Perinatal exposure to conventional synthetic disease-modifying anti-rheumatic drugs in women with rheumatic disease and neonatal outcomes: a population-based study

A. Howren[1-3], N. Rebić[1-3], E.C. Sayre[3], N.W. Tsao[1-3], N. Amiri[4], C. Baldwin[4], M.A. De Vera[1-3]

[1] Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada; [2]Collaboration for Outcomes Research and Evaluation, Vancouver, BC, Canada; [3]Arthritis Research Canada, Richmond, BC, Canada; [4]Division of Rheumatology, Department of Medicine, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada.

Abstract

Objective

Epidemiologic studies evaluating associations between specific arthritis medications and perinatal outcomes are limited. We evaluated the association between conventional synthetic DMARD (csDMARD) use among women with rheumatic disease (RD) and neonatal outcomes.

Methods

We linked population-based data in British Columbia, Canada from 01/01/2002 to 12/31/2012 on all inpatient/outpatient visits and medications with a perinatal registry. For small-for-gestational-age (SGA) births, we assessed csDMARD exposure 90 days preconception or during pregnancy until date of delivery. For congenital anomalies, we determined csDMARD exposure 90 days preconception or during the first trimester. We used multivariable logistic regression models fitted with generalised estimating equations and calculated post-hoc power.

Results

There were 185 pregnancies in 175 women (31.3±5.4 years) and 6,064 pregnancies in 4,387 women (31.1±5.4 years) in the csDMARD exposed and unexposed groups, respectively. Hydroxychloroquine, azathioprine, sulfasalazine, and methotrexate exposure before or during pregnancy were not associated with SGA births. The most sufficiently powered analyses were those for hydroxychloroquine, where exposure during pregnancy resulted in an adjusted odds ratio (aOR) of 1.12 (95% confidence interval [CI], 0.65–1.94) for SGA births. Although post-hoc power calculations indicate less power to detect associations between csDMARDs and congenital anomalies, results indicate methotrexate exposure during the first trimester is associated with elevated odds for congenital anomalies (aOR 6.58, 95% CI 1.15–37.75).

Conclusion

Findings are consistent with current guidelines regarding specific csDMARD use during the perinatal period for women with RD. It is important to report well-designed epidemiologic studies to facilitate future RD/csDMARD-specific meta-analyses.

Key words

rheumatic disease, DMARDs, pregnancy, small-for-gestational-age births, congenital anomalies

Alyssa Howren, MSc
Nevena Rebić, BSc(Pharm)
Eric C. Sayre, PhD
Nicole W. Tsao, BSc(Pharm), PhD
Neda Amiri, MD, MHSc
Corisande Baldwin, MSc, MD
Mary A. De Vera, PhD

Please address correspondence to:
Mary A. De Vera,
University of British Columbia,
Faculty of Pharmaceutical Sciences,
2405 Wesbrook Mall,
Vancouver V6T 1Z3 (BC), Canada.
E-mail: mdevera@mail.ubc.ca

Received on November 17, 2019; accepted in revised form on January 13, 2020.

Funding: this research was funded by an operating grant from The Arthritis Society (YIO-13-07). The funder played no role in the design or conduct of the study, or in writing this manuscript.

Data disclosure: All data were de-identified and no personal information was available at any point of the study. All inferences, opinions, and conclusions drawn in this manuscript are those of the authors and do not reflect the opinions or policies of the Data Stewards.

M. De Vera is an Assistant Professor, Canada Research Chair in Medication Adherence, Utilization, and Outcomes, The Arthritis Society Network Scholar, and Michael Smith Foundation for Health Research Scholar.
A. Howren is a recipient of a Canadian Institutes of Health Research Canada Graduate Scholarship Doctoral Award and the Wayne Riggs Interdisciplinary Doctoral Scholarship in Pharmaceutical Sciences.
N. Rebić is a recipient of a Canadian Institutes of Health Research Drug and Effectiveness Cross-Disciplinary Training (DSECT) program award.
N. Tsao is a recipient of a Canadian Institutes of Health Research Post-Doctoral Fellowship Award.

Competing interests: none declared.

Introduction

Rheumatic diseases (RD) are a group of chronic inflammatory conditions, including systematic lupus erythematosus (SLE) (1) and rheumatoid arthritis (RA) (2), that are more prevalent among women than among men (3) and often striking during childbearing years (4). Biological processes occurring during pregnancy, including immune and endocrine changes, contribute to clinical and therapeutic challenges in RD (2, 5), as autoimmunity may impact every aspect of pregnancy, including maternal complications and neonatal outcomes (6).

Managing RD during pregnancy with medications commonly used across diseases, including conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs; *e.g.* hydroxychloroquine, methotrexate) and targeted DMARDs (*e.g.* biologics), has been a longstanding therapeutic challenge, particularly with historically limited guidance on the perinatal use of certain agents. Significant advancements in the field include recent evidence on the perinatal impacts of these medications, particularly biologics (7-10), as well as guidelines by the European League Against Rheumatism in 2016 (11), the British Society for Rheumatology and British Health Professionals in Rheumatology in 2016 (12, 13), and the American College of Rheumatology (ACR) in 2018 (14). However, the moderate quality of evidence for some of these recommendations, particularly for csDMARDs, which may be used more frequently during pregnancy than biologics (9), highlights a continued need for well-designed studies to strengthen the evidence base. It is also important to report RD-specific and/or csDMARD-specific risk estimates (*e.g.* odds ratios [OR] and 95% confidence intervals [CI]) on the association between perinatal use of these medications with maternal and neonatal outcomes, which has not been consistently done in prior studies (15). Thus, our objective was to evaluate the association between perinatal csDMARD use among women with RD and adverse neonatal outcomes, specifically, small-for-gestational-age (SGA) births and congenital anomalies, which represent leading causes of infant morbidity.

