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# Use of biologics during pregnancy and risk of serious infections in the mother and baby: A population-based cohort study

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## Abstract

**Objectives:** To investigate the association between exposure to biologics during pregnancy and serious infections in mothers and infants.

**Design:** Retrospective cohort study

**Setting:** Population-based

**Participants:** Women with one or more autoimmune diseases identified by International Classification of Diseases 9th /10th revision codes in healthcare administrative databases in British Columbia, Canada, who had pregnancies ending in a live or still birth between January 1st, 2002 and December 31st, 2012. Women were defined as exposed if they had at least one biologic prescription during pregnancy, and infants born to these women were considered exposed in utero. Disease-matched women with no biologics prescriptions during pregnancy, and their infants, comprised the unexposed groups.

**Primary outcome measures:** Serious infections requiring hospitalization.

**Results:** Over the 10-year study period, there were 6,218 women (8,607 pregnancies) who had an autoimmune disease diagnosis; of which 90 women were exposed to biologics during pregnancy, with 100 babies born to these women. Among women exposed to biologics during pregnancy, occurrence of serious post-partum infections were low, ranging from 0 to 5%, depending on concomitant exposures to immunosuppressants. In multivariable models using logistic regression, the adjusted odds ratio (aOR) for the association of biologics exposure with serious maternal post-partum infections was 0.79 (95% confidence interval [CI] 0.24 to 2.54). In infants exposed to biologics in utero, occurrence of serious infections during the first year of life ranged from 0 to 7%, depending on concomitant exposures to immunosuppressants in utero. Multivariable models showed no association between biologics exposure in utero and serious infant infections (aOR 0.56, 95%CI 0.17 to 1.81).

**Conclusions:** These population-based data suggest that the use of biologics by women with autoimmune diseases during pregnancy is not associated with an increased risk of serious infections in mothers, during post-partum, or in infants during the first year of life.

## Article Summary

### Strengths and limitations of this study

- This is the first population-based cohort study to examine the risk of serious post-partum infections in mothers who were using biologics during pregnancy, and in infants exposed in utero.
- We used individual-level, de-identified, longitudinal data on all health services (physician visits, hospitalizations, and prescription medications) covering the entire population of the province, linked with a perinatal registry covering >99% of births.
- We used high-dimensional propensity score matching as a sensitivity analysis to the traditional multivariable models.
- The data sources come from administrative databases not primarily collected for research purposes and thus rely on accuracy of diagnostic coding.
- Exposures and outcomes remain relatively rare and as such, caution should be exercised when interpreting the findings in light of this context.

## Introduction

Biologics have revolutionized the management of several autoimmune chronic conditions, and are commonly used in inflammatory arthritis including rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA) as well as inflammatory bowel disease (IBD, ulcerative colitis and Crohn's disease) (1,2). They are typically genetically engineered parts of, or whole, immunoglobulin Gs (IgG) that inhibit specific components of the immune system that play pivotal roles in inflammation (3). Despite their established efficacy in managing autoimmune diseases, treatment with biologics is not without risks. Network meta-analyses show a significant increase in serious infections in RA patients treated with biologics alone (odds ratio [OR] 1.31; 95% credible interval 1.09 to 1.58) or in combination with traditional disease modifying anti-rheumatic drugs (DMARDs) (OR 1.34; 95% confidence interval [CI] 1.09 to 1.69) compared to DMARDs alone (4).

In pregnancy, infection risk is a unique safety outcome in that it can occur both in the mother and her infant possibly as a result of exposure to the same offending agent. Additionally, the risk of infections may already be elevated for the mother during the delivery and post-partum periods, and for the neonate after birth when their immune system is still naïve. During pregnancy, IgG is transferred from the maternal to the fetal circulation by receptor-mediated binding of the Fcγ portion of the IgG molecule and it's receptor, FcRn (Fc receptor neonatal) (5–7). The FcRn is also found to have a protective effect on IgG degradation, extending its lifespan, leading to accumulation in the infant for upwards of six to eight months (8). With infliximab and adalimumab having higher affinity for FcRn, levels of these biologics in offspring cord blood have been reported to be 300-400% higher than levels in the maternal circulation (9). Furthermore, detectable, and even therapeutic, levels of biologics in infant serum have been confirmed in case reports of infants exposed in utero (9–11). However, to date few epidemiologic studies have examined the risk of

infections in women using biologics during pregnancy, or in infants that were exposed to biologics in utero. Our objectives were to investigate the association between exposure to biologics during pregnancy and serious infections in 1) mothers during the post-partum period; and 2) infants during the first year of life.

## Methods

### Data sources

Data for mothers and babies were obtained through Population Data BC, a repository of individual-level, de-identified, longitudinal data on all health services covering the entire population of BC (estimated 4.6 million residents, December 2016 (12)). Specifically, respective data for mothers and babies comprised four linked databases including: 1) Medical Services Plan (MSP) database – all provincially-funded physician visits, ordered laboratory tests and diagnostic procedures (x-rays, ultrasounds etc.) (13); 2) Discharge Abstract Database (DAD) – all hospital admissions and discharges (14); 3) PharmaNet – a comprehensive prescription drug database that captures all prescriptions dispensed in community pharmacies regardless of payment source, since 1996 (15). The BC Perinatal Database Registry (BCPDR) facilitated the linkage between mothers' and babies' data. The BCPDR contains data abstracted from obstetrical and neonatal medical records on nearly 100% of births in the province of BC from over 60 acute care facilities as well as births occurring at home attended by BC registered midwives, including women who had pregnancies ending in a live or still birth of at least 20 weeks gestation or 500 grams birth weight, also collects data on maternal postpartum readmissions up to 42 days post-delivery and baby transfers and readmissions up to 28 days after birth (16–19). Details of these data sources are described in previous work (20) and databases and linkages are shown in Figure 1.

Study cohort

The source population comprised of women in BC who had 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 requirement of continuous insurance coverage ensures that we have complete data capture for all women and babies in our study population. We created a cohort of women from the source population who had a recorded diagnosis of one or more autoimmune diseases that could be treated with a biologic, including RA, IBD (Crohn's disease and ulcerative colitis), psoriasis (Ps)/PsA, AS, juvenile idiopathic arthritis, and systemic autoimmune rheumatic diseases. Women were considered to have been diagnosed with one of these conditions of they had the same International Classification of Diseases (ICD)-9$^{th}$ revision or 10$^{th}$ revision codes 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 at least one hospitalization with an ICD-9/10 code for an autoimmune disease any time prior to the date of conception (20). Given that the unit of analysis was individual pregnancy, each pregnancy had to satisfy the above criteria in order to be included in the analyses. All singleton live born infants from these pregnancies were included in the analyses of infant serious infections.

Biologics exposure

Using dispensation dates and Canadian Drug Identity Codes for biologics in PharmaNet linked with date of conception and date of delivery of each pregnancy in the BCPDR, exposure to biologics was identified in any woman in the autoimmune disease cohort with one or more prescriptions for a biologic anytime from the date of conception to the date of delivery (20). Infants born from these pregnancies were classified as being exposed to biologics in utero. Pregnancies that did not satisfy

this criteria and infants born from those pregnancies were considered unexposed. All biologics available in BC for the treatment of autoimmune diseases of interest during the study period, along with concomitant medications considered in this study, are listed in Supplementary Table S1.

Serious infections

The outcomes of interest were serious infections requiring hospitalization during the post-partum period in women, and serious infections requiring hospitalization anytime during the first year of life in infants. Serious post-partum infections were defined as any episode of hospitalization, including the delivery episode, with one or more ICD-9/10 codes for an infection anytime from the date of delivery until 42 days post-partum – the conventional definition for post-partum period of concern (21). Serious infections in infants were defined as any episode of hospitalization with one or more ICD-9/10 codes for an infection anytime during the first year of life – due to the lengthy accumulation of biologics in infant circulation – or until death, whichever occurred first. All infections considered are listed in Supplementary Table S2.

Covariates

All covariates considered were from the aforementioned data sources. Maternal factors included characteristics of current pregnancy, prior obstetrical history, comorbidities, and medication use. Characteristics of current pregnancy included maternal age at delivery (continuous), parity (primiparous or multiparous), neighborhood income quintile (based on postal code) at baseline, body mass index (BMI) at first antenatal visit (continuous; and categorical as underweight: <18.5, normal: 18.5-24.9, overweight: 25-29.9, obese: ≥30 kg/m$^2$), weight gain during pregnancy (binary, based on guidelines for weight gain during pregnancy by BMI category (22)), number of antenatal visits (continuous), and hospitalization at baseline (binary), and delivery by cesarean section (binary).

Prior obstetrical history included binary outcomes from previous pregnancies (if applicable) including premature delivery, spontaneous abortions, neonatal death, stillbirth, low birth weight, and congenital anomalies. Comorbidities considered included gestational hypertension, gestational diabetes, anxiety disorders, mood disorders, and asthma. Concomitant medications included DMARDs or immunosuppressants, glucocorticoids, antidepressants, anxiolytics, traditional and COX-2 non-steroidal anti-inflammatory drugs (NSAIDs). All maternal factors considered in analyses of post-partum infections in the mother that could be associated with serious infections in infants were also considered in analyses of this latter outcome in addition to infant characteristics. Infant characteristics included sex and Apgar scores at 1 minute, 5 minutes, and 10 minutes (continuous). Other infant characteristics including gestational age, birth weight, and presence of anomalies were considered but not included in the analysis as they may be possible mediators of the effect of exposure on serious infections in infants.

Statistical Analysis

Using logistic regression models we calculated ORs with 95% CIs between maternal exposure to biologics during pregnancy and the risk of serious post-partum infections in women, and the risk of serious infant infections during the first year of life; first as unadjusted models, by treatment categories only (model 1) and then adjusted for maternal and infant characteristics according to respective outcome (model 2). Multivariable models were constructed using forward selection and covariates were included in the final models if they were associated with the exposure in bivariate analyses and resulted in lower Akaike Information Criterion upon inclusion. Multivariable regression analyses using generalized estimating equation models with logit link and clustered by mother could not be completed as models did not converge. However, previous work on a larger sample from our

source population showed that accounting for correlations between multiple pregnancies within the same woman did not appreciably change effect estimates and confidence intervals (20).

As a sensitivity analysis, we estimated propensity for biologics exposure in each pregnancy using a high dimensional propensity score (HDPS) algorithm that incorporated investigator-specified covariates and additional factors that acted as proxy variables for unmeasured confounders from the four aforementioned data dimensions (model 3) (23). The HDPS was calculated using logistic regression then each biologic exposed pregnancy was matched with five unexposed pregnancies without replacement, based on HDPS. Match performance was evaluated by comparing the standardized mean differences in baseline characteristics of matched and unmatched cohorts. Odds ratios and 95% CIs for biologics exposure and serious post-partum infections, and serious infant infections were calculated using logistic regression in the HDPS-matched samples. All analyses were conducted using SAS statistical software v.9.3 (Cary, NC, USA).

Study Conduct

This study was approved by the University of British Columbia, Behavioural Research Ethics Board. 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. Due to data sharing agreements and confidentiality, cell sizes of less than five individuals are not reported.

Patient and Public Involvement

Patients were not involved in the design, recruitment, or conduct of the study as this is a retrospective cohort study using population-wide administrative data.

## Results

In the cohort of 6,218 women with autoimmune inflammatory disease diagnoses and 8,607 singleton pregnancies, there were 90 women exposed to biologics during pregnancy, and 100 babies born to these women. In the biologics exposed group, more women had IBD or RA, used at least one DMARD or glucocorticoid delivered via Cesarean section, or had gestational diabetes, anxiety, or mood disorders; whereas in the group not exposed to biologics during pregnancy, more women had Ps/PsA, were multiparous, and had gestational hypertension (Table 1). A larger proportion of infants exposed to biologics in utero were female, and those that were unexposed to biologics tended to have more advanced gestational age and higher birth weight (Table 1).

Among women exposed to biologics during pregnancy, occurrence of serious post-partum infections were rare, ranging from 0 to 5%, depending on concomitant exposures to DMARDs or glucocorticoids (Figure 2). Serious infections that occurred in those exposed to biologics included infection of the amniotic sac and membranes, and bacterial puerperal infections. In model 1 looking only at drug exposures, we found no independent associations between the use of biologics (OR 0.88, 95%CI 0.27 to 2.82), DMARDs (OR 0.98, 95%CI 0.68 to 1.40), or glucocorticoids (OR 1.07, 95%CI 0.64 to 1.77), with the risk of serious post-partum infections (Table 2). The results were similar when maternal factors were included (model 2), specifically, the association between biologics exposure and serious post-partum infections had an adjusted OR [aOR] of 0.79 (95%CI 0.24 to 2.54), DMARD/ immunosuppressants had an aOR of 0.98 (95%CI 0.68 to 1.40), and glucocorticoids an aOR of 1.00 (95%CI 0.60 to 1.67) (Table 2). In this model, we also found several independent maternal factors that were significantly associated with either increased or decreased post-partum infections; having an anxiety diagnosis, more previous hospitalizations, higher BMI at conception, and delivering via Cesarean section were all factors that increased the risk of serious

infection; while being multiparous appeared protective. Results from sensitivity analysis using HDPS-matching and logistic regression had higher uncertainty due to a wide confidence interval (model 3).

