Risk of congenital anomalies in infants born to women with autoimmune disease using biologics before or during pregnancy: a population-based cohort study

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Abstract

Objective

To determine the association between perinatal biologic use and congenital anomalies in women with autoimmune disease.

Methods

We linked population-based administrative health data including information on all medications with a perinatal registry in British Columbia, Canada. Women with one or more autoimmune diseases who had pregnancies between January 1st, 2002 and December 31st, 2012 were included. Exposure to biologics was defined as having at least one biologic prescription 3 months before conception or during the first trimester of pregnancy. Each exposed pregnancy was matched with five unexposed pregnancies using high dimensional propensity scores (HDPS). Logistic regression modelling was used to evaluate the association between biologics use and congenital anomalies.

Results

The HDPS-matched cohort included 117 pregnancies (107 women) exposed to biologics, and 585 pregnancies (562 women) that were not exposed to biologics during the period of interest; 6% of newborns had ≥1 congenital anomalies at birth, in the exposed and unexposed groups. There were no obvious patterns with regards to the congenital anomalies observed in the biologics exposed group. In primary analysis, the OR for the association between biologic exposure and congenital anomalies was 1.06 (95%CI 0.46–2.47). Secondary and sensitivity analyses did not change the results appreciably.

Conclusion

These population-based data suggest that the use of biologics before and during pregnancy is not associated with an increased risk of congenital anomalies.

Key words

biologics, pregnancy, congenital anomalies, autoimmune diseases

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Received on October 26, 2018; accepted in revised form on February 4, 2019.

Funding: this research was funded by an operating grant from The Arthritis Society (YIO-13-07). N.W. Tsao was supported by a Canadian Institutes of Health Research Fellowship for her doctoral training related to this work. G.E. Hanley is an Assistant Professor, Canadian Institutes of Health Research New Investigator, and a recipient of Canadian Cancer Society Research Institute Capacity Development Award. L.D. Lynd is a Professor, and Director of Collaboration for Outcomes Research and Evaluation. M.A. 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.

Competing interests: L.D. Lynd has received honoraria from AstraZeneca, Merck and Pfizer Canada for consulting services unrelated to this study. The other co-authors have declared no competing interests.

Introduction

Chronic inflammatory autoimmune diseases include over 70 types of disorders, collectively affecting more than 5% of the population in Western countries (1). Some of the most prevalent are rheumatoid arthritis (RA), affecting 0.5–1% of the population, and inflammatory bowel disease (IBD), affecting approximately 0.5% of the population (2, 3). A commonality is that nearly all autoimmune diseases have a female predominance, with more than 80% of autoimmune disease patients being women, resulting in a 'sex gap' (1, 4, 5). In light of this, there is growing recognition that autoimmunity may impact pregnancy, including maternal complications and neonatal outcomes (6). As such, treatment for autoimmune diseases may be required throughout pregnancy, as evidence shows that active disease at the time of conception and disease flares during pregnancy are both predictors of adverse outcomes (7-9). This presents a challenge given that several of the traditional disease-modifying agents and immunosuppressants are contraindicated in pregnancy, including methotrexate, leflunomide, mycophenolate mofetil, and cyclophosphamide.

Disease management with biologics could be a viable alternative depending on their risk-benefit profile in pregnancy. Prior population-based research in British Columbia (BC) shows that biologics are increasingly being used during pregnancy (10). As such, it is imperative to investigate potential adverse effects of biologics during pregnancy, including the risk of congenital anomalies. Our objective was to conduct a population-based cohort study to assess the association between biologics use in the 90 days before pregnancy or during the period of fetal organogenesis by women with autoimmune diseases, and the risk of congenital anomalies in their offspring.

Materials and methods

Data sources

Population Data BC is an extensive data repository that holds individual-level, de-identified, longitudinal data on all health services covering the entire population of BC (11). These include all provincially-funded physician visits, ordered laboratory tests and diagnostic procedures (x-rays, ultrasounds, etc.) from the Medical Services Plan (MSP) database (12), hospitalisations from the Discharge Abstract Database (DAD) (13), and demographics and vital statistics since 1985 (14-16). Population Data BC also includes the comprehensive prescription drug database, PharmaNet, which captures all outpatient dispensed prescriptions, since 1996 (17). These data were linked to the BC Perinatal Database Registry (BCPDR) (18), which contains data abstracted from obstetrical and neonatal medical records on nearly 100% of births in BC from over 60 acute care facilities as well as births occurring at home attended by registered midwives. A unique element of the BCPDR is the availability of data on the pregnancy start date that is derived from recommended algorithms for establishing gestational age using first ultrasound and start date of last menstrual period, and newborn clinical exam (19) - addressing challenges of pregnancy dating and the importance of establishing precise timing of medication exposures during pregnancy (20).