Materials and methods

Data sources

We linked three administrative health data holdings in British Columbia (BC), Canada, namely Population Data BC (16), PharmaNet (17), and the BC Perinatal Database Registry (BCPDR) (18), to create a population-based pregnancy cohort. Specifically, Population Data BC captures individual-level, de-identified, longitudinal data on health services for the provincial population (estimated 4.7 million residents) including outpatient visits (*e.g.* to general practitioners, rheumatologists) in the Medical Services Plan database (MSP) (19, 20), hospital admissions in the Discharge Abstract Database (DAD) (21), and vital statistics since 1985 (22, 23). PharmaNet captures complete information on all drug prescriptions dispensed including drug identification number, dispensation date, dispensation quantity, dosage, and duration since 1996 (17). Finally, the BCPDR contains data from obstetrical and neonatal medical records on ~99% of births in BC from over 60 hospitals as well as home births attended by registered midwives since 2002 (18). This registry facilitates the establishment of precise timing of perinatal medication exposures for pharmacoepidemiologic research (24) by providing data on pregnancy start date (date of conception), which is derived from recommended algorithms for establishing gestational age using first ultrasound and then, start date of last menstrual period and newborn clinical exam (25). Data across the three data holdings for mothers and babies were linked using provincial health numbers, which were replaced with scrambled identifiers to anonymise the data (online Supplementary Fig. S1). We then created a source population that included women (n=305,351) with pregnancies (n = 449,098) ending in delivery (live-births and stillbirths) between January 1st, 2002 and December 31st, 2012 covered by the BC provincial health plan 24 months prior to and 12 months post-delivery. The requirement for continuous health plan coverage was to ensure capture of all relevant data for the women and their pregnancies in this source population.

Study cohort

From the source population, we created an RD pregnancy study cohort that included women with RA, systemic autoimmune rheumatic diseases (SARDs), and other RD including ankylosing spondylititis (AS), psoriatic arthritis (PsA), and juvenile idiopathic arthritis (JIA) (see online Suppl. Table S1 for International Classification of Diseases [ICD] codes). As with prior studies, pregnancies among women with RD were included if, any time prior to the date of conception, they met the criteria of having two ICD-9 codes from two separate outpatient physician visits at least 60 days apart in MSP and within two years of each other, or at least one hospitalisation with an ICD-10 code in the DAD for RD of interest (7, 8). As the unit of analysis was individual pregnancy, each pregnancy had to satisfy the above criteria to be included.

Exposure ascertainment

Using drug identification numbers in PharmaNet, we identified csDMARDs including antimalarials (hydroxychloroquine, chloroquine), azathioprine, cyclosporine, cyclophosphamide, leflunomide, methotrexate, minocycline, mycophenolate mofetil, and sulfasalazine. We defined exposure in pregnancies among women with RD if at least one prescription has been filled during perinatal windows of interest – preconception and during pregnancy – for each study outcome. For both SGA and congenital anomaly outcomes, the preconception window of interest was 90 days prior to the date of conception. For SGA, the pregnancy window of interest was calculated from the date of conception to the date of delivery. For congenital anomalies, this was calculated from the date of conception to 90 days, that is, end of the first trimester (Fig. 1). Unexposed groups comprised pregnancies in women with RD without filled prescriptions for csDMARDs during aforementioned perinatal windows of interest.

Outcome ascertainment

We assessed two neonatal outcomes: SGA births and congenital anomalies. SGA was identified using ICD 9/10 codes (764.0, 764.1, 765.0, 765.1, P05.0, P05.1, P07.0-P07.3) in either MSP, DAD, or as a newborn weighing less than the 10th percentile of gestational age- and sex-specific weights for neonates in BC using birth weights recorded in the BCPDR(26). Congenital anomalies were identified using the congenital anomaly variable from the BCPDR, which is a binary (yes/no) indicator of observable anomalies that occurred at birth.

Covariates

We considered potential confounders, including maternal and pregnancy characteristics, maternal comorbidities, other medication use, and healthcare utilisation. Maternal and pregnancy characteristics spanned maternal age at delivery (continuous), parity (primiparous or multiparous), neighborhood income quintile (based on postal code), body mass index (BMI) at first antenatal visit (normal: <25, overweight: 25-29.9, obese: ≥30 kg/m^2), and prior adverse pregnancy outcome (binary outcome capturing premature delivery, spontaneous abortions, neonatal death, stillbirth, low birth weight, or congenital anomalies in previous pregnancy as captured in the BCPDR). Maternal comorbidities, defined using ICD9/10 codes in MSP and DAD, included anxiety, depression, and diabetes (see Suppl. Table S2 for ICD codes). Other medication use – defined in the 90-day period before pregnancy and during pregnancy – included biologics, glucocorticosteroids, antidepressants, anxiolytics, traditional and COX-2 non-steroidal anti-inflammatory drugs (NSAIDs). Finally, healthcare utilisation variables, considered markers of disease severity and health status, included number of admissions before conception and number of outpatient visits (to rheumatologists and non-rheumatologists) during pregnancy assessed using Population Data BC holdings. We also considered healthcare utilisation variables captured in the BCPDR including number of antenatal outpatient visits and admissions during pregnancy.

