/F estimates in the cohort. The final model excluded the least amount of data while retaining optimal model performance (all EBEs for clearance <99th percentile) and parameter estimates.

3.3.2 The effect of uncertain dosing time—The sensitivity of V/F and CL/F with varying HCQ administration time is presented in the Online Resource 4. Estimates for V/F were quite variable depending on assumed administration time; however, estimates for CL/F changed very little (<10%) with differences of administration times less than 12 hours earlier than actually taken.

3.3.3 The effect of imprecise estimation of V/F—Given imprecision with the estimation of V/F, we investigated the impact of the volume estimation on clearance. The impact of increasing volume on clearance for the final model was small. For a fixed V/F of 1500 L, CL/F was estimated to be 53 L/hr; for a V/F of 2000 L, the CL/F decreased to 51 L/hr; and for a V/F of 2500 L, the CL/F estimate decreased to 49 L/hr.

3.4 Pregnancy and postpartum comparisons

Models were developed for pregnancy and postpartum using data from 25 subjects with paired pregnancy and postpartum samples. Due to low sample sizes and model performance within subgroups, the pregnancy period was not further stratified by trimester. EBEs for model parameters and for secondary parameters calculated from each subject are depicted in Table 3. Compared with postpartum values, the median V/F was significantly higher during pregnancy ($p < 0.001$). However, CL/F values were not significantly different between pregnancy and postpartum samples.

3.5 Predicted drug concentrations in pregnancy and postpartum

Results from the prediction of drug concentrations from models generated from the pregnancy and postpartum samples are depicted in Fig. 1. The time-concentration profile appeared flatter during pregnancy, corresponding with the observed increase in V/F.

4. Discussion

To determine how the disposition of HCQ changes during pregnancy, we developed a population PK model of HCQ in pregnancies complicated by rheumatic diseases. To our knowledge, this is the first pregnancy population PK model for HCQ in these diseases.

Consistent with most studies using oral HCQ, we found that a one-compartment model provided the best fit for the data, although both one- (12, 16), two- (11) , and three-compartment (17)] PK models have been previously used to describe HCQ disposition. We tested a number of covariates (e.g., disease, race, maternal age, PMA, PNA, and weight) for influence on PK parameters and identified only weight as a significant covariate for V/F. While some reports suggest weight is a significant covariate on clearance for HCQ (12), we did not find this association in our pregnancy cohort.

Using a serum matrix, we estimated the population CL/F to be 51 L/hr, which was consistent with a previously published estimate of plasma HCQ clearance (50.2 L/hr) (16), although estimates in plasma as low as 10.9 L/hr (11) and as high as 68.2 L/hr (12) have also been reported. In addition, we estimated the V/F to be 1850 L/70kg, which is lower than other reports in plasma of 2440 L/70kg (12) and 3065 L/70kg (assuming a whole-blood-to-plasma ratio of 3.8) (16). While the current PK model estimated CL/F with little relative standard error (8%), the estimate for V/F had higher relative standard error (53%). The difficulty in precisely estimating V/F was likely secondary to the lack of precise dosage administration times. Further, dissimilarities in parameter estimates in our study may also be due to differences between matrices (e.g., serum vs. whole blood or plasma), sample collection times, and uncertainty regarding medication adherence. Although HCQ partitions into red blood cells, white blood cells, and platelets (9, 18, 19), serum/plasma or unbound drug levels may be preferred over whole blood testing for certain drugs during pregnancy due to confounding that may occur using whole blood levels in the setting of pregnancy-induced anemia (20). Further, whole blood levels may be impacted by the reductions in red blood cells, white blood cells, and platelets that can occur in some rheumatic diseases (e.g., SLE) [1].

During pregnancy, we observed a decrease in peak HCQ concentrations compared to postpartum, likely corresponding to the significant increase in the V/F during pregnancy. As demonstrated in our dosing simulations, changes to the drug's V/F may decrease peak concentrations while also leading to increased concentrations later in the dosing interval. The decrease in peak concentrations, however, may not be clinically significant for HCQ because the anti-rheumatic effects of the drug are mediated indirectly and require several months of drug exposure (8). Because HCQ CL/F did not change during pregnancy, the apparent total drug exposure (AUC_{24}/F) also did not change. As a result, our modeling in this small cohort of patients does not support dosing adjustments during pregnancy; however, larger studies will need to answer this question definitively. Further, changes in drug concentration were most pronounced late in pregnancy, and due to HCQ's long half-life, delivery would likely occur before a dose adjustment would reach steady state. Because drug concentrations change little in comparison to the inter-individual variability, the primary role of therapeutic drug monitoring for HCQ during pregnancy may be limited to identifying subjects with poor adherence. Adherence monitoring using HCQ concentration has been extensively discussed elsewhere (13–15, 19, 21).