In infants exposed to biologics in utero, proportion of serious infections ranged from 0 to 7% depending on the treatment combination used by the mother during pregnancy (Figure 3). The types of serious infections that occurred during infants' first year of life were lymphadenitis, urinary tract infection, and acute bronchiolitis. In model 1 examining categories of maternal drug exposures only, we found no increased risk of serious infections in infants who were exposed to biologics (OR 0.50, 95%CI 0.16 to 1.60), or DMARDs (OR 1.07, 95%CI 0.81 to 1.43) in utero, while glucocorticoids exposure appeared to possibly increase risk (OR 1.46, 95%CI 1.00 to 2.12). When maternal and infant factors were considered (model 2), the risk of serious infections associated with biologics exposure had an aOR of 0.56 (95%CI 0.17 to 1.81), DMARD/immunosuppressants had an aOR of 1.09 (95%CI 0.81 to 1.45), and glucocorticoids an aOR of 1.13 (95%CI 0.77 to 1.66) (Table 3). However, we found several maternal factors associated with an increased risk of infections in infants, including multiparity, maternal history of prior delivery resulting in a low birth weight infant, or premature infant, maternal use of anxiolytics, and maternal asthma diagnosis (Table 3). Factors associated with a lower risk of serious infections included being a female infant, having higher Apgar score at 1 minute, higher neighborhood income, and more antenatal visits. Sensitivity analysis using logistic regression in the HDPS-matched cohort did not change these results (model 3).

## Discussion

In this study using linked administrative health data and a perinatal registry for a population-based cohort of women with autoimmune disease and their babies, we examined the association between

exposure to biologics during pregnancy and risk of serious infections in mothers and infants, respectively. Specifically for mothers, these were infections requiring hospitalization during the post-partum period; and for infants, these were infections requiring hospitalization during their first year of life. We found that the proportion of serious infections in all groups was low. Our findings suggest that there was no difference in risk of serious post-partum infections in women who used biologics during pregnancy versus those who did not. Similarly, we did not observe a difference in risk of serious infections during the first year of life in infants born to mothers who used biologics during pregnancy compared to those who did not. While we examined all biologics used in the cohort, TNF-alpha inhibitor biologics (94%) were the most common, and as such our results mostly apply to these biologics and less so to those that are not TNF-alpha inhibitors. Our results did demonstrate the association between several known factors with the increased risk of infections in mothers, including higher BMI (24) and Cesarean section delivery (25,26); and in infants including multiparity in mothers (27) and maternal asthma diagnosis (28).

Indeed serious infections are a well-known safety outcome in patients using biologics to manage their autoimmune diseases, and despite pregnant women and infants being vulnerable populations there has been a dearth of evidence on this clinically important topic. One population-based study in the United States by Desai et al. compared serious intrapartum infections among 776 users of biologics compared to 1587 users of non-biologics and reported no meaningful increase risk of serious infection during pregnancy (adjusted hazard ratio [aHR] 1.36, 95%CI 0.47 to 3.93) (29). However, the authors did observe that the rate of infections increased noticeably in all treatment groups as pregnancies approached term (29), thus, providing a rationale for the objective of our study which examined the risk of infections around the time of childbirth, and post-partum. No other studies to date have specifically investigated the association between biologics use and the risk

of post-partum infections despite the fact that post-partum infections account for up to 10% of maternal deaths, and are a cause of short term morbidity and long term complications (30). It is therefore reassuring that our study did not show an association between biologics use during pregnancy and maternal risk of post-partum infections.

Infections is a theoretical concern in infants exposed to biologics in utero, due to evidence of accumulation of certain biologics in cord blood (9). The immunosuppressive effect of TNF-alpha inhibitor accumulation is illustrated by a fatal case of disseminated Bacillus Calmette–Guérin (BCG) infection after BCG vaccination in an infant born to a mother treated with infliximab throughout her pregnancy (31). The infant received a BCG vaccination at 3 months of age, subsequently became ill, and died at 4.5 months of age from disseminated infection (31). Current recommendations to stop some biologics in the third trimester are largely based on such case reports and expert opinion (32). To date, there have only been two published abstracts examining the association of biologics exposure and risk of serious infections in infants. Using data collected by the Organization of Teratology Information Specialists (OTIS), Chambers et al. found similar proportions of serious infections during the first year of life in infants born to women with RA using biologics during pregnancy (2.8%), compared to those born to women with RA not treated with a biologic (3.9%), with a relative risk of 0.71 (95%CI 0.30 to 1.71) (33). In a registry of women with IBD, Chaparro et al. found that after a median follow up of 33 months post-partum, similarly, infants exposed to biologics in utero were not at greater risk of serious infections (HR 0.5, 95%CI 0.2 to 1.3) (34). Our study is the first to corroborate these results using population-based data.

This study has a number of strengths and limitations. The use of population-wide databases with high coverage lends this study greater generalizability; linkages between databases containing valid

information on all dispensed prescriptions (PharmaNet) and antenatal, intrapartum, and postpartum maternal and infant information (BCPDR) provides the ability to accurately determine the timing of all medication dispensations with respect to conception dates. Linkages between maternal and infant data allows for ascertainment of infant exposure status in utero. Altogether, these strengths minimize potential biases caused by problems such as selection bias, patient recall bias, reporting bias, and exposure misclassification. The main limitation of our study stems from the uncertainty of risk estimates attributable to the relatively small sample size of the exposed, as such, a doubling to tripling in the risk of serious infections remains compatible with the upper bound of the confidence intervals of our estimates. 'Depletion of susceptibles' was also a possible phenomenon. Our previous studies have shown that the proportion of women discontinuing their biologic became more prevalent as pregnancy progressed resulting in fewer women being exposed close to delivery, which could be an explanation for the low numbers of outcomes observed (20). Also due to the rare occurrence of the outcomes of interest, subgroup analyses of specific biologics, or specific autoimmune disease types were not possible. Other limitations included potential misclassification of the outcome, as a code for an infection could have been in any diagnostic field in the discharge abstract data and may not have been the primary reason for hospitalization. Furthermore, we could not obtain any data on breastfeeding practices which has been shown to be protective against infections requiring hospitalizations (35). However, our findings of other factors independently associated with serious infections, such as maternal BMI (24), Cesarean section delivery (25,26), infant gender (36), and maternal asthma diagnosis (28), are consistent with that reported in literature and thus lend validity to our results.

In conclusion, from this population-based cohort we did not observe differences in the risk of serious infections in women using or not using TNF-alpha inhibitor biologics during pregnancies or

in their offspring during the first year of life. Our findings are compatible with current recommendations where discontinuation of TNF-alpha inhibitor biologics late in the pregnancy could be considered, or if indicated, can be continued throughout the pregnancy (32,37). Our study provides information for clinicians and women with autoimmune diseases regarding the risks of serious infections when using biologics during pregnancy.

**Author Statement**

Ms. Tsao had full access to all the data used in this study and takes responsibility for the integrity of the data and accuracy of data analysis. As the lead author, Ms. Tsao affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. Contributions of authors to this study are as follows, for concept and design: De Vera, Tsao; acquisition, analysis, and interpretation of data: De Vera, Tsao; drafting of manuscript: Tsao, De Vera; critical revision of manuscript for important intellectual content: Tsao, De Vera, Sadatsafavi, Hanley, Lynd; statistical analysis: Tsao; obtained funding: De Vera. Dr. Lynd has received honoraria from Boehringer Ingelheim and Pfizer Canada for consulting services unrelated to this study, all other authors have declared no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

**Data Sharing Statement**

Due to privacy agreements, data used in this study cannot be shared.

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**Conflicts of Interest**

Dr. Larry Lynd has received honoraria from Boehringer Ingelheim and Pfizer Canada for consulting services unrelated to this study. All other authors have declared no support from any organization for the submitted work.

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## Tables and Figures

**Figure 1. Schematic diagram of databases and linkages facilitating study analyses**

**Table 1. Characteristics of moms and infants in pregnancies exposed and unexposed to biologics**

| Maternal Characteristics | Biologic exposed | Biologic unexposed |
|---|---|---|
| **Current pregnancy** | | |
| Maternal age at delivery (mean (SD)) | 31.0 (4.7) | 31.2 (5.2) |
| Multiparous | 44 (44%) | 4998 (59%) |
| Antenatal visits (mean (SD)) | 8.9 (3.6) | 9.0 (3.9) |
| Gestational hypertension | 5 (5%) | 647 (8%) |
| Gestational diabetes | 12 (12%) | 669 (8%) |
| Delivery via Cesarean section | 40 (40%) | 2849 (33%) |
| Neighbourhood income quintiles | | |
| 5$^{th}$ percentile | 21 (21%) | 1763 (21%) |
| 25$^{th}$ percentile | 24 (24%) | 1699 (20%) |
| Median (50$^{th}$ percentile) | 17 (17%) | 1845 (22%) |
| 75$^{th}$ percentile | 22 (22%) | 1803 (21%) |
| 95$^{th}$ percentile | 16 (16%) | 1397 (16%) |
| Hospitalization at baseline | 99 (99%) | 8412 (99%) |
| BMI at baseline (mean (SD)) | 24.7 (4.6) | 24.6 (4.5) |
| BMI categories | | |
| Obese | 9 (9%) | 851 (10%) |
| Overweight | 15 (15%) | 1342 (16%) |
| **Prior obstetrical history** | | |
| Premature delivery | 5 (5%) | 500 (6%) |
| Spontaneous abortion | 28 (28%) | 2230 (26%) |
| Delivery with neonatal death | <5$^{\dagger}$ | 52 (0.6%) |
| Stillbirth | <5$^{\dagger}$ | 103 (1%) |
| Low birth weight infant | 5 (5%) | 243 (3%) |
| Infant with anomalies | - | 74 (1%) |
| **Autoimmune disease type*** | | |
| Inflammatory bowel disease | 50 (50%) | 2471 (29%) |
| Rheumatoid arthritis | 44 (44%) | 1756 (21%) |
| Psoriasis/psoriatic arthritis | 16 (16%) | 3441 (40%) |
| Juvenile idiopathic arthritis | 8 (8%) | 93 (1%) |

| | | |
|---|---|---|
| Systemic autoimmune rheumatic diseases | 5 (5%) | 1063 (12%) |
| Ankylosing spondylitis | 5 (5%) | 417 (5%) |
| **Biologics**‡ | | |
| Infliximab | 54 (54%) | |
| Etanercept | 41 (41%) | |
| Adalimumab | 39 (39%) | |
| Other biologic** | 18 (18%) | |
| **Concomitant medications** | | |
| DMARDs | 53 (53%) | 1843 (22%) |
| Glucocorticoids | 54 (54%) | 1065 (13%) |
| Traditional NSAIDs | 16 (16%) | 941 (11%) |
| Antidepressants | 16 (16%) | 783 (9%) |
| Anxiolytics | <5† | 394 (5%) |
| COX2 NSAIDs | <5† | 56 (0.7%) |
| **Comorbidities** | | |
| Anxiety | 19 (19%) | 1368 (16%) |
| Mood disorders | 10 (10%) | 432 (5%) |
| Asthma | <5† | 154 (2%) |
| **Infant Characteristics** | **Biologic exposed** | **Biologic unexposed** |
| Female sex | 55 (55%) | 4159 (49%) |
| Gestational age (mean (SD)) | 37.8 weeks (2.4) | 38.4 weeks (2.2) |
| Birth weight (mean (SD)) | 3158 grams (634) | 3385 grams (204) |
| Apgar score at 1 minute (mean (SD)) | 8.1 (1.6) | 8.0 (1.7) |
| Apgar score at 5 minutes (mean (SD)) | 8.9 (1.1) | 9.0 (1.0) |

SD = standard deviation, BMI = body mass index, DMARDs = disease modifying anti-rheumatic drugs, NSAIDs = non-steroidal anti-inflammatory drugs, COX = cyclooxygenase

*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

**Figure 2. Rates of maternal post-partum serious infections based on drug exposure categories**

**Figure 3. Rates of infant serious infections during the first year of life based on in utero drug exposure categories**

