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BRIEF REPORT

Reconciling Between Medication Orders and Medication Fills for Lupus in Pregnancy

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Objective. Most studies consider either medications ordered or filled, but not both. Medication underuse based on filling data cannot necessarily be ascribed to patient nonadherence. Using both data sources, we quantified primary medication adherence in a cohort of prevalent systemic lupus erythematosus (SLE) pregnancies.

Methods. We identified 419 pregnancies in Kaiser Permanente Northern California in patients with prevalent SLE from 2011 to 2020. We calculated the number of physician-initiated orders or pharmacy-initiated reorders during pregnancy and a comparable 9-month window the year before (prepregnancy) and the proportion of orders ever filled and filled within 30 days for hydroxychloroquine (HCQ), azathioprine, and corticosteroids. For pregnancies without an order or reorder, we identified the proportion with previous prescription fills overlapping into the respective study period.

Results. New orders for lupus medications were usually filled. HCQ was prescribed most often (45.8% pregnancies) and usually filled (89.7% in prepregnancy, 93.2% during pregnancy). The majority filled within 30 days (80.5% prepregnancy, 83.3% pregnancy). Some pregnancies without new HCQ orders had continuous refills from prior orders; 53% of 2011–2015 pregnancies either had a new order or fill coverage from a previous period, compared to 63.2% of pregnancies delivering in 2016–2019. Corticosteroid fill frequencies were 90.6% in prepregnancy and 83.6% during pregnancy. Fewer patients used azathioprine; however, most new orders were filled (94.3% prepregnancy, 91.7% pregnancy). For azathioprine and corticosteroids, fill rates were modestly higher in prepregnancy compared to pregnancy.

Conclusion. We observed that patients have high adherence to filling new orders for lupus medications, such as HCQ and azathioprine, in pregnancy.

INTRODUCTION

Recent guidelines recommend that management of systemic lupus erythematosus (SLE) and preconception counseling are critical to reduce risks of adverse outcomes, both regarding pregnancy and lupus disease activity (1,2). Although hydroxychloroquine (HCQ) has been shown to improve outcomes in lupus pregnancy, HCQ is underused in lupus pregnancy. We and others found that only about 40% of women with lupus use HCQ during pregnancy (3–8). When we interpret these proportions as reflecting patient adherence, we assume that all providers are prescribing the medication (and this may be false). In our current work, we have the opportunity to look at both prescriptions written and prescriptions filled.

Previous studies were unable to capture both medication orders and corresponding fills, the information needed to quantify underuse. Medication use depends both on the clinician ordering the prescription and on the patient filling it. If only fill data are present, low medication use may be misclassified as patient nonadherence without consideration of prescribing practices of treating physicians. To extend the knowledge base, we examined prescription orders and fills in a cohort of prevalent SLE pregnancies from Kaiser Permanente Northern California (KPNC).

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SIGNIFICANCE & INNOVATIONS

- Similar to other studies, we found that only about 50% of lupus pregnancies had a fill for hydroxychloroquine (HCQ), and when adding refills from before pregnancy, this proportion modestly increased.
- Using data on both medication orders and fills, we estimated primary medication adherence (ie, what proportion of patients with new orders for HCQ, azathioprine, and corticosteroids filled at least one order at the pharmacy).
- However, when restricting patient adherence measures to require that an order for the medication was placed by a clinician, we found that patients with lupus were adherent with filling their medications both during pregnancy and in the year before, with estimates ranging from 80% to 93% depending on the medication and period.

PATIENTS AND METHODS

Data source. KPNC is an integrated health care delivery system that operates its own pharmacy and provides both primary and specialty care to more than 4.1 million members. The membership is stable, with more than 97% of individuals having at least five continuous years of enrollment and nearly all having drug benefit coverage through KPNC. High-quality clinical data are available through an electronic health record database called HealthConnect. HealthConnect provides data on prescription orders, and medication fills are identified through the Pharmacy Information Management System (PIMS). PIMS includes cost, medication name, national drug code, dates, dosage, and refill data for any prescriptions filled at any inpatient and outpatient Kaiser Permanente pharmacy.