Altogether, these linkages allowed for the creation of the source population comprised of women in BC who had one or more pregnancies ending in a live or still birth between January 1st, 2002 and December 31st, 2012, and were continuously covered by BC's provincial health plan for at least 12 months prior to the start of pregnancy and in the 12 months following delivery. This continuous coverage requirement was to ensure we had all relevant data for all pregnancies in our cohort. Details of these data sources are described in previous work (10, 21).

Study cohort

To create the study cohort, we restricted the source population to include women who had a recorded diagnosis of one or more autoimmune diseases that could be treated with a biologic, which included RA, IBD, psoriasis (Ps)/psoriatic arthritis (PsA), ankylosing spondylitis (AS), juvenile idiopathic arthritis (JIA), and systemic autoimmune rheumatic diseases. This was

defined as having the same ICD-9/10 code for a specific autoimmune disease from two separate physician visits that were at least 60 days apart and within two years, any time prior to the date of conception; or having one or more hospitalisations with an ICD-9/10 code for an autoimmune disease (10, 21).

Ethics approval for this study was obtained from the University of British Columbia Behavioural Research Ethics Board (H13-02027). No personal identifying information was made available as part of this study; procedures used were in compliance with BC's Freedom of Information and Privacy Protection Act. 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. This study was funded by a grant from The Arthritis Society. The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Exposure ascertainment

Using dispensation dates and Canadian Drug Identity Codes for biologics in PharmaNet, women in the autoimmune disease cohort were considered to have a pregnancy that was exposed to biologics if they had at least one prescription for a biologic at any point during 90 days prior to the date of conception or during the first trimester. We considered all biologics available in BC for the treatment of autoimmune diseases of interest during the study period: abatacept, adalimumab, alefacept, anakinra, belimumab, certolizumab pegol, etanercept, golimumab, infliximab, natalizumab, rituximab, tocilizumab, and ustekinumab. This time frame was chosen because biologics have relatively long half-lives (*e.g.* from 10 to 20 days) and drug levels are considered to be cleared from the body after five half-lives. Disease-matched women with pregnancies that did not have prescriptions for any biologic during the drug exposure period of interest comprised the unexposed group. The use of other non-biologic medications for autoimmune disease management was allowed for both the exposed and unexposed groups. For sensitivity analyses, the exposure period was extended to 12 months prior to the date of conception until the end of the first trimester.

Outcomes

The primary outcome of interest was congenital anomalies occurring in the offspring, identified using the congenital anomaly variable from the BCPDR, which is a binary (yes/no) indicator of observable anomalies that occurred at birth. In order to know the specific types of anomalies that occurred we used the linkage between the BCPDR and the DAD to obtain the ICD-9/10 codes pertaining to the anomaly types for the delivery episode wherein the anomaly/anomalies were identified (ICD9 codes: 740-759, except 758, 759.81-83; ICD-10 codes: Q00-Q89). Some congenital anomalies may not be readily visible at birth, and are often diagnosed at a later date. Thus, our secondary outcome included anomalies identified at birth and during the first year of life based on ICD-9/10 codes in MSP or DAD. However as there are no widely accepted algorithms for identifying congenital anomalies in administrative databases, as such, we used a "1-2-3" algorithm of having: 1) an anomaly recorded in the BCPDR; or 2) two or more inpatient records in the DAD with diagnostic codes for an anomaly; or 3) three or more outpatient visits in the MSP database with diagnostic codes for an anomaly, during the offspring's first year of life.