**Table 2. Risk of serious maternal post-partum infections associated with biologics exposure during pregnancy**

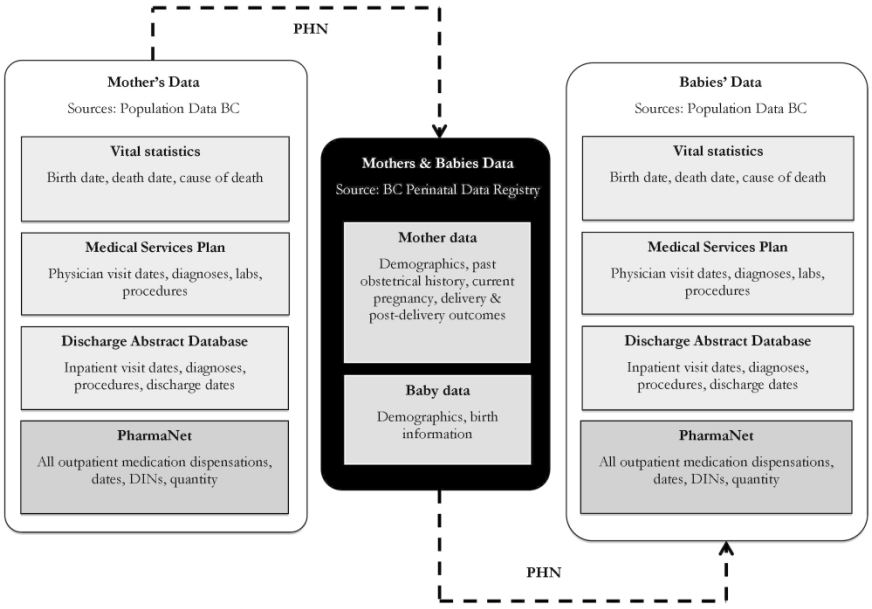
| | Maternal serious infections | |
|---|---|---|
| | **Parameter** | **OR (95% CI)** |
| **Unadjusted** | Biologics | 0.90 (0.28 to 2.84) |
| **Model 1** | Biologics | 0.88 (0.27 to 2.82) |
| | DMARDs/immunosuppressants | 0.98 (0.68 to 1.40) |
| | Glucocorticoids | 1.07 (0.64 to 1.77) |
| **Model 2** | Biologics | 0.79 (0.24 to 2.54) |
| | DMARDs/immunosuppressants | 0.98 (0.68 to 1.40) |
| | Glucocorticoids | 1.00 (0.60 to 1.67) |
| | Multiparity | 0.60 (0.47 to 0.76) |
| | Anxiety | 1.36 (1.02 to 1.82) |
| | Prior hospital admissions | 1.19 (1.06 to 1.34) |
| | BMI at baseline | 1.02 (1.00 to 1.05) |
| | Cesarean section delivery | 2.01 (1.58 to 2.55) |
| **Model 3 HDPS-matched cohort** | Biologics | 1.16 (0.34 to 4.14) |

OR = odds ratio, HDPS = high-dimensional propensity score, DMARDs = disease modifying anti-rheumatic drugs, BMI = body mass index

**Table 3. Risk of serious infant infections during the first year of life associated with biologics exposure in utero**

| | Infant serious infections | |
|---|---|---|
| | **Parameter** | **OR (95% CI)** |
| **Unadjusted** | Biologics | 0.58 (0.18 to 1.85) |
| **Model 1** | Biologics | 0.50 (0.16 to 1.60) |
| | DMARDs/immunosuppressants | 1.07 (0.81 to 1.43) |
| | Glucocorticoids | 1.46 (1.00 to 2.12) |
| **Model 2** | Biologics | 0.56 (0.17 to 1.81) |
| | DMARDs/immunosuppressants | 1.09 (0.81 to 1.45) |
| | Glucocorticoids | 1.13 (0.77 to 1.66) |
| | Female sex | 0.73 (0.60 to 0.89) |
| | Multiparity | 1.56 (1.25 to 1.95) |
| | Maternal antenatal visits | 0.97 (0.94 to 0.99) |
| | Prior delivery with anomaly | 2.04 (0.98 to 4.26) |
| | Prior delivery with low birth weight | 1.67 (1.05 to 2.64) |
| | Prior premature delivery | 1.73 (1.21 to 2.47) |
| | Maternal anti-depressant use | 1.30 (0.97 to 1.75) |
| | Maternal anxiolytics use | 1.66 (1.15 to 2.40) |
| | Maternal rheumatoid arthritis diagnosis | 1.17 (0.93 to 1.47) |
| | Maternal asthma diagnosis | 2.00 (1.18 to 3.39) |
| | Apgar score at 1 minute | 0.87 (0.83 to 0.92) |
| | Neighbourhood income quintile | 0.91 (0.85 to 0.98) |
| **Model 3 HDPS-matched cohort** | Biologics | 0.49 (0.15 to 1.62) |

OR = odds ratio, HDPS = high-dimensional propensity score, DMARDs = disease modifying anti-rheumatic drugs




BC = British Columbia, DIN = drug identification number, PHN = personal health number

Figure 1. Schematic diagram of databases and linkages facilitating study analyses

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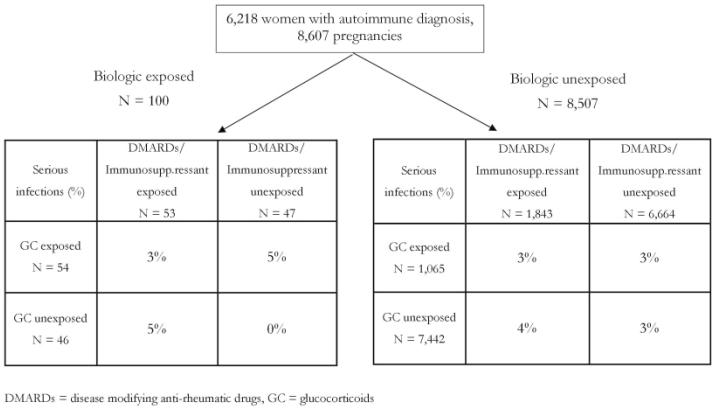


| Serious infections (%) | DMARDs/ Immunosupp.ressant exposed N = 53 | DMARDs/ Immunosuppressant unexposed N = 47 |
|---|---|---|
| GC exposed N = 54 | 3% | 5% |
| GC unexposed N = 46 | 5% | 0% |

| Serious infections (%) | DMARDs/ Immunosupp.ressant exposed N = 1,843 | DMARDs/ Immunosupp.ressant unexposed N = 6,664 |
|---|---|---|
| GC exposed N = 1,065 | 3% | 3% |
| GC unexposed N = 7,442 | 4% | 3% |

DMARDs = disease modifying anti-rheumatic drugs, GC = glucocorticoids

Figure 2. Rates of maternal post-partum serious infections based on drug exposure categories

279x215mm (300 x 300 DPI)

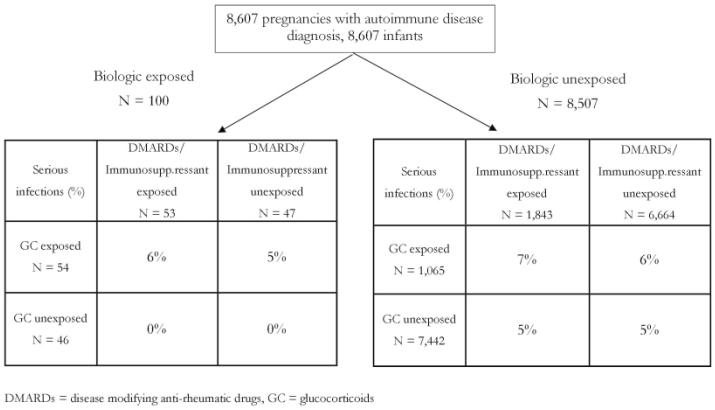


Figure 3. Rates of infant serious infections during the first year of life based on in utero drug exposure categories

279x215mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No | Recommendation | Page numbers |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | Page 1, title |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Page 3, abstract |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | Page 6 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | Page 7, top |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | Page 3, abstract; Pages 7-10, methods |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Pages 7, 8, data sources and study cohort |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | Page 8, study cohort and exposure definition |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | Pages 8-10, exposure, outcome and covariates |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | Pages 8-10, exposure, outcome and covariates |
| Bias | 9 | Describe any efforts to address potential sources of bias | Pages 9, 10, statistical analysis and sensitivity analysis |
| Study size | 10 | Explain how the study size was arrived at | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | Page 9, 10, covariates |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | Page 10, 11, statistical analysis |
| | | (*b*) Describe any methods used to examine subgroups and interactions | |
| | | (*c*) Explain how missing data were addressed | |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | |
| | | (*e*) Describe any sensitivity analyses | Page 10, 11, statistical analysis |

Continued on next page

| | | | |
|---|---|---|---|
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Page 11, results; Figures 2 and 3 |
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Page 11, 12, results; Table 1 |
| | | (b) Indicate number of participants with missing data for each variable of interest | Page 8, 9, methods (follow up defined in methods, there were no losses to follow up |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | Page 11-13, results; Figures 2 and 3 |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Tables 2 and 3 |
| | | (*b*) Report category boundaries when continuous variables were categorized | Pages 9-10, covariates |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | Tables 2 and 3 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | Page 13 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Pages 15, 16 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | Pages 15, 16 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | Page 16 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Page 2, end |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

# Use of biologics during pregnancy and risk of serious infections in the mother and baby: A Canadian population-based cohort study

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| | |

# Use of biologics during pregnancy and risk of serious infections in the mother and baby: A Canadian population-based cohort study

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## Abstract

**Objectives:** To investigate the association between exposure to biologics during pregnancy and serious infections in mothers and infants.

**Design:** Retrospective cohort study

**Setting:** Population-based

**Participants:** Women with one or more autoimmune diseases identified by International Classification of Diseases 9th /10th revision codes in healthcare administrative databases in British Columbia, Canada, who had pregnancies ending in a live or still birth between January 1st, 2002 and December 31st, 2012. Women were defined as exposed if they had at least one biologic prescription during pregnancy, and infants born to these women were considered exposed in utero. Disease-matched women with no biologics prescriptions during pregnancy, and their infants, comprised the unexposed groups.

**Primary outcome measures:** Serious infections requiring hospitalization.

**Results:** Over the 10-year study period, there were 6,218 women (8,607 pregnancies) who had an autoimmune disease diagnosis; of which 90 women were exposed to biologics during pregnancy, with 100 babies born to these women. Among women exposed to biologics during pregnancy, occurrence of serious post-partum infections were low, ranging from 0 to 5%, depending on concomitant exposures to immunosuppressants. In multivariable models using logistic regression, the adjusted odds ratio (aOR) for the association of biologics exposure with serious maternal post-partum infections was 0.79 (95% confidence interval [CI] 0.24 to 2.54). In infants exposed to biologics in utero, occurrence of serious infections during the first year of life ranged from 0 to 7%, depending on concomitant exposures to immunosuppressants in utero. Multivariable models showed no association between biologics exposure in utero and serious infant infections (aOR 0.56, 95%CI 0.17 to 1.81).

**Conclusions:** These population-based data suggest that the use of biologics by women with autoimmune diseases during pregnancy is not associated with an increased risk of serious infections in mothers, during post-partum, or in infants during the first year of life.

## Article Summary

### Strengths and limitations of this study

- This is the first population-based cohort study to examine the risk of serious post-partum infections in mothers who were using biologics during pregnancy, and in infants exposed in utero.
- We used individual-level, de-identified, longitudinal data on all health services (physician visits, hospitalizations, and prescription medications) covering the entire population of the province, linked with a perinatal registry covering >99% of births.
- We used high-dimensional propensity score matching as a sensitivity analysis to the traditional multivariable models.
- The data sources come from administrative databases not primarily collected for research purposes and thus rely on accuracy of diagnostic coding.
- Exposures and outcomes remain relatively rare and as such, caution should be exercised when interpreting the findings in light of this context.

## Introduction

Biologics have revolutionized the management of several autoimmune chronic conditions, and are commonly used in inflammatory arthritis including rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA) as well as inflammatory bowel disease (IBD, ulcerative colitis and Crohn's disease) (1,2). They are typically genetically engineered parts of, or whole, immunoglobulin Gs (IgG) that inhibit specific components of the immune system that play pivotal roles in inflammation (3). Despite their established efficacy in managing autoimmune diseases, treatment with biologics is not without risks. Network meta-analyses show a significant increase in serious infections in RA patients treated with biologics alone (odds ratio [OR] 1.31; 95% credible interval 1.09 to 1.58) or in combination with traditional disease modifying anti-rheumatic drugs (DMARDs) (OR 1.34; 95% confidence interval [CI] 1.09 to 1.69) compared to DMARDs alone (4).

In pregnancy, infection risk is a unique safety outcome in that it can occur both in the mother and her infant possibly as a result of exposure to the same offending agent. Additionally, the risk of infections may already be elevated for the mother during the delivery and post-partum periods, and for the neonate after birth when their immune system is still naïve. During pregnancy, IgG is transferred from the maternal to the fetal circulation by receptor-mediated binding of the Fcγ portion of the IgG molecule and it's receptor, FcRn (Fc receptor neonatal) (5–7). The FcRn is also found to have a protective effect on IgG degradation, extending its lifespan, leading to accumulation in the infant for upwards of six to eight months (8). With infliximab and adalimumab having higher affinity for FcRn (9), levels of these biologics in offspring cord blood have been reported to be 300-400% higher than levels in the maternal circulation (10). Furthermore, detectable, and even therapeutic, levels of biologics in infant serum have been confirmed in case reports of infants exposed in utero (10–12). However, to date few epidemiologic studies have examined the risk of

infections in women using biologics during pregnancy, or in infants that were exposed to biologics in utero. Our objectives were to investigate the association between exposure to biologics during pregnancy and serious infections in 1) mothers during the post-partum period; and 2) infants during the first year of life.