It is possible that subject non-adherence influenced the PK parameter estimates. Specifically, non-adherence (i.e., inappropriately low concentrations) could result in falsely high CL/F estimates. Conversely, by (wrongly) excluding adherent subjects with very low concentrations, CL/F estimates could be falsely low. HCQ non-adherence has been variably defined using whole blood levels ranging from <100 to 500 ng/mL (13, 15, 19, 22). We defined non-adherence as serum drug levels <100 ng/mL based on published literature of whole blood values and visual trends of both individual-level and population-level concentration vs. time profiles. Because whole blood levels may be higher than serum due to partitioning into cells, it is possible our definition over-classified non-adherence. However, we evaluated two additional models (models B and C) to determine the impact of excluding data consistent with non-adherence on PK parameters. Compared with models B and C, our final model retained good performance, biologically plausible CL/F estimates, and excluded the least amount of data. The observed estimates for apparent V/F differed only slightly between the three models (range 1842–2000 L/70kg), although the coefficient of variation was significantly lower for model B. Reassuringly, the CL/F was similar between all of the models (range 44–51 L/hr), although the estimate did decrease slightly as low concentrations were progressively excluded. Therefore, while our parameter estimates may differ slightly due to various assumptions of non-adherence, study conclusions would not change.

As mentioned previously, another limitation with our model is the lack of administration times for HCQ dosing. Although some reports suggest administration time may influence drug levels (19), the within-day changes to HCQ concentration is minimal due to the drug's long half-life (8, 23, 24). Our model assigned an administration time of 8:00 am for all subjects and explored the effect of altering HCQ timing on parameter estimates. The estimates for volume were sensitive to assumptions in administration timing. For example, assuming a subject took HCQ up to 12 hours earlier than imputed would increase the V/F estimate, while remaining within a plausible range (2543–3029 L/70kg) with little inter-individual variability (%CV 1–5). However, a subject taking a dose 1 hour later than imputed would significantly increase the V/F estimate and lead to very high inter-individual

variability (7220 L/70kg, %CV 247). Conversely, CL/F estimates changed <10% with differences of administration times less than 12 hours earlier than taken. Because dosing recommendations are most dependent on CL and drug exposure (e.g., AUC), it is unlikely that the assumptions for timing of HCQ administration in our modeling would change dosing implications.

Unfortunately, our samples were not amenable to testing for HCQ metabolites. Despite this potential limitation, the clinical significance of HCQ metabolites with regards to efficacy or toxicity in rheumatic diseases is questionable (19, 25, 26). Nevertheless, future studies should consider measuring both parent HCQ and metabolites during pregnancy to fully characterize drug disposition.

Lastly, we compared PK estimates and dosing implications between pregnancy and postpartum using paired data from a subgroup of participants with samples from both periods. Traditionally, the postpartum period lasts approximately 6 weeks (27); because postpartum visits in our study ranged from 2 to 19 weeks after delivery (median 7 weeks), it is possible that a few participants were not back to their physiologic baseline. Future studies may consider collecting pre-pregnancy (baseline) HCQ measurements or concentrations from a non-pregnant control group.

5. Conclusion

In summary, we developed a one-compartment population PK model for HCQ in pregnant women with rheumatic disease. Although limited by different matrices, estimates for CL/F were within the expected range of values in non-pregnant adults. While estimates for V/F were less precise due to the lack of administration timing, HCQ V/F increased significantly during pregnancy and corresponded to an observed decrease in serum concentrations. The lack of demonstrated changes in CL/F and AUC_{24}/F in our small cohort of patients does not support a need for HCQ dose adjustment during pregnancy. As demonstrated, PK studies capitalizing on registries of patients receiving usual care may be a transformative way to study drug disposition in vulnerable populations with rare diseases, and can be optimized by collecting specific measures of administration timing and medication adherence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grants/financial support:

NIGMS/NICHD 2T32GM086330-06, NICHD (5R01-HD076676-04, HHSN275201000003I), Derfner Foundation, Duke Health ENABLE, the Rheumatology Research Foundation's Scientist Development Award, and the Thrasher Research Fund

S.J.B. receives salary and research support from the National Institute of General Medical Sciences and the National Institute of Child Health and Human Development (2T32GM086330-06, 5R01-HD076676-04, HHSN275201000003I). Salary and/or research funding for this project was provided by the Rheumatology Research Foundation's Scientist Development Award, the Thrasher Research Fund, and the Derfner Foundation. The National Institutes of Health sponsor open access. M.C.W. receives support for research from the NIH (5R01-

HD076676, HHSN275201000003I), NIAID/NIH (HHSN272201500006I), FDA (1U18-FD006298), the Biomedical Advanced Research and Development Authority (HHSO1201300009C), and from the industry for the drug development in adults and children (www.dcri.duke.edu/research/coi.jsp).

A.M.E is a consultant for GlaxoSmithKline and was previously a graduate research assistant for GlaxoSmithKline. Dr. Eudy and Dr. Clowse have received an independent medical education grant from GlaxoSmithKline.

L.E.S receives research support from the National Institutes of Health (5R01-AR063890-02, 1U19AR069522-01, 1U34AR066294), Patient-Centered Outcomes Research Institute (CER-1408-20534 and PPRN-1306-04601), the Childhood Arthritis and Rheumatology Research Alliance (CARRA), Swedish Orphan Biovitrum AB, and participates in the Data Safety and Monitoring Board for UCB and Sanofi. M.E.B.C. serves as a consultant for UCB and AstraZeneca. She has received a grant from GlaxoSmithKline.

References

1. Clowse ME. Lupus activity in pregnancy. *Rheum Dis Clin North Am* 2007;33:237–52, v. [PubMed: 17499705]
2. Gotestam Skorpen C, Hoeltzenbein M, Tincani A, Fischer-Betz R, Elefant E, Chambers C, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis* 2016;75:795–810. [PubMed: 26888948]
3. Clowse ME, Magder L, Witter F, Petri M. Hydroxychloroquine in lupus pregnancy. *Arthritis Rheum* 2006;54:3640–7. [PubMed: 17075810]
4. Eudy AM, Siega-Riz AM, Engel SM, Franceschini N, Howard AG, Clowse MEB, et al. Effect of pregnancy on disease flares in patients with systemic lupus erythematosus. *Ann Rheum Dis* 2018;77:855–60. [PubMed: 29463519]
5. Fischer-Betz R, Specker C, Brinks R, Aringer M, Schneider M. Low risk of renal flares and negative outcomes in women with lupus nephritis conceiving after switching from mycophenolate mofetil to azathioprine. *Rheumatology (Oxford)* 2013;52:1070–6. [PubMed: 23382355]
6. Ke AB, Rostami-Hodjegan A, Zhao P, Unadkat JD. Pharmacometrics in pregnancy: An unmet need. *Annu Rev Pharmacol Toxicol* 2014;54:53–69. [PubMed: 24392692]
7. Abduljalil K, Furness P, Johnson TN, Rostami-Hodjegan A, Soltani H. Anatomical, physiological and metabolic changes with gestational age during normal pregnancy: a database for parameters required in physiologically based pharmacokinetic modelling. *Clin Pharmacokinet* 2012;51:365–96. [PubMed: 22515555]
8. Rainsford KD, Parke AL, Clifford-Rashotte M, Kean WF. Therapy and pharmacological properties of hydroxychloroquine and chloroquine in treatment of systemic lupus erythematosus, rheumatoid arthritis and related diseases. *Inflammopharmacology* 2015;23:231–69. [PubMed: 26246395]
9. Browning DJ. Pharmacology of Chloroquine and Hydroxychloroquine. In: *Hydroxychloroquine and Chloroquine Retinopathy* New York: Springer-Verlag New York; 2014:35–63.
10. NMS Labs. Hydroxychloroquine Test Summary Sheet Available at: <http://www.nmslabs.com/tests/Hydroxychloroquine--Serum-Plasma/2362SP>. Accessed 6th February 2018.
11. Lim HS, Im JS, Cho JY, Bae KS, Klein TA, Yeom JS, et al. Pharmacokinetics of hydroxychloroquine and its clinical implications in chemoprophylaxis against malaria caused by *Plasmodium vivax*. *Antimicrob Agents Chemother* 2009;53:1468–75. [PubMed: 19188392]
12. Morita S, Takahashi T, Yoshida Y, Yokota N. Population Pharmacokinetics of Hydroxychloroquine in Japanese Patients With Cutaneous or Systemic Lupus Erythematosus. *Therapeutic Drug Monitoring* 2016;38:259–67. [PubMed: 26587870]
13. Costedoat-Chalumeau N, Amoura Z, Hulot JS, Aymard G, Leroux G, Marra D, et al. Very low blood hydroxychloroquine concentration as an objective marker of poor adherence to treatment of systemic lupus erythematosus. *Ann Rheum Dis* 2007;66:821–4. [PubMed: 17324970]
14. Costedoat-Chalumeau N, VLEG, Piette JC. Routine Hydroxychloroquine Blood Concentration Measurement in Systemic Lupus Erythematosus Reaches Adulthood. *J Rheumatol* 2015;42:1997–9. [PubMed: 26523036]
15. Iudici M, Pantano I, Fasano S, Pierro L, Charlier B, Pingeon M, et al. Health status and concomitant prescription of immunosuppressants are risk factors for hydroxychloroquine non-