At the KPNC Division of Research, the Perinatal Research Unit's Obstetric Database (POD) captures all pregnancies with onsets from 2011 onward regardless of pregnancy outcome indexed on unique pregnancy episodes and KPNC's Neonatal Minimum Dataset and Infant Cohort (9). Pregnancy episodes include data on pregnancy onset and outcomes dates, fetal outcomes (live birth, stillbirth, spontaneous abortion, therapeutic abortion, ectopic, molar). Pregnancies resulting in a live birth are linked to the infant KPNC medical record number to facilitate linkage to neonatal data. There are more than 350 data elements currently being captured that include information on the entire pregnancy episode, including relevant prepregnancy care, medication use, hospitalization, delivery admission, and postpartum care. POD processes raw data from multiple electronic sources and includes both manual and automated checks on the quality of the data.

Study population. Patients with SLE (identified as ≥2 International Classification of Diseases (ICD) coded visits ≥7 days apart) with a pregnancy outcome observed in the POD (2011–2020) were eligible for our study population. Similar definitions have been used in numerous data sources, and validation studies have yielded positive predictive values ranging from 83% to 100% (10). Individual patients could contribute multiple pregnancies. To examine changing patterns of adherence before and during pregnancy, we required that patients satisfy the SLE definition 1 year before the last menstrual period (LMP) for their corresponding pregnancy. We further restricted the study population to pregnancies resulting in either a stillbirth or a live birth (ie, ≥20 gestational weeks).

Study period/follow-up. The pregnancy period started at the estimated LMP and continued through the end of pregnancy. The prepregnancy period was the corresponding 9-month period starting a year before the LMP.

Exposure. The primary medication of interest was HCQ, and secondarily we examined azathioprine and corticosteroids (methylprednisolone, prednisolone, prednisone). We did not differentiate between medications within the corticosteroid group when selecting the prescription order with the earliest date in each period.

We focused on physician-initiated orders or pharmacy-initiated reorders for outpatient dispenses (mail-order and in-person), which we refer to as a new order. Therefore, medications administered in the emergency or inpatient setting or while in the clinic were not included. We inspected the KPNC prescription data to determine whether an order for the medication was placed, as well as filled. When multiple orders were written within the same period for each medication group, we used the order with the shortest time to fill. Additionally, we observed whether patients with no new orders had an existing filled medication with days' supply extending to the observation period to estimate the proportion or number of patients potentially exposed.

Additional covariates. For each pregnancy, we had data on the patient's age at the start of pregnancy, maternal race and ethnicity, and prepregnancy body mass index (BMI). Data on maternal race and ethnicity were categorized as Asian, Black, Hispanic, Islander, Multiracial, Native American, White, and unknown or missing. Prepregnancy BMI was calculated using the prepregnancy (within 12 months prior to pregnancy) weight measured at a clinic visit closest to the start of pregnancy. If a measured weight within 12 months prior to pregnancy was not available, the first measured weight in the first 10 weeks of pregnancy was used.

Statistical analysis. Characteristics of patients and their pregnancies are described as medians and interquartile ranges, as well as frequencies and proportions. The unit of analysis was pregnancies, and the study period was divided into the

prepregnancy and pregnancy periods based on the observed 419 lupus pregnancies. We identified prescription orders and fills and calculated frequencies and the proportion filled ever and within 30 days of the order date for each medication group overall and by calendar year (deliveries in 2011–2015, 2016–2019, and 2020). Filled (ever) indicates that the order was filled at any point after the order date (could be in any period). Because of COVID-19-related HCQ supply issues, 2020 was considered separately. The number of orders, fills, and fills within 30 days were plotted for HCQ and calculated for all medications.

Additionally, we wanted to estimate the availability of fills (eg, either a new prescription order or refills available from an active prescription that has not yet ended and has carried over into another period, such as an order from preconception that has refills available in pregnancy). Therefore, we calculated the proportion of pregnancies with active refills carrying over into the study periods among those without a new order during each period and then calculated fill coverage to represent the proportion of pregnancies with an order for HCQ available for filling or refill. This study was approved by the KPNC Institutional Review Board.