## Methods

### Data sources

Data for mothers and babies were obtained through Population Data BC, a repository of individual-level, de-identified, longitudinal data on all health services covering the entire population of BC (estimated 4.6 million residents, December 2016 (13)). Specifically, respective data for mothers and babies comprised four linked databases including: 1) Medical Services Plan (MSP) database – all provincially-funded physician visits, ordered laboratory tests and diagnostic procedures (x-rays, ultrasounds etc.) (14); 2) Discharge Abstract Database (DAD) – all hospital admissions and discharges (15); 3) PharmaNet – a comprehensive prescription drug database that captures all prescriptions dispensed in community pharmacies regardless of payment source, since 1996 (16); and 4) BC Perinatal Database Registry (BCPDR) - facilitated the linkage between mothers' and babies' data. The BCPDR contains data abstracted from obstetrical and neonatal medical records on nearly 100% of births in the province of BC from over 60 acute care facilities as well as births occurring at home attended by BC registered midwives, including women who had pregnancies ending in a live or still birth of at least 20 weeks gestation or 500 grams birth weight (17–20). Details of these data sources are described in previous work (21) and databases and linkages are shown in Figure 1.

### Study cohort

The source population comprised of women in BC who had 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 requirement of continuous insurance coverage ensures that we have complete data capture for all women and babies in our study population. We created a cohort of women from the source population who had a recorded diagnosis of one or more autoimmune diseases that could be treated with a biologic, including RA, IBD (Crohn's disease and ulcerative colitis), psoriasis (Ps)/PsA, AS, juvenile idiopathic arthritis, and systemic autoimmune rheumatic diseases. Women were considered to have been diagnosed with one of these conditions of they had the same International Classification of Diseases (ICD)-9$^{th}$ revision or 10$^{th}$ revision codes 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 at least one hospitalization with an ICD-9/10 code for an autoimmune disease any time prior to the date of conception (21). Given that the unit of analysis was individual pregnancy, each pregnancy had to satisfy the above criteria in order to be included in the analyses. All singleton live born infants from these pregnancies were included in the analyses of infant serious infections.



Biologics exposure

Using dispensation dates and Canadian Drug Identity Codes for biologics in PharmaNet linked with date of conception and date of delivery of each pregnancy in the BCPDR, exposure to biologics was identified in any woman in the autoimmune disease cohort with one or more prescriptions for a biologic anytime from the date of conception to the date of delivery (21). Infants born from these pregnancies were classified as being exposed to biologics in utero. Pregnancies that did not satisfy this criteria and infants born from those pregnancies were considered unexposed. All biologics

available in BC for the treatment of autoimmune diseases of interest during the study period, along with concomitant medications considered in this study, are listed in Supplementary Table S1.

Serious infections

The outcomes of interest were serious infections requiring hospitalization during the post-partum period in women, and serious infections requiring hospitalization anytime during the first year of life in infants. Serious post-partum infections were defined as any episode of hospitalization, including the delivery episode, with one or more ICD-9/10 codes for an infection anytime from the date of delivery until 42 days post-partum – the conventional definition for post-partum period of concern (22). Serious infections in infants were defined as any episode of hospitalization with one or more ICD-9/10 codes for an infection anytime during the first year of life – due to the lengthy accumulation of biologics in infant circulation – or until death, whichever occurred first. All infections considered are listed in Supplementary Table S2.

Covariates

All covariates considered were from the aforementioned data sources. Maternal factors included characteristics of current pregnancy, prior obstetrical history, comorbidities, and medication use. Characteristics of current pregnancy included maternal age at delivery (continuous), parity (primiparous or multiparous), neighborhood income quintile (based on postal code) at baseline, body mass index (BMI) at first antenatal visit (continuous; and categorical as underweight: <18.5, normal: 18.5-24.9, overweight: 25-29.9, obese: ≥30 kg/m$^2$), weight gain during pregnancy (binary, based on guidelines for weight gain during pregnancy by BMI category (23)), number of antenatal visits (continuous), and hospitalization at baseline (binary), and delivery by cesarean section (binary). Prior obstetrical history included binary outcomes from previous pregnancies (if applicable)

including premature delivery, spontaneous abortions, neonatal death, stillbirth, low birth weight, and congenital anomalies. Comorbidities considered included gestational hypertension, gestational diabetes, anxiety disorders, mood disorders, asthma, hypertension, and diabetes. Concomitant medications included DMARDs or immunosuppressants, glucocorticoids, antidepressants, anxiolytics, traditional and COX-2 non-steroidal anti-inflammatory drugs (NSAIDs). All maternal factors considered in analyses of post-partum infections in the mother that could be associated with serious infections in infants were also considered in analyses of this latter outcome in addition to infant characteristics. Infant characteristics included sex and Apgar scores at 1 minute, 5 minutes, and 10 minutes (continuous). Other infant characteristics including gestational age, birth weight, and presence of anomalies were considered but not included in the analysis as they may be possible mediators of the effect of exposure on serious infections in infants.

Statistical Analysis

Using logistic regression models we calculated ORs with 95% CIs between maternal exposure to biologics during pregnancy and the risk of serious post-partum infections in women, and the risk of serious infant infections during the first year of life; first as unadjusted models, by treatment categories only (model 1) and then adjusted for maternal and infant characteristics according to respective outcome (model 2). Multivariable models were constructed using forward selection and covariates were included in the final models if they were associated with the exposure in bivariate analyses and resulted in lower Akaike Information Criterion upon inclusion. Multivariable regression analyses using generalized estimating equation models with logit link and clustered by mother could not be completed as models did not converge. However, previous work on a larger sample from our source population showed that accounting for correlations between multiple pregnancies within the same woman did not appreciably change effect estimates and confidence intervals (21).

As a sensitivity analysis, we estimated propensity for biologics exposure in each pregnancy using a high dimensional propensity score (HDPS) algorithm that incorporated investigator-specified covariates and additional factors that acted as proxy variables for unmeasured confounders from the four aforementioned data dimensions (model 3) (24). These variables included use of medications (e.g. DMARDs, glucocorticoids), comorbidities (e.g. depression), and healthcare utilization (e.g. outpatient visits, prenatal care, and tests and investigations. The HDPS was calculated using logistic regression then each biologic exposed pregnancy was matched with five unexposed pregnancies (1:5 ratio) without replacement, based on HDPS, whereby an unexposed pregnancy may only be used once as a match. Match performance was evaluated by comparing the standardized mean differences in baseline characteristics of matched and unmatched cohorts. Odds ratios and 95% CIs for biologics exposure and serious post-partum infections, and serious infant infections were calculated using logistic regression in the HDPS-matched samples. All analyses were conducted using SAS statistical software v.9.3 (Cary, NC, USA).

Study Conduct

This study was approved by the University of British Columbia, Behavioural Research Ethics Board. 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. Due to data sharing agreements and confidentiality, cell sizes of less than five individuals are not reported.

Patient and Public Involvement

Patients were not involved in the design, recruitment, or conduct of the study as this is a retrospective cohort study using population-wide administrative data.

## Results

In the cohort of 6,218 women with autoimmune inflammatory disease diagnoses and 8,607 singleton pregnancies, there were 90 women exposed to biologics during pregnancy, and 100 babies born to these women. As shown in Table 1, in the biologics exposed group, more women had IBD or RA, used at least one DMARD or glucocorticoid, or had mood disorders; whereas in the group not exposed to biologics during pregnancy, more women had Ps/PsA and were multiparous. Also shown in Table 1, infants from pregnancies that were unexposed to biologics had more advanced gestational age and higher birth weight.

Among women exposed to biologics during pregnancy, occurrence of serious post-partum infections were rare, ranging from 0 to 5%, depending on concomitant exposures to DMARDs or glucocorticoids (Figure 2). Serious infections that occurred in those exposed to biologics included infection of the amniotic sac and membranes, and bacterial puerperal infections. In model 1 looking only at drug exposures, we found no independent associations between the use of biologics (OR 0.88, 95%CI 0.27 to 2.82), DMARDs (OR 0.98, 95%CI 0.68 to 1.40), or glucocorticoids (OR 1.07, 95%CI 0.64 to 1.77), with the risk of serious post-partum infections (Table 2). The results were similar when maternal factors were included (model 2), specifically, the association between biologics exposure and serious post-partum infections had an adjusted OR [aOR] of 0.79 (95%CI 0.24 to 2.54), DMARD/ immunosuppressants had an aOR of 0.98 (95%CI 0.68 to 1.40), and glucocorticoids an aOR of 1.00 (95%CI 0.60 to 1.67) (Table 2). In this model, we also found several independent maternal factors that were significantly associated with either increased or decreased post-partum infections; having an anxiety diagnosis, more previous hospitalizations, higher BMI at conception, and delivering via Cesarean section were all factors that increased the risk of serious

infection; while being multiparous appeared protective. Results from sensitivity analysis using HDPS-matching and logistic regression had higher uncertainty due to a wide confidence interval (model 3).

In infants exposed to biologics in utero, proportion of serious infections ranged from 0 to 7% depending on the treatment combination used by the mother during pregnancy (Figure 3). The types of serious infections that occurred during infants' first year of life were lymphadenitis, urinary tract infection, and acute bronchiolitis. In model 1 examining categories of maternal drug exposures only, we found no increased risk of serious infections in infants who were exposed to biologics (OR 0.50, 95%CI 0.16 to 1.60), or DMARDs (OR 1.07, 95%CI 0.81 to 1.43) in utero, while glucocorticoids exposure appeared to possibly increase risk (OR 1.46, 95%CI 1.00 to 2.12). When maternal and infant factors were considered (model 2), the risk of serious infections associated with biologics exposure had an aOR of 0.56 (95%CI 0.17 to 1.81), DMARD/immunosuppressants had an aOR of 1.09 (95%CI 0.81 to 1.45), and glucocorticoids an aOR of 1.13 (95%CI 0.77 to 1.66) (Table 3). However, we found several maternal factors associated with an increased risk of infections in infants, including multiparity, maternal history of prior delivery resulting in a low birth weight infant, or premature infant, maternal use of anxiolytics, and maternal asthma diagnosis (Table 3). Factors associated with a lower risk of serious infections included being a female infant, having higher Apgar score at 1 minute, higher neighborhood income, and more antenatal visits. Sensitivity analysis using logistic regression in the HDPS-matched cohort did not change these results (model 3).

## Discussion

In this study using linked administrative health data and a perinatal registry for a population-based cohort of women with autoimmune disease and their babies, we examined the association between

exposure to biologics during pregnancy and risk of serious infections in mothers and infants, respectively. Specifically for mothers, these were infections requiring hospitalization during the post-partum period; and for infants, these were infections requiring hospitalization during their first year of life. We found that the proportion of serious infections in all groups was low. Our findings suggest that there was no difference in risk of serious post-partum infections in women who used biologics during pregnancy versus those who did not. Similarly, we did not observe a difference in risk of serious infections during the first year of life in infants born to mothers who used biologics during pregnancy compared to those who did not. While we examined all biologics used in the cohort, TNF-alpha inhibitor biologics (94%) were the most common, and as such our results mostly apply to these biologics and less so to those that are not TNF-alpha inhibitors.

Indeed serious infections are a well-known safety outcome in patients using biologics to manage their autoimmune diseases, and despite pregnant women and infants being vulnerable populations there has been a dearth of evidence on this clinically important topic. One population-based study in the United States by Desai et al. compared serious intrapartum infections among 776 users of biologics compared to 1587 users of non-biologics and reported no meaningful increase risk of serious infection during pregnancy (adjusted hazard ratio [aHR] 1.36, 95%CI 0.47 to 3.93) (25). However, the authors did observe that the rate of infections increased noticeably in all treatment groups as pregnancies approached term (25), thus, providing a rationale for the objective of our study which examined the risk of infections around the time of childbirth, and post-partum. No other studies to date have specifically investigated the association between biologics use and the risk of post-partum infections despite the fact that post-partum infections account for up to 10% of maternal deaths, and are a cause of short term morbidity and long term complications (26). It is

therefore reassuring that our study did not show an association between biologics use during pregnancy and maternal risk of post-partum infections.

Infections is a theoretical concern in infants exposed to biologics in utero, due to evidence of accumulation of certain biologics in cord blood (10). The immunosuppressive effect of TNF-alpha inhibitor accumulation is illustrated by a fatal case of disseminated Bacillus Calmette–Guérin (BCG) infection after BCG vaccination in an infant born to a mother treated with infliximab throughout her pregnancy (27). The infant received a BCG vaccination at 3 months of age, subsequently became ill, and died at 4.5 months of age from disseminated infection (27). Current recommendations to stop some biologics in the third trimester are largely based on such case reports and expert opinion (28). To date, there have only been two published abstracts examining the association of biologics exposure and risk of serious infections in infants. Using data collected by the Organization of Teratology Information Specialists (OTIS), Chambers et al. found similar proportions of serious infections during the first year of life in infants born to women with RA using biologics during pregnancy (2.8%), compared to those born to women with RA not treated with a biologic (3.9%), with a relative risk of 0.71 (95%CI 0.30 to 1.71) (29). In a registry of women with IBD, Chaparro et al. found that after a median follow up of 33 months post-partum, similarly, infants exposed to biologics in utero were not at greater risk of serious infections (HR 0.5, 95%CI 0.2 to 1.3) (30). Our study is the first to corroborate these results using population-based data.