adherence in systemic lupus patients with prolonged inactive disease. *Lupus* 2018;27:265–72. [PubMed: 28659047]

16. Carmichael SJ, Charles B, Tett SE. Population pharmacokinetics of hydroxychloroquine in patients with rheumatoid arthritis. *Ther Drug Monit* 2003;25:671–81. [PubMed: 14639053]
17. Tett SE, Cutler DJ, Day RO, Brown KF. A dose-ranging study of the pharmacokinetics of hydroxychloroquine following intravenous administration to healthy volunteers. *Br J Clin Pharmacol* 1988;26:303–13. [PubMed: 3179169]
18. Jallouli M, Galicier L, Zahr N, Aumaitre O, Frances C, Le Guern V, et al. Determinants of hydroxychloroquine blood concentration variations in systemic lupus erythematosus. *Arthritis Rheumatol* 2015;67:2176–84. [PubMed: 25989906]
19. Yeon Lee J, Lee J, Ki Kwok S, Hyeon Ju J, Su Park K, Park SH. Factors Related to Blood Hydroxychloroquine Concentration in Patients With Systemic Lupus Erythematosus. *Arthritis Care Res (Hoboken)* 2017;69:536–42. [PubMed: 27390146]
20. Hebert MF, Zheng S, Hays K, Shen DD, Davis CL, Umans JG, et al. Interpreting tacrolimus concentrations during pregnancy and postpartum. *Transplantation* 2013;95:908–15. [PubMed: 23274970]
21. Costedoat-Chalumeau N, Houssiau F, Izmirly P, Le Guern V, Navarra S, Jolly M, et al. A Prospective International Study on Adherence to Treatment in 305 Patients With Flaring SLE: Assessment by Drug Levels and Self-Administered Questionnaires. *Clin Pharmacol Ther* 2017; doi: 10.1002/cpt.885.
22. Durcan L, Clarke WA, Magder LS, Petri M. Hydroxychloroquine Blood Levels in Systemic Lupus Erythematosus: Clarifying Dosing Controversies and Improving Adherence. *J Rheumatol* 2015;42:2092–7. [PubMed: 26428205]
23. Costedoat-Chalumeau N, Amoura Z, Hulot JS, Hammoud HA, Aymard G, Cacoub P, et al. Low blood concentration of hydroxychloroquine is a marker for and predictor of disease exacerbations in patients with systemic lupus erythematosus. *Arthritis Rheum* 2006;54:3284–90. [PubMed: 17009263]
24. Tett SE, Cutler DJ, Beck C, Day RO. Concentration-effect relationship of hydroxychloroquine in patients with rheumatoid arthritis--a prospective, dose ranging study. *J Rheumatol* 2000;27:1656–60. [PubMed: 10914847]
25. Munster T, Gibbs JP, Shen D, Baethge BA, Botstein GR, Caldwell J, et al. Hydroxychloroquine concentration-response relationships in patients with rheumatoid arthritis. *Arthritis Rheum* 2002;46:1460–9. [PubMed: 12115175]
26. Lee JY, Vinayagamoorthy N, Han K, Kwok SK, Ju JH, Park KS, et al. Association of Polymorphisms of Cytochrome P450 2D6 With Blood Hydroxychloroquine Levels in Patients With Systemic Lupus Erythematosus. *Arthritis Rheumatol* 2016;68:184–90. [PubMed: 26316040]
27. Shaw E, Kaczorowski J. Postpartum care--what's new? *Curr Opin Obstet Gynecol* 2007;19:561–7. [PubMed: 18007134]