Statistical analysis

The unit of analysis was pregnancy. We calculated summary statistics to describe characteristics of the study cohort. We used logistic regression models fitted with generalised estimating equations (GEE) that accounted for multiple pregnancies per mother, to calculate ORs and 95% CIs for the association between csDMARDs use preconception and during pregnancy and the study outcomes of SGA and congenital anomalies. Although we considered all csDMARDs routinely used in RD management, we could only obtain drug-specific ORs and 95% CIs where there were sufficient exposures to al-

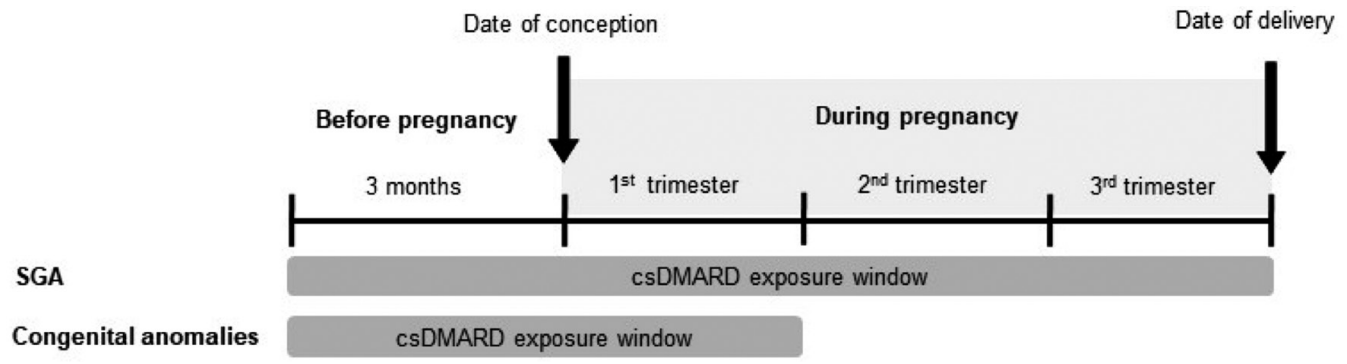

Fig. 1. Perinatal exposure windows of interest for study outcomes.

low convergence of statistical models. Multivariable models were adjusted for aforementioned maternal and pregnancy characteristics, maternal comorbidities, other medication use, and healthcare utilisation. For sensitivity analyses, we used information on csDMARD exposure-specific sample sizes before and during pregnancy and the proportion affected by each outcome in the reference category of no exposure, to compute the *post-hoc* power of detecting ORs of 1.5 and 2.0 at the alpha-level of 0.05 in the multivariable models. We conducted all analyses using SAS statistical software v. 9.4 (SAS Institute, Cary, North Carolina). This study was approved by the University of British Columbia, Behavioural Research Ethics Board.

Patient and public involvement

This study was supported by members of Arthritis Research Canada's Patient Advisory Board which provided feedback and a letter of support for the original grant submission. They also facilitated the presentation of this research through public forums.

Results

The study cohort comprised 4,562 women with RD contributing to 6,249 pregnancies, of which 185 (3.0%) pregnancies were exposed to at least one csDMARD preconception or during pregnancy (Table I). Among the pregnancies exposed to csDMARDs, the most common diagnosis pre-conception was RA (50.8%), followed by SARDs (33.5%) and other RD (15.7%). Conversely, other forms of RD, including AS, JIA, and PsA, were the predominant diagnoses (61.2%) among pregnancies unexposed to csDMARDs. Over half of the pregnancies were multiparous (56.2% csDMARDs exposed, 59.2% unexposed). Of the pregnancies exposed to csDMARDs, most were exposed to hydroxychloroquine (61.6%), followed by sulfasalazine (23.8%), methotrexate (13.0%), and azathioprine (12.4%). Prescriptions for leflunomide and other csDMARDs were rarely filled over the perinatal windows of interest (<3%); as such, analyses focused on hydroxychloroquine, sulfasalazine, methotrexate, and azathioprine.

Table I. Characteristics of pregnant women with rheumatic disease exposed and unexposed to csDMARDs preconception and during pregnancy.

Characteristics	Exposed to csDMARDs n (%) 175 women 185 pregnancies	Unexposed to csDMARDs n (%) 4,387 women 6,064 pregnancies
Rheumatic disease type		
Rheumatoid arthritis	94 (50.8)	1,470 (24.2)
Systemic autoimmune rheumatic diseases	62 (33.5)	882 (14.5)
Other rheumatic diseases*	29 (15.7)	3,712 (61.2)
Maternal and pregnancy characteristics		
BMI (at first antenatal visit)		
Normal	142 (76.8)	4,449 (73.4)
Overweight	29 (15.7)	960 (15.8)
Obese	14 (7.6)	655 (10.8)
Parity		
Primiparous	81 (43.8)	2,477 (40.8)
Multiparous	104 (56.2)	3,587 (59.2)
Age at delivery (mean (SD))	31.3 (5.4)	31.1 (5.4)
Gestational weeks at delivery (mean (SD))	37.4 (3.3)	38.5 (2.1)
Caeserean section delivery	58 (31.4)	1,992 (32.9)
Prior adverse pregnancy outcome		
Prior preterm delivery	20 (10.8)	339 (5.6)
Prior spontaneous abortion	47 (25.4)	1,594 (26.3)
Prior neonatal death	<5	37 (0.6)
Prior stillbirth	9 (4.9)	70 (1.2)
Prior low birth weight	10 (5.4)	178 (2.9)
Prior congenital anomaly	<5	53 (0.9)
Neighbourhood income quintile		
20th percentile	46 (24.9)	1,320 (21.8)
40th percentile	46 (24.9)	1,215 (20.0)
60th percentile	33 (17.8)	1,298 (21.4)
80th percentile	39 (21.1)	1,269 (20.9)
80-100th percentile	21 (11.4)	962 (15.9)
Maternal comorbidities		
Depression	11 (6.0)	271 (4.5)
Anxiety	17 (9.2)	594 (9.8)
Diabetes	<5	95 (1.6)
Medication use		
csDMARD use ¥		
Hydroxychloroquine	114 (61.6)	
Sulfasalazine	44 (23.8)	
Methotrexate	24 (13.0)	
Azathioprine	23 (12.4)	
Leflunomide	<5	
Other DMARDs •	5 (2.7)	
Other medication use ‖		
Biologics	7 (3.8)	33 (0.5)
Glucocorticosteroids	82 (44.3)	446 (7.4)
Traditional NSAIDs	83 (44.9)	1,127 (18.6)
Cox-2 inhibitors	14 (7.6)	179 (3.0)
Antidepressants	25 (13.5)	617 (10.2)
Anxiolytics	23 (12.4)	540 (8.9)
Maternal healthcare utilisation		
Number of admissions before pregnancy (mean (SD)) ¶	0.3 (0.7)	0.3 (0.6)
Number of outpatient visits during pregnancy (mean (SD)) **	17.7 10.5)	11.8 (11.3)
Number of rheumatologists' visits during pregnancy (mean (SD)) **	2.2 (2.8)	0.4 (1.2)
Number of antenatal outpatient visits (mean (SD)) §	8.8 (4.9)	9.0 (3.9)
Number of antenatal admissions (mean (SD)) §	0.3 (0.6)	0.2 (0.6)