Statistical analysis

To minimise bias due to confounding by indication, we used a high dimensional propensity score (HDPS) algorithm that incorporated investigator-specified covariates and additional factors that acted as proxy variables for unmeasured confounders (22). The HDPS was generated using logistic regression models. Covariates were derived from four dimensions of data comprised of aforementioned data sources: 1) MSP database; 2) DAD; 3) PharmaNet; and, 4) BCPDR. Within the MSP database, DAD, and PharmaNet, only claims or codes that occurred during the 12 months prior to the date of conception for each pregnancy were assessed as candidate covariates to be included in the HDPS. Candidate covariates across data dimensions were prioritised by their potential for controlling confounding (23, 24). The top 50 empirically derived covariates for each outcome were included along with investigator specified confounders for propensity score estimation. For each outcome, biologic exposed pregnancies were matched with unexposed pregnancies using HDPS in a ratio of 1:5 without replacement. Match performance was evaluated by comparing standardised mean differences in baseline characteristics of matched and unmatched cohorts.

Using logistic regression models we analysed the relationship between biologic exposure and occurrence of congenital anomalies in the offspring from each pregnancy in the HDPS-matched cohort, using both the BCPDR defined outcome (congenital anomalies diagnosed at birth) and the "1-2-3" algorithm defined outcome (congenital anomalies diagnosed at birth and within the first year of life). Further sensitivity analyses were conducted using multivariable logistic regression models with deciles of HDPS included as indicator terms and with continuous HDPS as a covariate. As sensitivity analysis for the exposure, we defined the exposure window beginning at 12 months prior to conception for both outcomes, and used HDPS matching. We omitted the use of generalised estimating equations with robust variance estimators to account for correlation between multiple pregnancies within the same woman, as analyses with this approach did not appreciably change estimates or confidence intervals in the outcome models. All analyses were conducted using SAS statistical software v. 9.3 (Cary, NC, USA).

Results

There were 6,218 women with 8,607 pregnancies in the autoimmune disease study cohort. Table I shows baseline characteristics for the unmatched cohorts as well as HDPS-matched cohorts. At baseline, there were marked imbalances between exposure groups

Table I. Characteristics of moms and infants in pregnancies exposed and unexposed to biologics, in the unmatched and HDPS-matched samples.