This study has a number of strengths and limitations. The use of population-wide databases with high coverage lends this study greater generalizability; linkages between databases containing valid information on all dispensed prescriptions (PharmaNet) and antenatal, intrapartum, and postpartum maternal and infant information (BCPDR) provides the ability to accurately determine the timing of

all medication dispensations with respect to conception dates. Linkages between maternal and infant data allows for ascertainment of infant exposure status in utero. Altogether, these strengths minimize potential biases caused by problems such as selection bias, patient recall bias, reporting bias, and exposure misclassification.

The main limitation of our study stems from the uncertainty of risk estimates attributable to the relatively small sample size of the exposed, as such, a doubling to tripling in the risk of serious infections remains compatible with the upper bound of the confidence intervals of our estimates. With respect to exposure, while prescription dispensations does not necessarily equate to medication use, research by the EuroMAP Group has shown that pregnant women report taking 43-50% of their prescribed medications, a level of medication adherence consistent with non-pregnant populations, and that adherence tends to be higher (70–100%) for drugs used in the treatment of chronic diseases in this population (31). Our previous studies have shown that the proportion of women discontinuing their biologic became more prevalent as pregnancy progressed resulting in fewer women being exposed close to delivery, which could be an explanation for the low numbers of outcomes observed (21). Also due to the rare occurrence of the outcomes of interest, subgroup analyses of specific biologics, or specific autoimmune disease types were not possible. Other limitations included potential misclassification of the outcome, as a code for an infection could have been in any diagnostic field in the discharge abstract data and may not have been the primary reason for hospitalization. Furthermore, we could not obtain any data on breastfeeding practices which has been shown to be protective against infections requiring hospitalizations (32), other potentially important factors that were unavailable included maternal smoking status and alcohol or other substance use. However, our findings of other factors independently associated with serious infections, such as maternal BMI (33), Cesarean section delivery (34,35), infant gender (36), and

maternal asthma diagnosis (37), are consistent with that reported in literature and thus lend validity to our results. Finally, although we used HDPS approaches in sensitivity analyses to address confounding by indication, an inherent limitation of administrative data, such as those used in our study, is that they do not provide clinical information to allow assessment of disease severity.

In conclusion, from this population-based cohort we did not observe differences in the risk of serious infections in women using or not using TNF-alpha inhibitor biologics during pregnancies or in their offspring during the first year of life. Our findings are compatible with current recommendations where discontinuation of TNF-alpha inhibitor biologics late in the pregnancy could be considered, or if indicated, can be continued throughout the pregnancy (28,38). Our study provides information for clinicians and women with autoimmune diseases regarding the risks of serious infections when using biologics during pregnancy.

**Author Statement**

Dr. Tsao had full access to all the data used in this study and takes responsibility for the integrity of the data and accuracy of data analysis. As the lead author, Dr. Tsao affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. Contributions of authors to this study are as follows, for concept and design: De Vera, Tsao; acquisition, analysis, and interpretation of data: De Vera, Tsao, Sayre; drafting of manuscript: Tsao, De Vera; critical revision of manuscript for important intellectual content: Tsao, De Vera, Sadatsafavi, Hanley, Lynd; statistical analysis: Tsao, Sayre; obtained funding: De Vera. Dr. Lynd has received honoraria from Boehringer Ingelheim and Pfizer Canada for consulting services unrelated to this study, all other authors have declared no support from any

organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

**Data Sharing Statement**

Due to privacy agreements, data used in this study cannot be shared.

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**Conflicts of Interest**

Dr. Larry Lynd has received honoraria from Boehringer Ingelheim and Pfizer Canada for consulting services unrelated to this study. All other authors have declared no support from any organization for the submitted work.

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## Tables and Figures

**Figure 1. Schematic diagram of databases and linkages facilitating study analyses**

**Table 1. Characteristics of moms and infants in pregnancies exposed and unexposed to biologics**

| Maternal Characteristics | Biologic exposed | Biologic unexposed | p-value |
|---|---|---|---|
| **Current pregnancy** | | | |
| Maternal age at delivery (mean (SD)) | 31.0 (4.7) | 31.2 (5.2) | 0.657 |
| Multiparous | 44 (44%) | 4998 (59%) | 0.003 |
| Antenatal visits (mean (SD)) | 8.9 (3.6) | 9.0 (3.9) | 0.749 |
| Gestational hypertension | 5 (5%) | 647 (8%) | 0.328 |
| Gestational diabetes | 12 (12%) | 669 (8%) | 0.128 |
| Delivery via Cesarean section | 40 (40%) | 2849 (33%) | 0.171 |
| Neighbourhood income quintiles | | | |
| 5$^{th}$ percentile | 21 (21%) | 1763 (21%) | 0.836 |
| 25$^{th}$ percentile | 24 (24%) | 1699 (20%) | |
| Median (50$^{th}$ percentile) | 17 (17%) | 1845 (22%) | |
| 75$^{th}$ percentile | 22 (22%) | 1803 (21%) | |
| 95$^{th}$ percentile | 16 (16%) | 1397 (16%) | |
| Hospitalization at baseline | 99 (99%) | 8412 (99%) | 0.912 |
| BMI at baseline (mean (SD)) | 24.7 (4.6) | 24.6 (4.5) | 0.867 |
| BMI categories | | | |
| Obese | 9 (9%) | 851 (10%) | 0.979 |
| Overweight | 15 (15%) | 1342 (16%) | |
| **Prior obstetrical history** | | | |
| Premature delivery | 5 (5%) | 500 (6%) | 0.711 |
| Spontaneous abortion | 28 (28%) | 2230 (26%) | 0.686 |
| Delivery with neonatal death | <5$^{\dagger}$ | 52 (0.6%) | 0.621 |
| Stillbirth | <5$^{\dagger}$ | 103 (1%) | 0.107 |
| Low birth weight infant | 5 (5%) | 243 (3%) | 0.203 |
| Infant with anomalies | 0 (0%) | 74 (1%) | 0.349 |
| **Autoimmune disease type*** | | | |
| Inflammatory bowel disease | 50 (50%) | 2471 (29%) | <0.001 |
| Rheumatoid arthritis | 44 (44%) | 1756 (21%) | <0.001 |
| Psoriasis/psoriatic arthritis | 16 (16%) | 3441 (40%) | <0.001 |
| Juvenile idiopathic arthritis | 8 (8%) | 93 (1%) | <0.001 |

| | | | |
|---|---|---|---|
| Systemic autoimmune rheumatic diseases | 5 (5%) | 1063 (12%) | 0.024 |
| Ankylosing spondylitis | 5 (5%) | 417 (5%) | 0.964 |
| **Biologics‡** | | | |
| Infliximab | 54 (54%) | | |
| Etanercept | 41 (41%) | | |
| Adalimumab | 39 (39%) | | |
| Other biologic** | 18 (18%) | | |
| **Concomitant medications** | | | |
| DMARDs | 53 (53%) | 1843 (22%) | <0.001 |
| Glucocorticoids | 54 (54%) | 1065 (13%) | <0.001 |
| Traditional NSAIDs | 16 (16%) | 941 (11%) | 0.118 |
| Antidepressants | 16 (16%) | 783 (9%) | 0.020 |
| Anxiolytics | <5† | 394 (5%) | 0.765 |
| COX2 NSAIDs | <5† | 56 (0.7%) | <0.001 |
| **Comorbidities** | | | |
| Anxiety | 19 (19%) | 1368 (16%) | 0.430 |
| Mood disorders | 10 (10%) | 432 (5%) | 0.027 |
| Asthma | <5† | 154 (2%) | 0.888 |
| Diabetes | <5† | 563 (6.6%) | 0.294 |
| Hypertension | 6 (6%) | 975 (11.5%) | 0.088 |
| **Infant Characteristics** | **Biologic exposed** | **Biologic unexposed** | |
| Female sex | 55 (55%) | 4159 (49%) | 0.224 |
| Gestational age (mean (SD)) | 37.8 weeks (2.4) | 38.4 weeks (2.2) | 0.004 |
| Birth weight (mean (SD)) | 3158 grams (634) | 3385 grams (204) | <0.001 |
| Apgar score at 1 minute (mean (SD)) | 8.1 (1.6) | 8.0 (1.7) | 0.730 |
| Apgar score at 5 minutes (mean (SD)) | 8.9 (1.1) | 9.0 (1.0) | 0.595 |

SD = standard deviation, BMI = body mass index, DMARDs = disease modifying anti-rheumatic drugs, NSAIDs = non-steroidal anti-inflammatory drugs, COX = cyclooxygenase

*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

††p-values based on t-tests or Chi-square tests

**Figure 2. Rates of maternal post-partum serious infections based on drug exposure categories**

**Figure 3. Rates of infant serious infections during the first year of life based on in utero drug exposure categories**

**Table 2. Risk of serious maternal post-partum infections associated with biologics exposure during pregnancy**

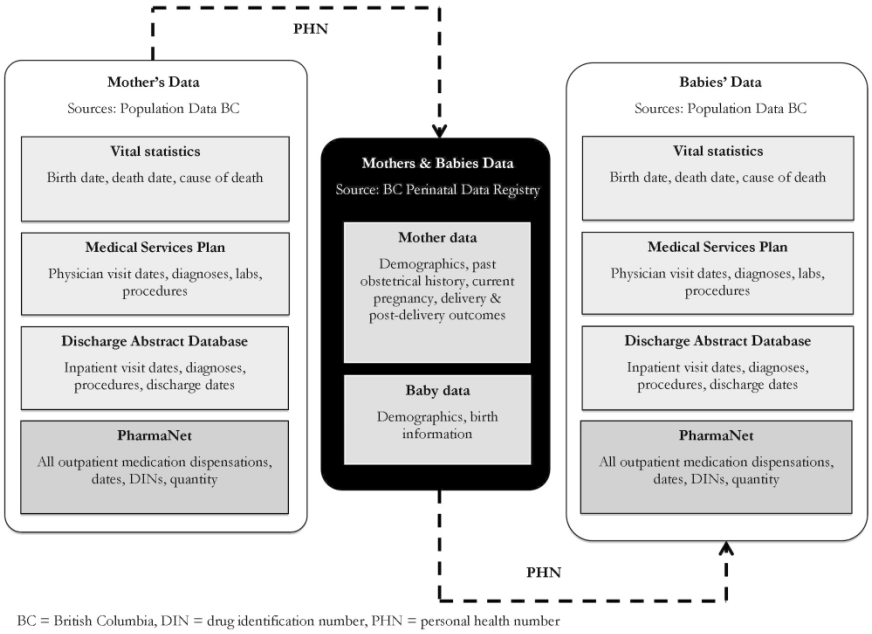
| | Maternal serious infections | |
|---|---|---|
| | **Parameter** | **OR (95% CI)** |
| **Unadjusted** | Biologics | 0.90 (0.28 to 2.84) |
| **Model 1** | Biologics | 0.88 (0.27 to 2.82) |
| | DMARDs/immunosuppressants | 0.98 (0.68 to 1.40) |
| | Glucocorticoids | 1.07 (0.64 to 1.77) |
| **Model 2** | Biologics | 0.79 (0.24 to 2.54) |
| | DMARDs/immunosuppressants | 0.98 (0.68 to 1.40) |
| | Glucocorticoids | 1.00 (0.60 to 1.67) |
| | Multiparity | 0.60 (0.47 to 0.76) |
| | Anxiety | 1.36 (1.02 to 1.82) |
| | Prior hospital admissions | 1.19 (1.06 to 1.34) |
| | BMI at baseline | 1.02 (1.00 to 1.05) |
| | Cesarean section delivery | 2.01 (1.58 to 2.55) |
| **Model 3 HDPS-matched cohort** | Biologics | 1.16 (0.34 to 4.14) |

OR = odds ratio, HDPS = high-dimensional propensity score, DMARDs = disease modifying anti-rheumatic drugs, BMI = body mass index