*other includes JIA, AS, and Ps/PsA. ¥percentages do not add to 100 as each pregnancy can be exposed to more than one category of csDMARDs. • other csDMARDs include gold, cyclosporine, cyclophosphamide, penicillamine, mycophenolate, chlorambucil, minocycline. ‖ other medication use during 90 days preconception and/or during pregnancy. ¶ number of hospital admissions before pregnancy assessed in the year before conception using Discharge Abstract Database. ** number of outpatient (any doctor) and rheumatologists' visits assessed during pregnancy using Medical Services Plan database. §number of antenatal outpatient visits and number of antenatal admissions obtained from BC Perinatal Database Registry.

Table II. Association between exposure to csDMARDs before and during pregnancy and SGA births.

	Hydroxychloroquine OR (95% CI)	Sulfasalazine OR (95% CI)	Methotrexate OR (95% CI)	Azathioprine OR (95% CI)
1: Model(s) with only csDMARD exposure				
csDMARD exposure before pregnancy	2.52 (1.26, 5.06)	1.70 (0.56, 5.17)	1.27 (0.36, 4.43)	2.56 (0.66, 9.90)
csDMARD exposure during pregnancy	1.97 (1.19, 3.28)	1.78 (0.71, 4.45)	4.45 (0.99, 19.91)	6.96 (2.33, 20.75)
2: Multivariable model(s)				
csDMARD exposure before pregnancy	1.58 (0.76, 3.25)	1.07 (0.33, 3.44)	1.11 (0.31, 3.97)	1.71 (0.41, 7.19)
csDMARD exposure during pregnancy	1.12 (0.65, 1.94)	1.03 (0.40, 2.70)	1.73 (0.35, 8.51)	2.68 (0.81, 8.85)
Rheumatoid arthritis (vs. other RD)	1.25 (1.05, 1.50)	1.25 (1.05, 1.50)	1.25 (1.05, 1.50)	1.25 (1.05, 1.50)
SARDs (*vs*. other RD)	1.59 (1.30, 1.95)	1.59 (1.30, 1.95)	1.60 (1.31, 1.95)	1.58 (1.29, 1.93)
Multiparous (*vs*. nulliparous)	0.53 (0.45, 0.61)	0.53 (0.45, 0.61)	0.53 (0.45, 0.62)	0.53 (0.45, 0.62)
Prior adverse pregnancy outcomes	1.37 (1.17, 1.61)	1.37 (1.17, 1.61)	1.37 (1.17, 1.61)	1.37 (1.17, 1.60)
Age at delivery	1.02 (1.00, 1.03)	1.02 (1.00, 1.03)	1.02 (1.00, 1.03)	1.02 (1.00, 1.03)
BMI overweight (*vs*. normal)	0.78 (0.63, 0.97)	0.78 (0.63, 0.97)	0.78 (0.63, 0.96)	0.77 (0.62, 0.96)
BMI obese (*vs*. normal)	0.72 (0.55, 0.93)	0.71 (0.55, 0.93)	0.72 (0.55, 0.93)	0.72 (0.55, 0.93)
Neighbourhood income quintile	0.94 (0.89, 0.99)	0.94 (0.89, 0.99)	0.94 (0.89, 0.99)	0.94 (0.89, 0.99)
Anxiety	0.96 (0.75, 1.24)	0.96 (0.75, 1.24)	0.96 (0.75, 1.24)	0.96 (0.75, 1.24)
Depression	0.77 (0.53, 1.11)	0.77 (0.53, 1.11)	0.77 (0.53, 1.11)	0.77 (0.53, 1.11)
Diabetes	1.45 (0.86, 2.43)	1.44 (0.86, 2.42)	1.44 (0.86, 2.42)	1.45 (0.86, 2.44)
Biologics •	1.20 (0.53, 2.71)	1.20 (0.53, 2.71)	1.22 (0.54, 2.74)	1.18 (0.52, 2.68)
Other csDMARD • [¥]	1.05 (0.75, 1.46)	1.13 (0.85, 1.49)	1.10 (0.83, 1.45)	1.11 (0.85, 1.46)
Glucocorticosteroids •	1.47 (1.16, 1.87)	1.48 (1.16, 1.88)	1.47 (1.16, 1.87)	1.45 (1.14, 1.84)
Traditional NSAIDs •	1.11 (0.93, 1.34)	1.12 (0.93, 1.34)	1.11 (0.93, 1.34)	1.12 (0.93, 1.34)
Cox-2 inhibitors •	0.71 (0.46, 1.09)	0.70 (0.46, 1.08)	0.71 (0.46, 1.09)	0.71 (0.46, 1.08)
Antidepressants •	0.92 (0.72, 1.18)	0.92 (0.72, 1.18)	0.92 (0.72, 1.18)	0.92 (0.72, 1.18)
Anxiolytics •	1.06 (0.82, 1.37)	1.07 (0.83, 1.38)	1.07 (0.83, 1.38)	1.07 (0.83, 1.38)
Number of admissions before pregnancy	0.99 (0.88, 1.12)	0.99 (0.88, 1.11)	0.99 (0.88,1.11)	0.99 (0.88,1.12)
Number of outpatient visits during pregnancy	1.02 (1.01, 1.02)	1.02 (1.01, 1.02)	1.02 (1.01, 1.02)	1.02 (1.01, 1.02)
Number of rheumatologist visits during pregnancy	1.04 (0.98, 1.09)	1.04 (0.98, 1.09)	1.04 (0.98, 1.09)	1.03 (0.98, 1.09)
Number of antenatal outpatient visits	0.92 (0.90, 0.94)	0.92 (0.90, 0.94)	0.92 (0.90, 0.94)	0.92 (0.90, 0.94)
Number of antenatal hospital admissions	1.24 (1.12, 1.38)	1.24 (0.12, 1.38)	1.24 (1.12, 1.38)	1.24 (1.12, 1.38)