	Unmatched sample overall			HDPS matched sample		
Maternal characteristics	Biologic exposed	Biologic unexposed	SMD	Biologic exposed	Biologic unexposed	SMD
Current pregnancy						
Maternal age at delivery (mean (SD))	31.4 (4.7)	31.2 (5.2)	0.038	31.4 (4.7)	31.3 (5.5)	0.019
Multiparous	52 (44%)	4990 (59 %)	0.290	52 (44%)	244 (42%)	0.055
Antenatal visits (mean (SD))	9.1 (3.6)	9.0 (3.9)	0.019	9.1 (3.6)	9.0 (3.9)	0.015
Gestational hypertension	7 (6%)	645 (8%)	0.064	7 (6%)	64 (11%)	0.179
Gestational diabetes	13 (11%)	668 (8%)	0.111	13 (11%)	46 (8%)	0.111
Neighbourhood income quintiles						
5th percentile	24 (21%)	1760 (21%)	-	24 (21%)	124 (21%)	-
25th percentile	26 (22%)	1697 (20%)	-	26 (22%)	128 (22%)	-
Median (50th percentile)	21 (18%)	1841 (22%)	-	21 (18%)	128 (22%)	-
75th percentile	28 (24%)	1797 (21%)	-	28 (24%)	119 (20%)	-
95th percentile	18 (15%)	1395 (16%)	-	18 (15%)	86 (15%)	-
Hospitalisation at baseline	39 (33%)	2072 (24%)	0.198	39 (33%)	181 (31%)	0.051
BMI at baseline (mean (SD))	24.6 (4.3)	24.6 (4.5)	0.005	24.6 (4.3)	24.5 (4.6)	0.036
Prior obstetrical history						
Premature delivery	5 (4%)	500 (6%)	0.074	5 (4%)	32 (5%)	0.056
Spontaneous abortion	37 (32%)	2221 (26%)	0.121	37 (32%)	156 (27%)	0.109
Delivery with neonatal death	<5	52 (1%)	0.028	<5	<5	-
Stillbirth	<5	103 (1%)	0.099	<5	13 (2%)	0.022
Low birth weight infant	5 (4%)	243 (3%)	0.076	5 (4%)	27 (5%)	0.017
Infant with anomalies	<5	74 (1%)	0.133	<5	<5	-
*Autoimmune disease type**						
Inflammatory bowel disease	54 (46%)	2467 (29%)	0.359	54 (46%)	252 (43%)	0.062
Rheumatoid arthritis	55 (47%)	1745 (21%)	0.583	55 (47%)	298 (51%)	0.079
Psoriasis/psoriatic arthritis	20 (17%)	3437 (40%)	0.535	20 (17%)	95 (16%)	0.023
Juvenile idiopathic arthritis	9 (8%)	92 (1%)	0.327	9 (8%)	46 (8%)	0.006
Systemic autoimmune rheumatic diseases	7 (6%)	1061 (13%)	0.226	7 (6%)	30 (5%)	0.037
Ankylosing spondylitis	5 (4%)	417 (5%)	0.030	5 (4%)	31 (5%)	0.048
Biologics‡						
Infliximab	62 (34%)	-	-	62 (34%)	-	-
Etanercept	48 (27%)	-	-	48 (27%)	-	-
Adalimumab	45 (25%)	-	-	45 (25%)	-	-
Other biologic**	25 (14%)	-	-	25 (14%)	-	-
Concomitant medications						
DMARDs	60 (51%)	1714 (20%)	0.686	60 (51%)	307 (52%)	0.024
Glucocorticoids	55 (47%)	891 (10%)	0.882	55 (47%)	250 (43%)	0.086
Traditional NSAIDs	34 (29%)	2231 (26%)	0.062	34 (29%)	189 (32%)	0.070
COX2 NSAIDs	6 (5%)	282 (3%)	0.090	6 (5%)	31 (5%)	0.008
Antidepressants	25 (21%)	1285 (15%)	0.162	25 (21%)	117 (20%)	0.034
Anxiolytics	11 (9%)	642 (8%)	0.066	11 (9%)	54 (9%)	0.006
Comorbidities						
Anxiety	16 (14%)	816 (10%)	0.127	16 (14%)	80 (14%)	0.000
Mood disorders	10 (9%)	432 (5%)	0.138	10 (9%)	42 (7%)	0.051
Infant characteristics						
Female sex	63 (54%)	4515 (49%)	0.099	63 (54%)	301 (51%)	0.048
Gestational age, weeks (mean (SD))	37.9 (2.3)	38.4 (2.2)	0.223	37.9 (2.3)	38.0 (2.6)	0.031
Birth weight, grams (mean (SD))	3200 (609)	3384 (596)	0.305	3200 (609)	3266 (665)	0.102
Apgar score at 1 minute (mean (SD))	8.1 (1.5)	8.0 (1.7)	0.072	8.1 (1.5)	7.8 (2.0)	0.176
Apgar score at 5 minutes (mean (SD))	8.9 (1.0)	9.0 (1.0)	0.036	8.9 (1.0)	8.8 (1.5)	0.108

SD: standard deviation; BMI: body mass index; DMARDs: disease-modifying anti-rheumatic drugs; NSAIDs: non-steroidal anti-inflammatory drugs; COX: cyclooxygenase; SMD: standardised mean differences.
*Sum of percentages exceed 100% due to some individuals having more than one diagnosis. †All cell sizes <5 are suppressed due to privacy restrictions of data sharing agreements. ‡Sum of percentages exceed 100% due to some pregnancies being exposed to more than one drug. **Other biologics include: abatacept, alefacept, certolizumab pegol, golimumab, rituximab, tocilizumab, and ustekinumab.

in the distribution of autoimmune disease types and concomitant medication use, as seen with large standardised mean differences in the unmatched cohort. The HDPS-matching was able to mitigate this imbalance. The HDPS-matched cohort included 117 pregnancies (107 women) exposed to biologics 90 days before pregnancy or during the first trimester, and 585 HDPS-matched pregnancies (562 women) that were not exposed to biologics during the same

period. In the HDPS-matched cohort, most of the women had a diagnosis of RA or IBD (50% and 44%, respectively) and filled prescriptions for one of three commonly prescribed TNF-alpha inhibitors (infliximab 34%, etanercept 27%, or adalimumab 25%).