**Table 3. Risk of serious infant infections during the first year of life associated with biologics exposure in utero**

| | Infant serious infections | |
|---|---|---|
| | **Parameter** | **OR (95% CI)** |
| **Unadjusted** | Biologics | 0.58 (0.18 to 1.85) |
| **Model 1** | Biologics | 0.50 (0.16 to 1.60) |
| | DMARDs/immunosuppressants | 1.07 (0.81 to 1.43) |
| | Glucocorticoids | 1.46 (1.00 to 2.12) |
| **Model 2** | Biologics | 0.56 (0.17 to 1.81) |
| | DMARDs/immunosuppressants | 1.09 (0.81 to 1.45) |
| | Glucocorticoids | 1.13 (0.77 to 1.66) |
| | Female sex | 0.73 (0.60 to 0.89) |
| | Multiparity | 1.56 (1.25 to 1.95) |
| | Maternal antenatal visits | 0.97 (0.94 to 0.99) |
| | Prior delivery with anomaly | 2.04 (0.98 to 4.26) |
| | Prior delivery with low birth weight | 1.67 (1.05 to 2.64) |
| | Prior premature delivery | 1.73 (1.21 to 2.47) |
| | Maternal anti-depressant use | 1.30 (0.97 to 1.75) |
| | Maternal anxiolytics use | 1.66 (1.15 to 2.40) |
| | Maternal rheumatoid arthritis diagnosis | 1.17 (0.93 to 1.47) |
| | Maternal asthma diagnosis | 2.00 (1.18 to 3.39) |
| | Apgar score at 1 minute | 0.87 (0.83 to 0.92) |
| | Neighbourhood income quintile | 0.91 (0.85 to 0.98) |
| **Model 3 HDPS-matched cohort** | Biologics | 0.49 (0.15 to 1.62) |

OR = odds ratio, HDPS = high-dimensional propensity score, DMARDs = disease modifying anti-rheumatic drugs




BC = British Columbia, DIN = drug identification number, PHN = personal health number

Figure 1. Schematic diagram of databases and linkages facilitating study analyses

215x279mm (300 x 300 DPI)

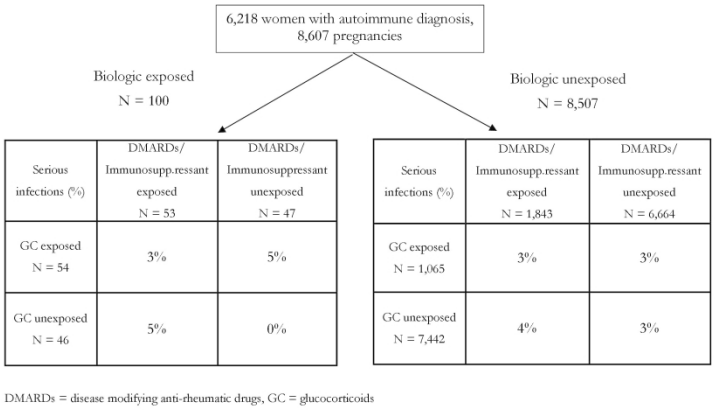



Figure 2. Rates of maternal post-partum serious infections based on drug exposure categories

279x215mm (300 x 300 DPI)

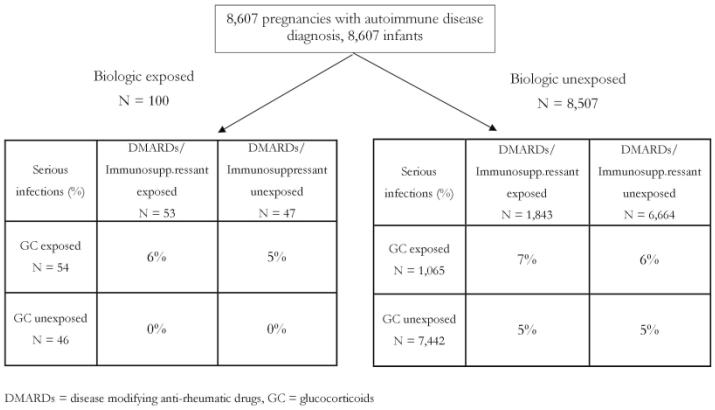



Figure 3. Rates of infant serious infections during the first year of life based on in utero drug exposure categories

279x215mm (300 x 300 DPI)

## Supplementary Materials

### Table S1. List of biologics, disease-modifying agents, immunosuppressive agents, and corticosteroids considered for inclusion

| | |
|---|---|
| Biologics | abatacept, adalimumab, alefacept, anakinra, belimumab, certolizumab pegol, etanercept, golimumab, infliximab, natalizumab, rituximab, tocilizumab, and ustekinumab. |
| Disease-modifying and immunosuppressive agents | 5-aminosalycylic acid, 6-mercaptopurine, apremilast, azathioprine, cyclophosphamide, cyclosporine, hydroxychloroquine, leflunomide, methotrexate, minocycline, mycophenolate mofetil, and sulfasalazine. |
| Corticosteroids* | Betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, prednisolone, and triamcinolone. |

* Only systemically administered agents included, excluded if route of administration is topical

### Table S2. Infections and corresponding ICD-9 and -10 codes for outcomes ascertainment

| Infection types | ICD-9 Codes | ICD-10 codes |
|---|---|---|
| Respiratory infections (acute respiratory infections, pneumonia, influenza) | 460-466; 480-488 | J00-J06, J09-J18, J20-J22 |
| Urogenital infections (cystitis, urethritis [not sexually transmitted], kidney infections, prostatitis, orchitis, epididymitis, vaginitis, other infections originating in the perinatal period) | 590, 597, 599, 601.0-601.4, 604, 616.1-616.4, 647, 670, 760.2, 771 | N30, N34, N37.0, N39.0, N41.0, N41.3, N45, N76.0, N76.2, N77, P35-P39 |
| Skin and soft tissue infections (cellulitis, impetigo, herpes virus, varicella zoster virus) | 680-686, 053, 054 | L00-L08 |
| Obstetrics-related infections* (infection of amniotic cavity, major puerperal infxn, inflammatory disease of uterus, unspec inflammatory disease of uterus, infxn of GU tract in pregnancy, maternal pyrexia during labour, generalized infxn during labour, pyrexia unknown during puerperium, septicemia, other infxn) | 658.4, 670.0, 615.0, 615.9, 646.6, 659.2, 659.3, 672.0, 038, 999.3, 041 | O41.1, O85.x, O86.x, N71.0, N71.9, O23.x, O75.2, O75.3, A40, A41 |

*Applied to maternal infections analyses only

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No | Recommendation | Page numbers |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | Page 1, title |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Page 3, abstract |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | Page 6 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | Page 7, top |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | Page 3, abstract; Pages 7-10, methods |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Pages 7, 8, data sources and study cohort |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | Page 8, study cohort and exposure definition |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | Pages 8-10, exposure, outcome and covariates |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | Pages 8-10, exposure, outcome and covariates |
| Bias | 9 | Describe any efforts to address potential sources of bias | Pages 9, 10, statistical analysis and sensitivity analysis |
| Study size | 10 | Explain how the study size was arrived at | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | Page 9, 10, covariates |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | Page 10, 11, statistical analysis |
| | | (*b*) Describe any methods used to examine subgroups and interactions | |
| | | (*c*) Explain how missing data were addressed | |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | |
| | | (*e*) Describe any sensitivity analyses | Page 10, 11, statistical analysis |

Continued on next page

| | | | |
|---|---|---|---|
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Page 11, results; Figures 2 and 3 |
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Page 11, 12, results; Table 1 |
| | | (b) Indicate number of participants with missing data for each variable of interest | Page 8, 9, methods (follow up defined in methods, there were no losses to follow up |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | Page 11-13, results; Figures 2 and 3 |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Tables 2 and 3 |
| | | (*b*) Report category boundaries when continuous variables were categorized | Pages 9-10, covariates |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | Tables 2 and 3 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | Page 13 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Pages 15, 16 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | Pages 15, 16 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | Page 16 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Page 2, end |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

# Use of biologics during pregnancy and risk of serious infections in the mother and baby: A Canadian population-based cohort study

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| | |

# Use of biologics during pregnancy and risk of serious infections in the mother and baby: A Canadian population-based cohort study

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## Abstract

**Objectives:** To investigate the association between exposure to biologics during pregnancy and serious infections in mothers and infants.

**Design:** Retrospective cohort study

**Setting:** Population-based

**Participants:** Women with one or more autoimmune diseases identified by International Classification of Diseases 9th /10th revision codes in healthcare administrative databases in British Columbia, Canada, who had pregnancies ending in a live or still birth between January 1st, 2002 and December 31st, 2012. Women were defined as exposed if they had at least one biologic prescription during pregnancy, and infants born to these women were considered exposed in utero. Disease-matched women with no biologics prescriptions during pregnancy, and their infants, comprised the unexposed groups.

**Primary outcome measures:** Serious infections requiring hospitalization.

**Results:** Over the 10-year study period, there were 6,218 women (8,607 pregnancies) who had an autoimmune disease diagnosis; of which 90 women were exposed to biologics during pregnancy, with 100 babies born to these women. Among women exposed to biologics during pregnancy, occurrence of serious post-partum infections were low, ranging from 0 to 5%, depending on concomitant exposures to immunosuppressants. In multivariable models using logistic regression, the adjusted odds ratio (aOR) for the association of biologics exposure with serious maternal post-partum infections was 0.79 (95% confidence interval [CI] 0.24 to 2.54). In infants exposed to biologics in utero, occurrence of serious infections during the first year of life ranged from 0 to 7%, depending on concomitant exposures to immunosuppressants in utero. Multivariable models showed no association between biologics exposure in utero and serious infant infections (aOR 0.56, 95%CI 0.17 to 1.81).

**Conclusions:** These population-based data suggest that the use of biologics by women with autoimmune diseases during pregnancy is not associated with an increased risk of serious infections in mothers, during post-partum, or in infants during the first year of life.

## Article Summary

### Strengths and limitations of this study

- This is the first population-based cohort study to examine the risk of serious post-partum infections in mothers who were using biologics during pregnancy, and in infants exposed in utero.
- We used individual-level, de-identified, longitudinal data on all health services (physician visits, hospitalizations, and prescription medications) covering the entire population of the province, linked with a perinatal registry covering >99% of births.
- We used high-dimensional propensity score matching as a sensitivity analysis to the traditional multivariable models.
- The data sources come from administrative databases not primarily collected for research purposes and thus rely on accuracy of diagnostic coding.
- Exposures and outcomes remain relatively rare and as such, caution should be exercised when interpreting the findings in light of this context.

## Introduction

Biologics have revolutionized the management of several autoimmune chronic conditions, and are commonly used in inflammatory arthritis including rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA) as well as inflammatory bowel disease (IBD, ulcerative colitis and Crohn's disease) (1,2). They are typically genetically engineered parts of, or whole, immunoglobulin Gs (IgG) that inhibit specific components of the immune system that play pivotal roles in inflammation (3). Despite their established efficacy in managing autoimmune diseases, treatment with biologics is not without risks. Network meta-analyses show a significant increase in serious infections in RA patients treated with biologics alone (odds ratio [OR] 1.31; 95% credible interval 1.09 to 1.58) or in combination with traditional disease modifying anti-rheumatic drugs (DMARDs) (OR 1.34; 95% confidence interval [CI] 1.09 to 1.69) compared to DMARDs alone (4).

In pregnancy, infection risk is a unique safety outcome in that it can occur both in the mother and her infant possibly as a result of exposure to the same offending agent. Additionally, the risk of infections may already be elevated for the mother during the delivery and post-partum periods, and for the neonate after birth when their immune system is still naïve. During pregnancy, IgG is transferred from the maternal to the fetal circulation by receptor-mediated binding of the Fcγ portion of the IgG molecule and it's receptor, FcRn (Fc receptor neonatal) (5–7). The FcRn is also found to have a protective effect on IgG degradation, extending its lifespan, leading to accumulation in the infant for upwards of six to eight months (8). With infliximab and adalimumab having higher affinity for FcRn (9), levels of these biologics in offspring cord blood have been reported to be 300-400% higher than levels in the maternal circulation (10). Furthermore, detectable, and even therapeutic, levels of biologics in infant serum have been confirmed in case reports of infants exposed in utero (10–12). However, to date few epidemiologic studies have examined the risk of

infections in women using biologics during pregnancy, or in infants that were exposed to biologics in utero. Our objectives were to investigate the association between exposure to biologics during pregnancy and serious infections in 1) mothers during the post-partum period; and 2) infants during the first year of life.

## Methods

### Data sources

Data for mothers and babies were obtained through Population Data BC, a repository of individual-level, de-identified, longitudinal data on all health services covering the entire population of BC (estimated 4.6 million residents, December 2016 (13)). Specifically, respective data for mothers and babies comprised four linked databases including: 1) Medical Services Plan (MSP) database – all provincially-funded physician visits, ordered laboratory tests and diagnostic procedures (x-rays, ultrasounds etc.) (14); 2) Discharge Abstract Database (DAD) – all hospital admissions and discharges (15); 3) PharmaNet – a comprehensive prescription drug database that captures all prescriptions dispensed in community pharmacies regardless of payment source, since 1996 (16); and 4) BC Perinatal Database Registry (BCPDR) - facilitated the linkage between mothers' and babies' data. The BCPDR contains data abstracted from obstetrical and neonatal medical records on nearly 100% of births in the province of BC from over 60 acute care facilities as well as births occurring at home attended by BC registered midwives, including women who had pregnancies ending in a live or still birth of at least 20 weeks gestation or 500 grams birth weight (17–20). Details of these data sources are described in previous work (21) and databases and linkages are shown in Figure 1.