•Use of other medications was assessed in the preconception period and during pregnancy. [¥]Other refers to all csDMARDs aside from the drug exposure being evaluated.
OR: odds ratio; CI: confidence interval; csDMARD: conventional synthetic disease-modifying anti-rheumatic drugs; RD: rheumatic diseases; SARD: systemic autoimmune rheumatic disease.

SGA births

From 6,249 pregnancies, we recorded 904 (14.5%) infants born SGA. SGA births were observed among 12 of 38 (31.6%) pregnancies exposed to hydroxychloroquine before pregnancy and 21 of 81 (25.9%) exposed during pregnancy. Fewer SGA births were observed among pregnancies unexposed to hydroxychloroquine before pregnancy (892/6,211, 14.4%) and during pregnancy (883/6,168, 14.3%). Unadjusted ORs for the association between hydroxychloroquine use and SGA births for exposures 90-days preconception and during pregnancy were 2.52 (95% CI, 1.26–5.06) and 1.97 (95% CI, 1.19–3.28), respectively (Table II). The multivariable models attenuated the ORs describing this association for exposure preconception (adjusted OR [aOR] 1.58; 95% CI, 0.76–3.25) and during pregnancy (aOR 1.12; 95% CI, 0.65–1.94) (Table II). *Post-hoc* calculations show power to detect ORs of 1.5 and 2.0 for hydroxychloroquine exposure before conception was 0.28 and 0.67 and during pregnancy was 0.45 and 0.91 in our multivariable analyses. The multivariable model found an inverse association with multiparity and odds of SGA births (aOR 0.53; 95% CI, 0.45–0.61) and several factors significantly associated with higher odds of having an SGA birth including a history of adverse pregnancy outcome (aOR 1.37; 95% CI, 1.17–1.61) and a diagnosis of RA (aOR 1.25; 95% CI, 1.05–1.50) or SARDs (aOR 1.59; 95% CI, 1.30–1.95), as compared to other forms of RD. We also found that glucocorticosteroid use before or during pregnancy was associated with up to 50% higher odds of having an SGA birth (aOR 1.47; 95% CI, 1.16–1.87). This association persisted when the preconception (aOR 1.34; 95% CI, 1.02–1.74) and pregnancy (aOR 1.53; 95% CI, 1.03–2.27) windows were evaluated separately.

Few pregnancies were exposed to sulfasalazine, methotrexate, and azathioprine either before or during pregnancy. Adjusted ORs for the association between sulfasalazine exposure before and during pregnancy and SGA birth were 1.07 (95% CI, 0.33–3.44) and 1.03 (95% CI, 0.40–2.70), respectively (Table II). *Post-hoc* calculations show power to detect ORs of 1.5 and 2.0 for sulfasalazine exposure before conception was 0.18 and 0.43 and during pregnancy was 0.22 and 0.54. For methotrexate, adjusted ORs were 1.11 (95% CI, 0.31–3.97) before pregnancy and 1.73 (95% CI, 0.35–8.51) during pregnancy. *Post-hoc* calculated power to detect ORs of 1.5 and 2.0 were 0.18 and 0.42 before pregnancy and 0.13 and 0.26 during pregnancy in multivariable models. Finally, adjusted ORs for azathioprine exposure before and

Table III. Association between exposure to csDMARDs before pregnancy and during the first trimester and congenital anomalies.

	Hydroxychloroquine OR (95% CI)	Methotrexate OR (95% CI)
1: Model(s) with only csDMARD exposure		
csDMARD exposure before pregnancy	0.47 (0.06, 3.44)	1.09 (0.14, 8.23)
csDMARD exposure during first trimester	2.90 (1.00, 8.41)	8.71 (1.59, 47.72)
2: Multivariable model(s)		
csDMARD exposure before pregnancy	0.40 (0.05, 2.95)	1.12 (0.15, 8.59)
csDMARD exposure during first trimester	2.74 (0.92, 8.13)	6.58 (1.15, 37.75)
Rheumatoid arthritis (*vs*. other RD)	0.78 (0.58, 1.04)	0.76 (0.57, 1.01)
SARDs (*vs*. other RD)	1.06 (0.78, 1.45)	1.06 (0.77, 1.44)
Multiparous (*vs*. nulliparous)	0.75 (0.60, 0.95)	0.76 (0.60, 0.95)
Prior adverse pregnancy outcomes	1.09 (0.86, 1.40)	1.09 (0.85, 1.39)
Age at delivery	1.02 (1.00, 1.04)	1.02 (1.00, 1.04)
BMI overweight (*vs*. normal)	0.95 (0.69, 1.30)	0.95 (0.69, 1.30)
BMI obese (*vs*. normal)	1.21 (0.86, 1.69)	1.23 (0.88, 1.72)
Neighbourhood income quintile	1.02 (0.94, 1.10)	1.02 (0.94, 1.10)
Anxiety	0.77 (0.51, 1.17)	0.78 (0.52, 1.19)
Depression	0.59 (0.30, 1.14)	0.58 (0.30, 1.14)
Diabetes	1.06 (0.45, 2.46)	1.07 (0.46, 2.48)
Biologics •	1.35 (0.41, 4.51)	1.36 (0.41, 4.51)
Other csDMARD •[¥]	0.88 (0.51, 1.53)	1.27 (0.83, 1.94)
Glucocorticosteroids •	1.06 (0.72, 1.58)	0.98 (0.66, 1.47)
Traditional NSAIDs •	1.22 (0.92, 1.61)	1.18 (0.89, 1.57)
Cox-2 inhibitors•	0.75 (0.38, 1.50)	0.74 (0.37, 1.48)
Antidepressants •	1.37 (0.97, 1.95)	1.36 (0.96, 1.93)
Anxiolytics •	1.07 (0.73, 1.59)	1.07 (0.72, 1.58)
Number of admissions before pregnancy	0.87 (0.70, 1.08)	0.87 (0.70, 1.08)
Number of outpatient visits during pregnancy	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)
Number of rheumatologist visits during pregnancy	1.06 (0.98, 1.15)	1.05 (0.97, 1.14)
Number of antenatal outpatient visits	0.99 (0.96, 1.02)	0.99 (0.96, 1.02)
Number of antenatal hospital admissions	1.02 (0.86, 1.21)	1.02 (0.85, 1.21)