KEY POINTS

- Hydroxychloroquine volume of distribution increased significantly during pregnancy compared to postpartum; however, the total drug exposure did not change.
- Dosing simulations in this cohort did not support the need to adjust hydroxychloroquine dose during pregnancy; however, larger studies are needed to answer this question definitively.

Figure Legend: red circles = pregnancy concentrations; blue circles = postpartum concentrations.

Fig. 1.

Simulated Hydroxychloroquine (HCQ) Concentrations during Pregnancy and Postpartum

Table 1:**Model-Building Steps**

	Model	ETA	# Parameters	OFV	Change in OFV
1	1 compartment	$\eta V_d, \eta CL$	5	-100.8	
2	1 compartment, dVdWT (estimated)	$\eta V_d, \eta CL$	6	-108.6	-7.8
3	1 compartment, dVdWT (fixed = 1)	$\eta V, \eta CL$	5	-107.5	-6.7
4	2 compartments, dVdWT (fixed = 1)	$\eta V, \eta CL, \eta V_2, \eta Q$	9	-104.8	-4
5	1 compartment, dVdWT (fixed = 1) dCldWT (estimated)	$\eta V_d, \eta CL$	6	-108.3	-7.5
6	1 compartment, dVdWT (fixed = 1)	ηV_d	4	-61.6	50
7	1 compartment, dVdWT (fixed = 1)	ηCL	4	-107.7	-6.9

CL, clearance; dVdWT, exponential, allometric scaling of weight/70 on volume; dCldWT, exponential, allometric scaling of weight/70 on clearance; ETA (η) individual deviations from the population parameter value; OFV, objective function value; Q, intercompartmental clearance; V_d , volume; WT, weight (in kilograms)

Table 2:

Population Pharmacokinetic Parameter Estimates

Parameters	Estimate	RSE (%)	Bootstrap median	2.5%	97.5%	Bootstrap RSE (%)
K_a^* (1/hr)	1.15		1.15			
V/F (L/70kg)	1850	53	2332	1085	5346	
CL/F (L/hr)	51	8	52	44	61	
dVdWT [*]	1		1			
BSV CL (% CV)	44	4	42			4
Residual error (%)	0.37	11	0.37	0.29	0.44	

BSV, between-subject variability; CL/F, apparent clearance; CV, coefficient of variation; dVdWT, exponential, allometric scaling of weight/70 on volume; K_a , absorption rate constant; RSE, relative standard error; V/F, apparent volume.

^{*} Fixed parameter values.

Table 3:

Empirical Bayesian Parameter Estimates for Pregnancy and Postpartum Periods

	Prenatal			Postnatal			Differences		
	V/F (L/70kg)	CL/F (L/h)	AUC ₂₄ /F (mg*h/L)	V/F (L/70kg)	CL/F (L/h)	AUC ₂₄ /F (mg*h/L)	V/F (L/70kg)	CL/F (L/h)	AUC ₂₄ /F (mg*h/L)
Median	4631.5	52.5	7.6	1720.7	52.2	7.7	2803.2	3.9	-0.6
25%	3985.6	42.5	6.3	1517.7	43.1	6.9	2512.8	-2.3	-1.3
75%	5236.5	63.0	9.3	1966.6	57.1	9.3	3271.1	10.8	0.4
Mean	4753.7	54.7	8.5	1799.4	49.9	8.3	2954.3	4.8	0.2
SD	971.7	25.6	3.8	361.4	10.2	2.5	642.8	22.0	2.7
SE	194.3	5.1	0.8	72.3	2.0	0.5	128.6	4.4	0.5
p-value							<0.001	0.2	0.7

AUC₂₄/F; Apparent 24-hour area under the curve; CL/F, apparent clearance; SD, standard deviation; SE, standard error; V/F, apparent volume.