### Study cohort

The source population comprised of women in BC who had 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 requirement of continuous insurance coverage ensures that we have complete data capture for all women and babies in our study population. We created a cohort of women from the source population who had a recorded diagnosis of one or more autoimmune diseases that could be treated with a biologic, including RA, IBD (Crohn's disease and ulcerative colitis), psoriasis (Ps)/PsA, AS, juvenile idiopathic arthritis, and systemic autoimmune rheumatic diseases. Women were considered to have been diagnosed with one of these conditions of they had the same International Classification of Diseases (ICD)-9$^{th}$ revision or 10$^{th}$ revision codes 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 at least one hospitalization with an ICD-9/10 code for an autoimmune disease any time prior to the date of conception (21). Given that the unit of analysis was individual pregnancy, each pregnancy had to satisfy the above criteria in order to be included in the analyses. All singleton live born infants from these pregnancies were included in the analyses of infant serious infections.



Biologics exposure

Using dispensation dates and Canadian Drug Identity Codes for biologics in PharmaNet linked with date of conception and date of delivery of each pregnancy in the BCPDR, exposure to biologics was identified in any woman in the autoimmune disease cohort with one or more prescriptions for a biologic anytime from the date of conception to the date of delivery (21). Infants born from these pregnancies were classified as being exposed to biologics in utero. Pregnancies that did not satisfy this criteria and infants born from those pregnancies were considered unexposed. All biologics

available in BC for the treatment of autoimmune diseases of interest during the study period, along with concomitant medications considered in this study, are listed in Supplementary Table S1.

Serious infections

The outcomes of interest were serious infections requiring hospitalization during the post-partum period in women, and serious infections requiring hospitalization anytime during the first year of life in infants. Serious post-partum infections were defined as any episode of hospitalization, including the delivery episode, with one or more ICD-9/10 codes for an infection anytime from the date of delivery until 42 days post-partum – the conventional definition for post-partum period of concern (22). Serious infections in infants were defined as any episode of hospitalization with one or more ICD-9/10 codes for an infection anytime during the first year of life – due to the lengthy accumulation of biologics in infant circulation – or until death, whichever occurred first. All infections considered are listed in Supplementary Table S2.

Covariates

All covariates considered were from the aforementioned data sources. Maternal factors included characteristics of current pregnancy, prior obstetrical history, comorbidities, and medication use. Characteristics of current pregnancy included maternal age at delivery (continuous), parity (primiparous or multiparous), neighborhood income quintile (based on postal code) at baseline, body mass index (BMI) at first antenatal visit (continuous; and categorical as underweight: <18.5, normal: 18.5-24.9, overweight: 25-29.9, obese: ≥30 kg/m$^2$), weight gain during pregnancy (binary, based on guidelines for weight gain during pregnancy by BMI category (23)), number of antenatal visits (continuous), and hospitalization at baseline (binary), and delivery by cesarean section (binary). Prior obstetrical history included binary outcomes from previous pregnancies (if applicable)

including premature delivery, spontaneous abortions, neonatal death, stillbirth, low birth weight, and congenital anomalies. Comorbidities considered included gestational hypertension, gestational diabetes, anxiety disorders, mood disorders, asthma, hypertension, and diabetes. Concomitant medications included DMARDs or immunosuppressants, glucocorticoids, antidepressants, anxiolytics, traditional and COX-2 non-steroidal anti-inflammatory drugs (NSAIDs). All maternal factors considered in analyses of post-partum infections in the mother that could be associated with serious infections in infants were also considered in analyses of this latter outcome in addition to infant characteristics. Infant characteristics included sex and Apgar scores at 1 minute, 5 minutes, and 10 minutes (continuous). Other infant characteristics including gestational age, birth weight, and presence of anomalies were considered but not included in the analysis as they may be possible mediators of the effect of exposure on serious infections in infants.

Statistical Analysis

Using logistic regression models we calculated ORs with 95% CIs between maternal exposure to biologics during pregnancy and the risk of serious post-partum infections in women, and the risk of serious infant infections during the first year of life; first as unadjusted models, by treatment categories only (model 1) and then adjusted for maternal and infant characteristics according to respective outcome (model 2). Multivariable models were constructed using forward selection and covariates were included in the final models if they were associated with the exposure in bivariate analyses and resulted in lower Akaike Information Criterion upon inclusion. Multivariable regression analyses using generalized estimating equation models with logit link and clustered by mother could not be completed as models did not converge. However, previous work on a larger sample from our source population showed that accounting for correlations between multiple pregnancies within the same woman did not appreciably change effect estimates and confidence intervals (21).

As a sensitivity analysis, we estimated propensity for biologics exposure in each pregnancy using a high dimensional propensity score (HDPS) algorithm that incorporated investigator-specified covariates and additional factors that acted as proxy variables for unmeasured confounders from the four aforementioned data dimensions (model 3) (24). These variables included use of medications (e.g. DMARDs, glucocorticoids), comorbidities (e.g. depression), and healthcare utilization (e.g. outpatient visits, prenatal care, and tests and investigations. The HDPS was calculated using logistic regression then each biologic exposed pregnancy was matched with five unexposed pregnancies (1:5 ratio) without replacement, based on HDPS, whereby an unexposed pregnancy may only be used once as a match. Match performance was evaluated by comparing the standardized mean differences in baseline characteristics of matched and unmatched cohorts. Odds ratios and 95% CIs for biologics exposure and serious post-partum infections, and serious infant infections were calculated using logistic regression in the HDPS-matched samples. All analyses were conducted using SAS statistical software v.9.3 (Cary, NC, USA).

Study Conduct

This study was approved by the University of British Columbia, Behavioural Research Ethics Board. 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. Due to data sharing agreements and confidentiality, cell sizes of less than five individuals are not reported.

Patient and Public Involvement

Patients were not involved in the design, recruitment, or conduct of the study as this is a retrospective cohort study using population-wide administrative data.

## Results

In the cohort of 6,218 women with autoimmune inflammatory disease diagnoses and 8,607 singleton pregnancies, there were 90 women exposed to biologics during pregnancy, and 100 babies born to these women. As shown in Table 1, in the biologics exposed group, more women had IBD or RA, used at least one DMARD or glucocorticoid, or had mood disorders; whereas in the group not exposed to biologics during pregnancy, more women had Ps/PsA and were multiparous. Also shown in Table 1, infants from pregnancies that were unexposed to biologics had more advanced gestational age and higher birth weight.

Among women exposed to biologics during pregnancy, occurrence of serious post-partum infections were rare, ranging from 0 to 5%, depending on concomitant exposures to DMARDs or glucocorticoids (Figure 2). Serious infections that occurred in those exposed to biologics included infection of the amniotic sac and membranes, and bacterial puerperal infections. In model 1 looking only at drug exposures, we found no independent associations between the use of biologics (OR 0.88, 95%CI 0.27 to 2.82), DMARDs (OR 0.98, 95%CI 0.68 to 1.40), or glucocorticoids (OR 1.07, 95%CI 0.64 to 1.77), with the risk of serious post-partum infections (Table 2). The results were similar when maternal factors were included (model 2), specifically, the association between biologics exposure and serious post-partum infections had an adjusted OR [aOR] of 0.79 (95%CI 0.24 to 2.54), DMARD/ immunosuppressants had an aOR of 0.98 (95%CI 0.68 to 1.40), and glucocorticoids an aOR of 1.00 (95%CI 0.60 to 1.67) (Table 2). In this model, we also found several independent maternal factors that were significantly associated with either increased or decreased post-partum infections; having an anxiety diagnosis, more previous hospitalizations, higher BMI at conception, and delivering via Cesarean section were all factors that increased the risk of serious

infection; while being multiparous appeared protective. Results from sensitivity analysis using HDPS-matching and logistic regression had higher uncertainty due to a wide confidence interval (model 3).

In infants exposed to biologics in utero, proportion of serious infections ranged from 0 to 7% depending on the treatment combination used by the mother during pregnancy (Figure 3). The types of serious infections that occurred during infants' first year of life were lymphadenitis, urinary tract infection, and acute bronchiolitis. In model 1 examining categories of maternal drug exposures only, we found no increased risk of serious infections in infants who were exposed to biologics (OR 0.50, 95%CI 0.16 to 1.60), or DMARDs (OR 1.07, 95%CI 0.81 to 1.43) in utero, while glucocorticoids exposure appeared to possibly increase risk (OR 1.46, 95%CI 1.00 to 2.12). When maternal and infant factors were considered (model 2), the risk of serious infections associated with biologics exposure had an aOR of 0.56 (95%CI 0.17 to 1.81), DMARD/immunosuppressants had an aOR of 1.09 (95%CI 0.81 to 1.45), and glucocorticoids an aOR of 1.13 (95%CI 0.77 to 1.66) (Table 3). However, we found several maternal factors associated with an increased risk of infections in infants, including multiparity, maternal history of prior delivery resulting in a low birth weight infant, or premature infant, maternal use of anxiolytics, and maternal asthma diagnosis (Table 3). Factors associated with a lower risk of serious infections included being a female infant, having higher Apgar score at 1 minute, higher neighborhood income, and more antenatal visits. Sensitivity analysis using logistic regression in the HDPS-matched cohort did not change these results (model 3).

## Discussion

In this study using linked administrative health data and a perinatal registry for a population-based cohort of women with autoimmune disease and their babies, we examined the association between

exposure to biologics during pregnancy and risk of serious infections in mothers and infants, respectively. Specifically for mothers, these were infections requiring hospitalization during the post-partum period; and for infants, these were infections requiring hospitalization during their first year of life. We found that the proportion of serious infections in all groups was low. Our findings suggest that there was no difference in risk of serious post-partum infections in women who used biologics during pregnancy versus those who did not. Similarly, we did not observe a difference in risk of serious infections during the first year of life in infants born to mothers who used biologics during pregnancy compared to those who did not. While we examined all biologics used in the cohort, TNF-alpha inhibitor biologics (94%) were the most common, and as such our results mostly apply to these biologics and less so to those that are not TNF-alpha inhibitors.

Indeed serious infections are a well-known safety outcome in patients using biologics to manage their autoimmune diseases, and despite pregnant women and infants being vulnerable populations there has been a dearth of evidence on this clinically important topic. One population-based study in the United States by Desai et al. compared serious intrapartum infections among 776 users of biologics compared to 1587 users of non-biologics and reported no meaningful increase risk of serious infection during pregnancy (adjusted hazard ratio [aHR] 1.36, 95%CI 0.47 to 3.93) (25). However, the authors did observe that the rate of infections increased noticeably in all treatment groups as pregnancies approached term (25), thus, providing a rationale for the objective of our study which examined the risk of infections around the time of childbirth, and post-partum. No other studies to date have specifically investigated the association between biologics use and the risk of post-partum infections despite the fact that post-partum infections account for up to 10% of maternal deaths, and are a cause of short term morbidity and long term complications (26). It is

therefore reassuring that our study did not show an association between biologics use during pregnancy and maternal risk of post-partum infections.

Infections is a theoretical concern in infants exposed to biologics in utero, due to evidence of accumulation of certain biologics in cord blood (10). The immunosuppressive effect of TNF-alpha inhibitor accumulation is illustrated by a fatal case of disseminated Bacillus Calmette–Guérin (BCG) infection after BCG vaccination in an infant born to a mother treated with infliximab throughout her pregnancy (27). The infant received a BCG vaccination at 3 months of age, subsequently became ill, and died at 4.5 months of age from disseminated infection (27). Current recommendations to stop some biologics in the third trimester are largely based on such case reports and expert opinion (28). To date, there have only been two published abstracts examining the association of biologics exposure and risk of serious infections in infants. Using data collected by the Organization of Teratology Information Specialists (OTIS), Chambers et al. found similar proportions of serious infections during the first year of life in infants born to women with RA using biologics during pregnancy (2.8%), compared to those born to women with RA not treated with a biologic (3.9%), with a relative risk of 0.71 (95%CI 0.30 to 1.71) (29). In a registry of women with IBD, Chaparro et al. found that after a median follow up of 33 months post-partum, similarly, infants exposed to biologics in utero were not at greater risk of serious infections (HR 0.5, 95%CI 0.2 to 1.3) (30). Our study is the first to corroborate these results using population-based data.

This study has a number of strengths and limitations. The use of population-wide databases with high coverage lends this study greater generalizability; linkages between databases containing valid information on all dispensed prescriptions (PharmaNet) and antenatal, intrapartum, and postpartum maternal and infant information (BCPDR) provides the ability to accurately determine the timing of

all medication dispensations with respect to conception dates. Linkages between maternal and infant data allows for ascertainment of infant exposure status in utero. Altogether, these strengths minimize potential biases caused by problems such as selection bias, patient recall bias, reporting bias, and exposure misclassification.