•Use of other medications was assessed in the preconception period and during pregnancy.
[¥]Other refers to all csDMARDs aside from the drug exposure being evaluated.
OR: odds ratio; CI: confidence interval; csDMARD: conventional synthetic disease-modifying antirheumatic drugs; RD: rheumatic diseases; SARD: systemic autoimmune rheumatic disease.

during pregnancy and SGA birth were 1.71 (95% CI, 0.41–7.19) and 2.68 (95%, 0.81–8.85), respectively. *Post-hoc* calculated power to detect ORs of 1.5 and 2.0 were 0.14 and 0.31 before pregnancy and 0.16 and 0.36 in multivariable models.

Congenital anomalies

Of 6,249 pregnancies, there were 341 (5.5%) infants born with congenital anomalies. Table III shows unadjusted and adjusted ORs for the association between hydroxychloroquine and methotrexate – for which regression models converged – and congenital anomalies. Adjusted ORs for the association between hydroxychloroquine exposure before pregnancy and during the first trimester and congenital anomalies were 0.40 (95% CI, 0.05–2.95) and 2.74 (95% CI 0.92–8.13), respectively. *Post-hoc* calculations show power to detect ORs of 1.5 and 2.0 as 0.25 and 0.61 for hydroxychloroquine exposure before pregnancy and as 0.21 and 0.51 during the first trimester. With respect to methotrexate, adjusted ORs for the association between exposure in the preconception period and during the first trimester and congenital anomalies was 1.12 (95% CI, 0.15–8.59) and 6.58 (95% CI, 1.15–37.75), respectively (Table III). *Post-hoc* calculations to detect ORs of 1.5 and 2.0 ranged from 0.17 to 0.38 for methotrexate exposure before pregnancy and 0.12 and 0.23 for methotrexate exposure during the first trimester.

Discussion

We used population-based administrative health data to evaluate the association between perinatal csDMARD exposure among women with RD and adverse neonatal outcomes, specifically, SGA and congenital anomalies. Within our large cohort of 6,249 pregnancies in 4,562 women with RD over 10 years, overall perinatal exposure to csDMARDs was low at 3.0%. Drug-specific risk estimates from our study align with guidelines regarding the compatibility of hydroxychloroquine, sulfasalazine, and azathioprine before and during pregnancy, as well as the teratogenic effects of methotrexate (11, 12). However, our *post-hoc* power calculations suggest insufficient power to detect associations between specific csDMARDs and outcomes evaluated, with the exception of hydroxychloroquine and SGA. Nonetheless, given current limitations to understanding adverse perinatal outcomes associated with csDMARD use among women with RD, which include a dearth of RD-specific and csDMARD-specific risk estimates and insufficient adjustment for the potential impacts of underlying RD disease, it is important to report these (15, 27-29). Moreover, pooling risk estimates of studies that involve comparator groups and apply multivariable approaches may be the best way to understand relationships between specific csDMARDs and perinatal outcomes given that both exposures and outcomes in this context are relatively rare.

Among specific csDMARDs evaluated in the current paper, arguably the most studied to date is hydroxychloroquine. A 2016 meta-analysis by Kaplan *et al*. pooling findings of studies with a comparator group included six studies (698 hydroxychloroquine exposed, 1,026 unexposed) that assessed major congenital malformations and found no significant increase in risk between pregnancies exposed and unexposed to hydroxychloroquine (pooled OR 1.13, 95% CI 0.59–2.17) (30). A study included in this meta-analysis by Cooper *et al*. involving analyses of claims data for three US health plans and application of propensity score methods to control for confounding by indication yielded a propensity score-adjusted relative risk of 3.11 (95% CI, 0.99–9.77) (31). With no studies assessing the impact of hydroxychloroquine on SGA, we drew from findings on its impact on the related outcome of low birthweight.

Specifically, the same meta-analysis by Kaplan *et al*. (30) pooled results of two studies (32, 33) (110 HCQ exposed, 189 unexposed) to find no significant difference in the rate of low birth weight babies exposed to HCQ as compared to those unexposed (OR 0.69, 95% CI 0.21–2.27).