In the HDPS-matched cohort, there were 7/117 (6%) and 33/585 (6%) newborns that had the primary outcome of congenital anomalies diagnosed at birth in the biologic exposed and unexposed groups, respectively (Table IIA). Types of congenital anomalies that occurred in the biologic exposed group included: atrial septal defect, patent ductus arteriosus, other specified malformation of kidney, accessory auricle, ankyloglossia, and other specified congenital anomalies of the skin. Table IIA shows the results of crude analyses of the association between biologic exposure and congenital anomalies with an unadjusted odds ratio (OR) of 1.09 (95% confidence interval [CI] 0.51–2.36) compared to unexposed. In the primary analysis, the OR for the association between biologic exposure and congenital anomalies was 1.06 (95% CI 0.46– 2.47), suggesting no association (Table IIA, Model 1). Sensitivity analyses involving multivariable logistic regression based on the unmatched cohort adjusting for HDPS deciles (Model 2) and continuous HDPS (Model 3) did not appreciably change the results. Sensitivity analysis extending the exposure window to 12 months preconception (Model 4) resulted in higher rates of congenital anomalies diagnosed at birth in both exposed (11/140, 8%) and unexposed groups (42/706, 6%).

When considering the secondary outcome of congenital anomalies at birth and during the first year of life, rates in the exposed group remained the same while a few more events were identified in the unexposed group; however the overall results did not differ substantially (Table IIB). Specifically, we observed an OR of 0.95 and 95% CI of 0.44 to 2.06 in the main model (Model 1). Sensitivity analyses involving multivariable logistic regression based on the unmatched cohort adjusting for HDPS deciles (Model 2) and continuous HDPS (Model 3) did not appreciably change the results. As with the primary outcome, sensitivity analysis extending the exposure window to 12 months preconception (Model 4) resulted in higher rates of congenital anomalies diagnosed at birth and during the first year of life in both exposed (11/140, 8%) and unexposed groups (50/706, 7%).

Table II. Crude and adjusted analyses of the association between biologic use and congenital anomalies.

	A. Congenital anomalies diagnosed at birth		Congenital anomalies diagnosed at birth and during the 1st year of life	
	Biologic exposed	Biologic unexposed	Biologic exposed	Biologic unexposed
Crude analyses				
Exposure window				
3 months preconception	7/114 (6%)	46/732 (6%)	7/114 (6%)	54/732 (7%)
1st trimester	7/96 (7%)	46/750 (6%)	7/96 (7%)	54/750 (7%)
Combined	7/117 (6%)	33/585 (6%)	7/117 (6%)	35/585 (6%)
Unadjusted OR (95%CI)	1.09 (0.51 to 2.36)		0.95 (0.44 to 2.06)	
Adjusted analyses				
Model 1 OR (95%CI)*	1.06 (0.46 to 2.47)		1.00 (0.43 to 2.31)	
Model 2 OR (95%CI)**	1.02 (0.46 to 2.26)		0.88 (0.40 to 1.93)	
Model 3 OR (95%CI)***	1.12 (0.10 to 12.22)		1.21 (0.12 to 11.74)	
Model 4 OR (95%CI)‡	1.16 (0.56 to 2.37)		1.41 (0.70 to 2.81)	

*Logistic regression in matched cohort. **Multivariable logistic regression with HDPS deciles. ***Multivariable logistic regression with continuous HDPS as covariate. ‡Exposure window starting from 12 months preconception, logistic regression in HDPS matched cohort.

Discussion

In this population-based cohort study using administrative health data in BC linked to the provincial perinatal registry, we examined the association of biologics – primarily TNF-alpha inhibitors – before pregnancy, or during the first trimester, in women with autoimmune diseases and the risk of congenital anomalies in their offspring. We applied HDPS methods – primarily matching – to account for differences in baseline characteristics between women exposed and unexposed to biologics. We found that in the HDPS-matched cohort, 7/117 (6%) and 33/585 (6%) of newborns had ≥1 congenital anomalies at birth, in the exposed and unexposed groups, respectively. There were no obvious patterns with regards to the congenital anomalies observed in the biologics exposed group. In primary, secondary, and sensitivity analyses, all of the results suggest that there is no association between biologic exposure in women with autoimmune diseases and the risk of congenital anomalies in their offspring.