RESULTS

We identified 419 pregnancies to 330 patients with SLE receiving care at KPNC with a delivery (99% live births) from 2011 to 2020. The median age at pregnancy was 33 years, and the study population was 27% Asian, 27% non-Hispanic White, 25% Hispanic, 11% Black, 1.4% Islander, 7% Multiracial, and 0.7% Native American (five pregnancies [1.2%] were among patients of unknown race and ethnicity). The median

Table 1. Orders and first fills for common lupus medications during prepregnancy and pregnancy by calendar period in a population of 419 lupus pregnancies between 2011 and 2020

	Total pregnancies (n)	Total orders (n)	Filled (n)	Filled (%)	30-day fill (n)	30-day fill (%)
Hydroxychloroquine						
2011–2015						
Pregnancy	175	78	72	92.3	69	88.5
Prepregnancy	175	75	66	88.0	63	84.0
2016–2019						
Pregnancy	193	89	86	96.6	72	80.9
Prepregnancy	193	84	77	91.7	68	81.0
2020						
Pregnancy	51	25	21	84.0	19	76.0
Prepregnancy	51	26	23	88.5	18	69.2
Overall						
Pregnancy	419	192	179	93.2	160	83.3
Prepregnancy	419	185	166	89.7	149	80.5
Azathioprine						
2011–2015						
Pregnancy	175	16	14	87.5	14	87.5
Prepregnancy	175	11	11	100.0	11	100.0
2016–2019						
Pregnancy	193	16	15	93.8	11	68.8
Prepregnancy	193	21	20	95.2	17	81.0
2020						
Pregnancy	51	4	4	100.0	4	100.0
Prepregnancy	51	3	2	66.7	2	66.7
Overall						
Pregnancy	419	36	33	91.7	29	80.6
Prepregnancy	419	35	33	94.3	30	85.7
Corticosteroids						
2011–2015						
Pregnancy	175	59	49	83.1	47	79.7
Prepregnancy	175	52	45	86.5	45	86.5
2016–2019						
Pregnancy	193	37	32	86.5	27	73.0
Prepregnancy	193	53	50	94.3	47	88.7
2020						
Pregnancy	51	14	11	78.6	9	64.3
Prepregnancy	51	22	20	90.9	20	90.9
Overall						
Pregnancy	419	110	92	83.6	83	75.5
Prepregnancy	419	127	115	90.6	112	88.2

Table 2. Summary of available refills and orders of common medications in pregnancy among 419 lupus pregnancies in Kaiser Permanente Northern California from 2011 to 2020

	Pregnancies with orders (%)	Pregnancies without orders (n)	Pregnancies without orders with refill coverage n (%)	Pregnancies with an order or refill coverage (%)
Hydroxychloroquine				
2011–2015				
Pregnancy	44.6	97	15 (15.5)	53.1
Prepregnancy	42.9	100	23 (23.0)	56.0
2016–2019				
Pregnancy	46.1	104	33 (31.7)	63.2
Prepregnancy	43.5	109	33 (30.3)	60.6
2020				
Pregnancy	49.0	26	10 (38.5)	68.6
Prepregnancy	51.0	25	11 (44.0)	72.5
Azathioprine				
2011–2015				
Pregnancy	9.1	159	0 (0.0)	9.1
Prepregnancy	6.3	164	6 (3.7)	9.7
2016–2019				
Pregnancy	8.3	177	6 (3.4)	11.4
Prepregnancy	10.9	172	3 (1.7)	12.4
2020				
Pregnancy	7.8	47	1 (2.1)	9.8
Prepregnancy	5.9	48	0 (0.0)	5.9
Corticosteroids				
2011–2015				
Pregnancy	33.7	116	5 (4.3)	36.6
Prepregnancy	29.7	123	11 (8.9)	36.0
2016–2019				
Pregnancy	19.2	156	8 (5.1)	23.3
Prepregnancy	27.5	140	5 (3.6)	30.1
2020				
Pregnancy	27.5	37	1 (2.7)	29.4
Prepregnancy	43.1	29	0 (0.0)	43.1

prepregnancy BMI was 25.0 (interquartile range: 22.0–30.3). (Supplementary Table 1).