In contrast to hydroxychloroquine, the number of prior studies involving comparator groups is far more limited for methotrexate, azathioprine, and sulfasalazine. We identified one 2014 study by Weber *et al*. (34) that included a disease-matched comparator group adjusted using propensity score methods and assessed methotrexate exposure (before conception/first trimester) among women with autoimmune disease (n=324 exposed). Authors reported no significant effect of methotrexate exposure on mean birth weight or gestational age, and similar to our findings there was an increased odds for major birth defects among women with autoimmune disease exposed to methotrexate post-conception when compared to women without autoimmune disease (aOR 3.1, 95% CI 1.03–9.5), but this estimate attenuated when compared to disease-matched controls (aOR 1.8, 95% CI 0.6–5.7) (34). With regard to azathioprine, in 2007, Langagergaard *et al*. (35) used population-based administrative databases in Denmark that included 76 pregnancies, and while they did not evaluate SGA, they reported unadjusted relative risks of 5.6 (95% CI, 3.5–9.1) for preterm birth (gestational age <37 weeks) and 3.0 (95% CI, 0.7–12.4) for low birthweight at term (<2500 grams at ≥37 weeks). In addition, using data from the Swedish Medical Birth Register in 2009, Cleary *et al*. (36) studied outcomes associated with azathioprine use among 476 women with autoimmune disease, of which 300 had a diagnosis of IBD, and reported an adjusted OR of 1.83 (95% CI, 1.02–3.28) for SGA. The aforementioned studies on azathioprine did not provide RD-specific outcomes and risk-estimates, thus highlighting the importance of studies such as ours. Finally, studies on sulfasalazine that include a comparator group are limited (37) and have previously not used population-based administrative data to evaluate associations between sulfasalazine use during pregnancy and SGA births.

Our study strengths include data on date of conception and data for all dispensed prescriptions regardless of funding source, which address challenges of pregnancy dating and the importance of establishing precise timing of medication exposures during pregnancy. Importantly, our study provides data on perinatal outcomes associated with specific csDMARDs among women with RD, given that prior studies have largely included women with IBD. Furthermore, multivariable approaches accounted for multiple pregnancies in women with RD and adjusted for the potential impacts of underlying RD by using variables such as concomitant medications and healthcare utilisation as markers of disease severity and health status. An inherent limitation of administrative data is diagnostic uncertainty as they are not collected for research purposes. However, we used a previously described algorithm for identifying RA, SLE, and AS in administrative data in BC (38-40). Despite a large source population of all pregnancies in the province of BC and a large RD cohort, the main limitation of our study is the relatively small sample sizes of the analytic cohorts due to rare exposures and rare outcomes. While we could not mitigate this limitation, we conducted post hoc power calculations for all analyses to inform our reporting.

Altogether, evaluation of perinatal exposure to csDMARDs – namely, hydroxychloroquine, sulfasalazine, azathioprine, and methotrexate – among women with RD and risk of adverse neonatal outcomes yielded no-statistically significant risk estimates, aside from methotrexate exposure during the first trimester of pregnancy which was associated with increased odds for congenital anomalies. While most analyses were underpowered, we emphasise the continued need for well-designed studies that involve a comparison group of non-exposed women/pregnancies, control for the effect of underlying disease, and report csDMARD-specific estimates.

References

1. CLOWSE ME: Lupus activity in pregnancy. *Rheum Dis Clin North Am* 2007; 33: 237-52.
2. KRAUSE ML, MAKOL A: Management of rheumatoid arthritis during pregnancy: challenges and solutions. *Open Access Rheumatol* 2016; 8: 23-36.
3. BADLEY EM, KASMAN NM: The impact of arthritis on Canadian women. *BMC Womens Health* 2004; 4 (Suppl. 1): S18.
4. CHAKRAVARTY EF, NELSON L, KRISHNAN E: Obstetric hospitalizations in the United States for women with systemic lupus erythematosus and rheumatoid arthritis. *Arthritis Rheum* 2006; 54: 899-907.
5. DORIA A, TINCANI A, LOCKSHIN M: Challenges of lupus pregnancies. *Rheumatology* (Oxford) 2008; 47 (Suppl. 3): iii9-12.
6. BORCHERS AT, NAGUWA SM, KEEN CL, GERSHWIN ME: The implications of autoimmunity and pregnancy. *J Autoimmun* 2010; 34: J287-99.
7. TSAO NW, SAYRE EC, HANLEY G *et al*.: Risk of preterm delivery and small-for-gestational-age births in women with autoimmune disease using biologics before or during pregnancy: a population-based cohort study. *Ann Rheum Dis* 2018; 77: 869-74.
8. TSAO NW, LYND LD, SAYRE EC, SADATSAFAVI M, HANLEY G, DE VERA MA: Use of biologics during pregnancy and risk of serious infections in the mother and baby: a Canadian population-based cohort study. *BMJ Open* 2019; 9: e023714.
9. DESAI RJ, BATEMAN BT, HUYBRECHTS KF *et al*.: Risk of serious infections associated with use of immunosuppressive agents in pregnant women with autoimmune inflammatory conditions: cohort study. *BMJ* 2017; 356: j895.
10. TSAO NW, HANLEY GE, LYND LD, AMIRI N, DE VERA MA: Risk of congenital anomalies in infants born to women with autoimmune disease using biologics before or during pregnancy: a population-based cohort study. *Clin Exp Rheumatol* 2019; 37: 976-82.
11. GOTESTAM SKORPEN C, HOELTZENBEIN M, TINCANI A *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.
12. FLINT J, PANCHAL S, HURRELL A *et al*.: BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying antirheumatic drugs and corticosteroids. *Rheumatology* (Oxford) 2016; 55: 1693-7.
13. FLINT J, PANCHAL S, HURRELL A *et al*.: BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part II: analgesics and other drugs used in rheumatology practice. *Rheumatology* (Oxford) 2016; 55: 1698-702.
14. SAMMARITANO L: (Ed.) Reproductive Health in Rheumatic Diseases Guideline. American College of Rheumatology Conference; 2018; Chicago, USA.
15. BALDWIN C, AVINA-ZUBIETA A, RAI SK, CARRUTHERS E, DE VERA MA: Disease-modifying anti-rheumatic drug use in pregnant women with rheumatic diseases: a systematic review of the risk of congenital malformations. *Clin Exp Rheumatol* 2016; 34: 172-83.