Indeed, congenital anomalies are one of the most widely studied outcomes among questions on the safety of medications during pregnancy. Earlier reports raised concerns for the association of biologics exposure with VACTERL (vertebral defects, anal atresia, cardiac defects, trachea-esophageal fistula, renal anomalies, and limb) constellation of abnormalities (25). Though this association has since been disputed by Winger and Reed who drew attention to the inherent limitations of the data source used in the earlier study, which only consisted of spontaneous adverse event reports (26). Due to the nature of the data, accumulated reports cannot be used to calculate the incidence of anomalies or to compare risks of anomalies between drugs (26). Furthermore, the criterion for VACTERL diagnosis requires the identification of three or more of the anomalies within a single patient, while the individually reported anomalies in their data can be regarded only as sporadic and not as a manifestation of the VACTERL constellation (26).

Due to challenges with a rare outcome, and a relatively rare exposure, no studies to date have shown a significant association and few are able to adjust for potential confounders relating to autoimmune disease activity, concomitant medications, comorbidities, or obstetrical characteristics due to small

sample sizes (ranging from around 50 to 250 subjects) (27-33). Even among those with larger sample sizes that have adjusted for some potential confounders, the reported risk estimates in those studies are wide-ranging, with overlapping confidence intervals. Two published studies with particularly large sample sizes, Broms (n=22,232) and Carman (n=3,927) reported very divergent estimates of the association between biologic exposure before or during pregnancy and the risk of congenital anomalies as OR 1.32 (95% CI 0.93 to 1.87) and 0.52 (95% CI 0.13–2.08), respectively (34, 35). There has been one abstract published by Chambers *et al*., which uses traditional propensity score matching to examine the association between exposure to adalimumab and risk of adverse pregnancy outcomes including congenital anomalies, with a similar sample size of 720, which reported an OR of 0.91 (95% CI 0.37–2.24) (36). Indeed, as our study adds to the evidence on the impacts of biologics on congenital anomalies, they provide support to guidelines including those from the British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) (37) and the European League Against Rheumatism (38). This in turn may address practice limitations including reported lack of consensus on use of biologics during pregnancy in a 2013 survey in the UK (39) and moderate concordance with aforementioned guidelines in a 2018 survey in Lebanon (40).

The strengths and limitations of our work warrant discussion. Although our objective was to study all biologics, the majority of exposures in our cohort were to TNF-alpha inhibitors. The main limitation of our study remains the relatively small sample size in the matched cohorts. However, the use of HDPS matching inherently prioritises validity over precision of estimates, of which, the latter can only be overcome by accumulation of evidence drawn from studies using consistent methodological approaches or from pooling data across multiple databases. Nevertheless, a major strength of our study is the high internal validity afforded by the use of the methodology – HDPS matching – which allows for better adjustment of confounding by indication and adjustment of proxies of unmeasured confounders (22). Ensuring internal validity, and appropriate comparison of exposure groups is of utmost importance in this population of women with autoimmune disease given the association between disease activity and adverse pregnancy outcomes (9, 41), and the fact that those with worse disease activity are also more likely to be on biologics given the current treatment pathways. Furthermore, in studies of medication safety in pregnancy and risk of congenital anomalies, the accuracy in establishing the timing of potentially harmful exposures with respect to fetal organogenesis cannot be understated. The high quality and high coverage population-based prescription dispensations database (PharmaNet), linked with the perinatal registry (BCPDR) covering nearly all births in the province, allowed us to accurately determine the timing of all medication dispensations with respect to milestone pregnancy dates, thus minimising misclassification and other potential biases. This dataset also provided a "gold standard" for ascertainment of the outcome, congenital anomalies at birth, as it is taken directly from chart documentation and subsequent record in the BCPDR.

These population-based data suggest that use of biologic before pregnancy or during the first trimester is unlikely to be associated with a congenital anomaly in infants born to women with autoimmune inflammatory diseases. Given the effectiveness of biologics in controlling disease activity, and the risks of teratogenicity with certain commonly used traditional DMARDs, these findings emphasise the importance of balancing benefits and risks of treatments for patients who may be pregnant or considering pregnancy.

Acknowledgements

The authors would like to acknowledge Dr Jeremy Rassen for his help in answering questions and confirming our understanding of the HDPS programming.

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