Of the 419 pregnancies, 45.8% (n = 192) had a new HCQ order during pregnancy throughout the entire study period (44.6% in 2011–2015; 46.1% in 2016–2019). Fill rates were slightly higher in pregnancy; in 2011–2015, 92% were filled (89% filled within 30 days), and in 2016–2019, 97% were filled (81% within 30 days) (Table 1). As expected, the frequencies were lower for 2020, possibly because of supply issues. A considerable proportion of pregnancies without a new order during these periods had an existing HCQ order that carried over into the study periods. For example, for 2011–2015 deliveries without

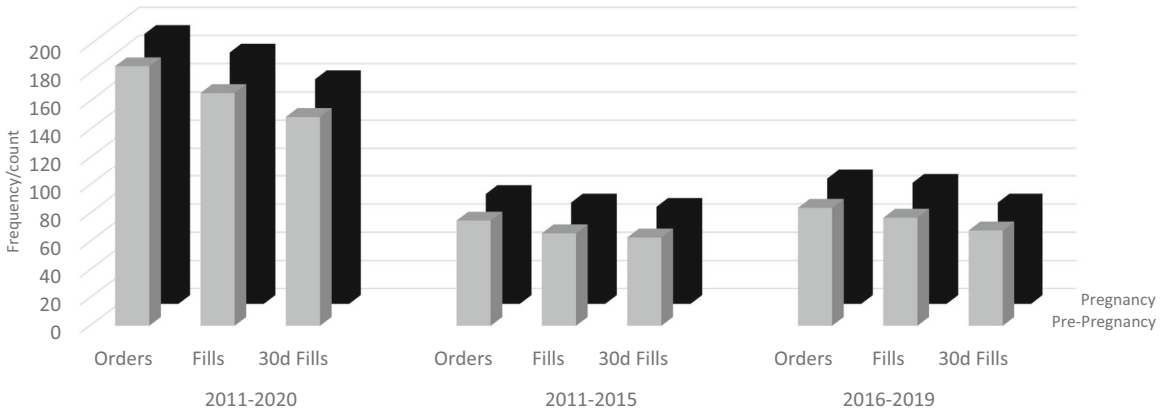

Figure 1. Number of new orders, and corresponding fills (ever and within 30 days [30d]) for hydroxychloroquine during pregnancy and in the corresponding 9-month period the year before among 419 pregnancies in patients with lupus in Northern California between 2011 and 2020.

new orders for HCQ written during pregnancy, nearly 16% had supply of their HCQ carryover into pregnancy, and 32% had supply of their HCQ carryover with 2016–2019 deliveries (Table 2).

In the prepregnancy period for 2011–2020 deliveries, 44.2% (n = 185) had at least one new prescription order for HCQ. For 2011–2015 deliveries, 88% were filled (84% within 30 days), and for 2016–2019 deliveries, nearly 92% were filled (81% within 30 days) (Figure 1, Table 1). The mean days to fill were relatively similar in the prepregnancy (12.58 days) and pregnancy (14.15 days) periods.

Prepregnancy prescription orders for corticosteroids were common in the 1 year before lupus pregnancy (n = 127, 30.3%). Fills overall (83.6% pregnancy, 90.6% prepregnancy) and fills within 30 days of the order (75.5% pregnancy, 88.2% prepregnancy) were relatively frequent (Table 1). Fills were made shortly after the order date in prepregnancy (mean 2.73 days) versus within an average of 9.13 days in pregnancy. A smaller proportion of pregnancies already had filled prescriptions for corticosteroids (ie, 3% and 9% had previous corticosteroid fills that overlapped with the prepregnancy and pregnancy periods, respectively).

Only 8.6% (n = 36) had a new order for azathioprine during pregnancy, with slightly lower fill rates (Table 1). Few pregnancies without new orders had pre-existing fills (Table 2). Similarly, 8.4% (n = 35) of pregnancies had a new prescription order for azathioprine during the prepregnancy period, of which 100% were filled within 30 days (2011–2015), compared to 81% among 2016–2019 pregnancies (95.2% ever filled) (Table 1). The mean days to fill for azathioprine was 6.21 days in the prepregnancy period and 8.48 days in the pregnancy period.

DISCUSSION

HCQ is almost universally indicated for the management of all SLE pregnancies, whereas other compatible medications (azathioprine, corticosteroids) are used for specific manifestations in a subset of lupus pregnancies. As expected, HCQ was the most common new prescription medication ordered in 419 lupus pregnancies. Over the study period, the overwhelming majority of patients were filling their orders both in the prepregnancy (89.7%–94.3%) and pregnancy periods (83.6%–93.2%), most within 30 days of the order. A considerable proportion of patients were already actively filling HCQ prescriptions before the study periods. In the year before pregnancy (prepregnancy period) we found that between 56% and 72.5% of lupus pregnancies were either actively filling or receiving new orders from 2011 to 2020, and during pregnancy, this varied from 53.1% to 68.6%. We noted only small differences in patient fill practices between prepregnancy and pregnancy periods. Although new orders of corticosteroids and azathioprine were less frequent, we found that most of these prescription orders were filled.