16. BC MINISTRY OF HEALTH: About PopData [Internet]. Population Data BC 2019 [updated 2018 August 23; cited 2019 January 3]. Available from: https://www.popdata.bc.ca/aboutus.
17. BC MINISTRY OF HEALTH: [creator] (2014): PharmaNet. V2. BC Ministry of Health [publisher]. Data Extract. Data Stewardship Committee (2014). [Available from: http://www.popdata.bc.ca/data.
18. PERINATAL SERVICES BC [creator] (2015): British Columbia Perinatal Data Registry. Population Data BC [publisher]. Data Extract. PSBC (2014). [Available from: http://www.perinatalservicesbc.ca/health-professionals/data-surveillance/perinatal-data-registry.
19. BRITISH COLUMBIA MINISTRY OF HEALTH [creator] (2014): Medical Services Plan (MSP) Payment Information File. V2. Population Data BC [publisher]. Data Extract. MOH (2014). [Available from: http://www.popdata.bc.ca/data.
20. BRITISH COLUMBIA MINISTRY OF HEALTH [creator] (2014): Consolidation File (MSP Registration & Premium Billing). V2. Population Data BC [publisher]. Data Extract. MOH (2014). [Available from: http://www.popdata.bc.ca/data.
21. CANADIAN INSTITUTE FOR HEALTH INFORMATIOn [creator] (2014): Discharge Abstract Database (Hospital Separations). V2. Population Data BC [publisher]. Data Extract. MOH (2014). [Available from: http://www.popdata.bc.ca/data.
22. BC VITAL STATISTICS AGENCY [creator] (2013): Vital Statistics Births. V2. Population Data BC [publisher]. Data Extract. BC Vital Statistics Agency (2014). [Available from: http://www.popdata.bc.ca/data.
23. BC VITAL STATISTICS AGENCY [creator] (2013): Vital Statistics Stillbirths. V2. Population Data BC [publisher]. Data Extract. BC Vital Statistics Agency (2014). [Available from: http://www.popdata.bc.ca/data.
24. HYRICH KL, SYMMONS DP, WATSON KD, SILMAN AJ: Pregnancy outcome in women who were exposed to anti-tumor necrosis factor agents: results from a national population register. *Arthritis Rheum* 2006; 54: 2701-2.
25. MARDER W, LITTLEJOHN EA, SOMERS EC: Pregnancy and autoimmune connective tissue diseases. *Best Prac Res Clin Rheumatol* 2016; 30: 63-80.
26. KIERANS WJ, KENDALL P, FOSTER LT, LISTON RM, TUK T: New birth weight and gestational age charts for the British Columbia population. *BMC Medical Jounral* 2006; 48: 28-32.
27. DE MAN YA, HAZES JM, VAN DER HEIDE H *et al*.: Association of higher rheumatoid arthritis disease activity during pregnancy with lower birth weight: results of a national prospective study. *Arthritis Rheum* 2009; 60: 3196-206.
28. ZBINDEN A, VAN DEN BRANDT S, OSTENSEN M, VILLIGER PM, FORGER F: Risk for adverse pregnancy outcome in axial spondyloarthritis and rheumatoid arthritis: disease activity matters. *Rheumatology* (Oxford) 2018; 30: 30.
29. HARRIS N, EUDY A, CLOWSE M: Patient-reported disease activity and adverse pregnancy outcomes in systemic lupus erythematosus and rheumatoid arthritis. *Arthritis Care Res* 2018; 15: 15.
30. KAPLAN YC, OZSARFATI J, NICKEL C, KOREN G: Reproductive outcomes following hydroxychloroquine use for autoimmune diseases: a systematic review and meta-analysis. *Br J Clin Pharmacol* 2016; 81: 835-48.
31. COOPER WO, CHEETHAM TC, LI D-K *et al*.: Brief report: Risk of adverse fetal outcomes associated with immunosuppressive medications for chronic immune-mediated diseases in pregnancy. *Arthritis Rheumatol* (Hoboken, NJ) 2014; 66: 444-50.
32. BUCHANAN NM, TOUBI E, KHAMASHTA MA, LIMA F, KERSLAKE S, HUGHES GR: Hydroxychloroquine and lupus pregnancy: review of a series of 36 cases. *Ann Rheum Dis* 1996; 55: 486-8.
33. CLOWSE ME, MAGDER L, WITTER F, PETRI M: Hydroxychloroquine in lupus pregnancy. *Arthritis Rheum* 2006; 54: 3640-7.
34. WEBER-SCHOENDORFER C, CHAMBERS C, WACKER E *et al*.: Pregnancy outcome after methotrexate treatment for rheumatic disease prior to or during early pregnancy: a prospective multicenter cohort study. *Arthritis Rheumatol* 2014; 66: 1101-10.
35. LANGAGERGAARD V, PEDERSEN L, GISLUM M, NORGARD B, SORENSEN HT: Birth outcome in women treated with azathioprine or mercaptopurine during pregnancy: A Danish nationwide cohort study. *Aliment Pharmacol Ther* 2007; 25: 73-81.
36. CLEARY BJ, KALLEN B: Early pregnancy azathioprine use and pregnancy outcomes. *Birth Defects Res A Clin Mol Teratol* 2009; 85: 647-54.
37. VIKTIL KK, ENGELAND A, FURU K: Outcomes after anti-rheumatic drug use before and during pregnancy: a cohort study among 150,000 pregnant women and expectant fathers. *Scand J Rheumatol* 2012; 41: 196-201.
38. ØSTENSEN M, FÖRGER F: Management of RA medications in pregnant patients. *Nature Rev Rheumatol* 2009; 5: 382-90.
39. AVINA-ZUBIETA JA, TO F, VOSTRETSOVA K, DE VERA M, SAYRE EC, ESDAILE JM: Risk of myocardial infarction and stroke in newly diagnosed systemic lupus erythematosus: a general population-based study. *Arthritis Care Res* (Hoboken) 2017; 69: 849-56.
40. AVINA-ZUBIETA JA, CHAN J, DE VERA M, SAYRE EC, CHOI H, ESDAILE J: Risk of venous thromboembolism in ankylosing spondylitis: a general population-based study. *Ann Rheum Dis* 2019; 78: 480-5.