Studies in clinical cohorts and large databases around the world have reported a wide range of HCQ use during pregnancy over the past 20 years. Using both private and public insurance in the United States, one study found an increase in HCQ use over time, with 37.7% using HCQ during pregnancy in 2015 (compared to 12.4% in 2001) (3). In a retrospective cohort using Truven Health Marketscan data from 2006 to 2012, 42.8% of 1634 pregnant women with lupus used HCQ (11). In two clinical settings, 63.7% of 215 lupus pregnancies from 1993 to 2019 in a tertiary hospital in Portugal used HCQ (12), and 78.9% of 513 pregnancies from 2010 to 2018 from a single center in Shanghai, China, took HCQ (13). Using Swedish Registers (2006–2012), we showed that during lupus pregnancy, 36.4% filled HCQ, 20.7% filled azathioprine, and 48.0% filled a corticosteroid prescription. In the Shanghai study above, 97.7% received corticosteroids in pregnancy and 8.8% received an immunosuppressive agent, such as azathioprine (as well as tacrolimus and cyclosporine A). In comparison, we found that when accounting for refills and new orders, between 53% and 68% of lupus pregnancies may be using HCQ, about 30% may be using corticosteroids, and about 10% may be using azathioprine. Methodologic differences in how medication use was defined across studies may account for some of the differences, as well as regional and temporal trends related to updates to clinical guidelines and recommendations (1,2).

Studies of medication adherence tend to either report the proportion of patients self-reporting use, leverage fill data from pharmacies or reimbursement claims, or use other measures such as the medication possession ratio (MPR). These measures focus on continued use, days' supply, and persistence but frequently lack the denominator of who has an order to begin with. For example, using reimbursement or dispensing data from KPNC between 2006 and 2014, Liu et al calculated the MPR, that is, the proportion of time a patient had supply among patients with at least two medication fills (and they did not specifically look at a pregnant population) (14). Similarly, azathioprine refills 80% of the time or more were observed in less than 25% of Medicaid beneficiaries with lupus (15).

We address a different question about adherence and medication use: among patients with a new prescription order, what proportion is likely to fill? And secondarily, how might this compare during pregnancy and the year before? We specifically excluded conditioning on patients with any medication fills because that excludes the individuals who we tend to think of as nonadherent: those who were prescribed a medication but never filled it.

Little is known about the accuracy of order data or the underlying reasons for duplicate orders. Given that patients with lupus likely see many different specialists, we had to account for numerous possible fills. To avoid overestimating fill frequencies by including multiple fills during a period (those who refill are more likely to have orders and fills noted more frequently) we focused on at least one order during each period. By using the shortest

time to fill, we avoided underestimation of the fill rate and did not include canceled orders.

Although the absence of an order means that a patient could not fill a prescription, we cannot infer the clinician's intention. Without details about patient–provider conversations, we do not know whether a provider advised use of a medication and the patient declined during the visit. Therefore, we cannot infer provider compliance to guidelines. Additionally, because these prescriptions are often ordered and filled as 90-day prescriptions, we were limited in granularity both in the 3-month preconception period and in examining specific pregnancy trimesters.

Filling of prescriptions is done nearly exclusively within the KPNC pharmacy network, meaning we are unlikely to underestimate the proportion of filled new orders. In addition to these well-characterized data, strengths of our study include the innovative use of both order and fill data to evaluate adherence without overestimation due to refills. Additionally, we required at least two SLE-related visits, which has been shown to reduce misclassification.

Numerous studies on use of medications during lupus pregnancy are informed by data from reimbursement in claims, prescription dispensing from pharmacies, or self-report either in clinical notes or surveys. This study used data on both prescription orders and corresponding fills to estimate the likelihood that a patient with lupus, before and during pregnancy, will fill a new order for HCQ, azathioprine, or corticosteroids. We found that patients with lupus are very likely to fill these prescriptions, often within 30 days of the order.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Simard had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Simard.

Acquisition of data. Liu, Hedderson.

Analysis and interpretation of data. Simard, Liu, Chakravarty, Rector, Cantu, Kuo, Shaw, Druzin, Weisman, Hedderson.

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