The main limitation of our study stems from the uncertainty of risk estimates attributable to the relatively small sample size of the exposed, as such, a doubling to tripling in the risk of serious infections remains compatible with the upper bound of the confidence intervals of our estimates. With respect to exposure, while prescription dispensations does not necessarily equate to medication use, research by the EuroMAP Group has shown that pregnant women report taking 43-50% of their prescribed medications, a level of medication adherence consistent with non-pregnant populations, and that adherence tends to be higher (70–100%) for drugs used in the treatment of chronic diseases in this population (31). Our previous study within the same cohort showed that the proportion of women discontinuing their biologic became larger as pregnancy progressed, resulting in fewer women being exposed close to delivery, which could be an explanation for the low numbers of outcomes observed in this study (21). Also due to the rare occurrence of the outcomes of interest, subgroup analyses of specific biologics, or specific autoimmune disease types were not possible. Other limitations included potential misclassification of the outcome, as a code for an infection could have been in any diagnostic field in the discharge abstract data and may not have been the primary reason for hospitalization. Furthermore, we could not obtain any data on breastfeeding practices which has been shown to be protective against infections requiring hospitalizations (32), other potentially important factors that were unavailable included maternal smoking status and alcohol or other substance use. However, our findings of other factors independently associated with serious infections, such as maternal BMI (33), Cesarean section

delivery (34,35), infant gender (36), and maternal asthma diagnosis (37), are consistent with that reported in literature and thus lend validity to our results. Finally, although we used HDPS approaches in sensitivity analyses to address confounding by indication, an inherent limitation of administrative data, such as those used in our study, is that they do not provide clinical information to allow assessment of disease severity.

In conclusion, from this population-based cohort we did not observe differences in the risk of serious infections in women using or not using TNF-alpha inhibitor biologics during pregnancies or in their offspring during the first year of life. Our findings are compatible with current recommendations where discontinuation of TNF-alpha inhibitor biologics late in the pregnancy could be considered, or if indicated, can be continued throughout the pregnancy (28,38). Our study provides information for clinicians and women with autoimmune diseases regarding the risks of serious infections when using biologics during pregnancy.

**Author Statement**

Dr. Tsao had full access to all the data used in this study and takes responsibility for the integrity of the data and accuracy of data analysis. As the lead author, Dr. Tsao affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. Contributions of authors to this study are as follows, for concept and design: De Vera, Tsao; acquisition, analysis, and interpretation of data: De Vera, Tsao, Sayre; drafting of manuscript: Tsao, De Vera; critical revision of manuscript for important intellectual content: Tsao, De Vera, Sadatsafavi, Hanley, Lynd; statistical analysis: Tsao, Sayre; obtained funding: De Vera. Dr. Lynd has received honoraria from Boehringer Ingelheim and Pfizer Canada for

consulting services unrelated to this study, all other authors have declared no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

**Data Sharing Statement**

Due to privacy agreements, data used in this study cannot be shared.

**Acknowledgements**

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**Conflicts of Interest**

Dr. Larry Lynd has received honoraria from Boehringer Ingelheim and Pfizer Canada for consulting services unrelated to this study. All other authors have declared no support from any organization for the submitted work.

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## Tables and Figures

**Figure 1. Schematic diagram of databases and linkages facilitating study analyses**

**Table 1. Characteristics of moms and infants in pregnancies exposed and unexposed to biologics**

| Maternal Characteristics | Biologic exposed | Biologic unexposed | p-value |
|---|---|---|---|
| **Current pregnancy** | | | |
| Maternal age at delivery (mean (SD)) | 31.0 (4.7) | 31.2 (5.2) | 0.657 |
| Multiparous | 44 (44%) | 4998 (59%) | 0.003 |
| Antenatal visits (mean (SD)) | 8.9 (3.6) | 9.0 (3.9) | 0.749 |
| Gestational hypertension | 5 (5%) | 647 (8%) | 0.328 |
| Gestational diabetes | 12 (12%) | 669 (8%) | 0.128 |
| Delivery via Cesarean section | 40 (40%) | 2849 (33%) | 0.171 |
| Neighbourhood income quintiles | | | |
| 5$^{th}$ percentile | 21 (21%) | 1763 (21%) | 0.836 |
| 25$^{th}$ percentile | 24 (24%) | 1699 (20%) | |
| Median (50$^{th}$ percentile) | 17 (17%) | 1845 (22%) | |
| 75$^{th}$ percentile | 22 (22%) | 1803 (21%) | |
| 95$^{th}$ percentile | 16 (16%) | 1397 (16%) | |
| Hospitalization at baseline | 99 (99%) | 8412 (99%) | 0.912 |
| BMI at baseline (mean (SD)) | 24.7 (4.6) | 24.6 (4.5) | 0.867 |
| BMI categories | | | |
| Obese | 9 (9%) | 851 (10%) | 0.979 |
| Overweight | 15 (15%) | 1342 (16%) | |
| **Prior obstetrical history** | | | |
| Premature delivery | 5 (5%) | 500 (6%) | 0.711 |
| Spontaneous abortion | 28 (28%) | 2230 (26%) | 0.686 |
| Delivery with neonatal death | <5† | 52 (0.6%) | 0.621 |
| Stillbirth | <5† | 103 (1%) | 0.107 |
| Low birth weight infant | 5 (5%) | 243 (3%) | 0.203 |
| Infant with anomalies | 0 (0%) | 74 (1%) | 0.349 |
| **Autoimmune disease type*** | | | |
| Inflammatory bowel disease | 50 (50%) | 2471 (29%) | <0.001 |
| Rheumatoid arthritis | 44 (44%) | 1756 (21%) | <0.001 |
| Psoriasis/psoriatic arthritis | 16 (16%) | 3441 (40%) | <0.001 |
| Juvenile idiopathic arthritis | 8 (8%) | 93 (1%) | <0.001 |

| | | | |
|---|---|---|---|
| Systemic autoimmune rheumatic diseases | 5 (5%) | 1063 (12%) | 0.024 |
| Ankylosing spondylitis | 5 (5%) | 417 (5%) | 0.964 |
| **Biologics‡** | | | |
| Infliximab | 54 (54%) | | |
| Etanercept | 41 (41%) | | |
| Adalimumab | 39 (39%) | | |
| Other biologic** | 18 (18%) | | |
| **Concomitant medications** | | | |
| DMARDs | 53 (53%) | 1843 (22%) | <0.001 |
| Glucocorticoids | 54 (54%) | 1065 (13%) | <0.001 |
| Traditional NSAIDs | 16 (16%) | 941 (11%) | 0.118 |
| Antidepressants | 16 (16%) | 783 (9%) | 0.020 |
| Anxiolytics | <5† | 394 (5%) | 0.765 |
| COX2 NSAIDs | <5† | 56 (0.7%) | <0.001 |
| **Comorbidities** | | | |
| Anxiety | 19 (19%) | 1368 (16%) | 0.430 |
| Mood disorders | 10 (10%) | 432 (5%) | 0.027 |
| Asthma | <5† | 154 (2%) | 0.888 |
| Diabetes | <5† | 563 (6.6%) | 0.294 |
| Hypertension | 6 (6%) | 975 (11.5%) | 0.088 |
| **Infant Characteristics** | **Biologic exposed** | **Biologic unexposed** | |
| Female sex | 55 (55%) | 4159 (49%) | 0.224 |
| Gestational age (mean (SD)) | 37.8 weeks (2.4) | 38.4 weeks (2.2) | 0.004 |
| Birth weight (mean (SD)) | 3158 grams (634) | 3385 grams (204) | <0.001 |
| Apgar score at 1 minute (mean (SD)) | 8.1 (1.6) | 8.0 (1.7) | 0.730 |
| Apgar score at 5 minutes (mean (SD)) | 8.9 (1.1) | 9.0 (1.0) | 0.595 |

SD = standard deviation, BMI = body mass index, DMARDs = disease modifying anti-rheumatic drugs, NSAIDs = non-steroidal anti-inflammatory drugs, COX = cyclooxygenase

*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

††p-values based on t-tests or Chi-square tests

**Figure 2. Rates of maternal post-partum serious infections based on drug exposure categories**

**Figure 3. Rates of infant serious infections during the first year of life based on in utero drug exposure categories**

**Table 2. Risk of serious maternal post-partum infections associated with biologics exposure during pregnancy**

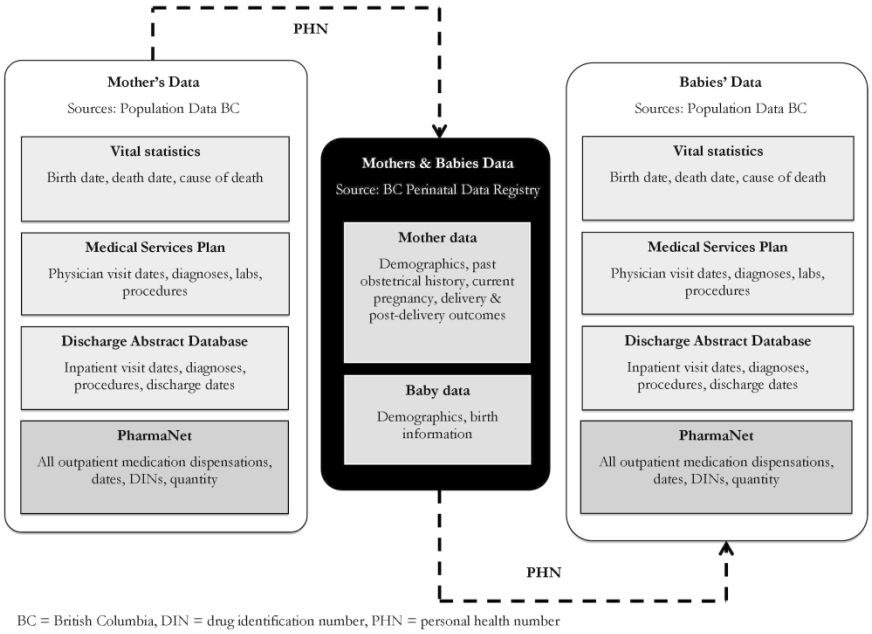
| | Maternal serious infections | |
|---|---|---|
| | **Parameter** | **OR (95% CI)** |
| **Unadjusted** | Biologics | 0.90 (0.28 to 2.84) |
| **Model 1** | Biologics | 0.88 (0.27 to 2.82) |
| | DMARDs/immunosuppressants | 0.98 (0.68 to 1.40) |
| | Glucocorticoids | 1.07 (0.64 to 1.77) |
| **Model 2** | Biologics | 0.79 (0.24 to 2.54) |
| | DMARDs/immunosuppressants | 0.98 (0.68 to 1.40) |
| | Glucocorticoids | 1.00 (0.60 to 1.67) |
| | Multiparity | 0.60 (0.47 to 0.76) |
| | Anxiety | 1.36 (1.02 to 1.82) |
| | Prior hospital admissions | 1.19 (1.06 to 1.34) |
| | BMI at baseline | 1.02 (1.00 to 1.05) |
| | Cesarean section delivery | 2.01 (1.58 to 2.55) |
| **Model 3 HDPS-matched cohort** | Biologics | 1.16 (0.34 to 4.14) |

OR = odds ratio, HDPS = high-dimensional propensity score, DMARDs = disease modifying anti-rheumatic drugs, BMI = body mass index

**Table 3. Risk of serious infant infections during the first year of life associated with biologics exposure in utero**

| | Infant serious infections | |
|---|---|---|
| | **Parameter** | **OR (95% CI)** |
| **Unadjusted** | Biologics | 0.58 (0.18 to 1.85) |
| **Model 1** | Biologics | 0.50 (0.16 to 1.60) |
| | DMARDs/immunosuppressants | 1.07 (0.81 to 1.43) |
| | Glucocorticoids | 1.46 (1.00 to 2.12) |
| **Model 2** | Biologics | 0.56 (0.17 to 1.81) |
| | DMARDs/immunosuppressants | 1.09 (0.81 to 1.45) |
| | Glucocorticoids | 1.13 (0.77 to 1.66) |
| | Female sex | 0.73 (0.60 to 0.89) |
| | Multiparity | 1.56 (1.25 to 1.95) |
| | Maternal antenatal visits | 0.97 (0.94 to 0.99) |
| | Prior delivery with anomaly | 2.04 (0.98 to 4.26) |
| | Prior delivery with low birth weight | 1.67 (1.05 to 2.64) |
| | Prior premature delivery | 1.73 (1.21 to 2.47) |
| | Maternal anti-depressant use | 1.30 (0.97 to 1.75) |
| | Maternal anxiolytics use | 1.66 (1.15 to 2.40) |
| | Maternal rheumatoid arthritis diagnosis | 1.17 (0.93 to 1.47) |
| | Maternal asthma diagnosis | 2.00 (1.18 to 3.39) |
| | Apgar score at 1 minute | 0.87 (0.83 to 0.92) |
| | Neighbourhood income quintile | 0.91 (0.85 to 0.98) |
| **Model 3 HDPS-matched cohort** | Biologics | 0.49 (0.15 to 1.62) |

OR = odds ratio, HDPS = high-dimensional propensity score, DMARDs = disease modifying anti-rheumatic drugs




BC = British Columbia, DIN = drug identification number, PHN = personal health number

Figure 1. Schematic diagram of databases and linkages facilitating study analyses

215x279mm (300 x 300 DPI)

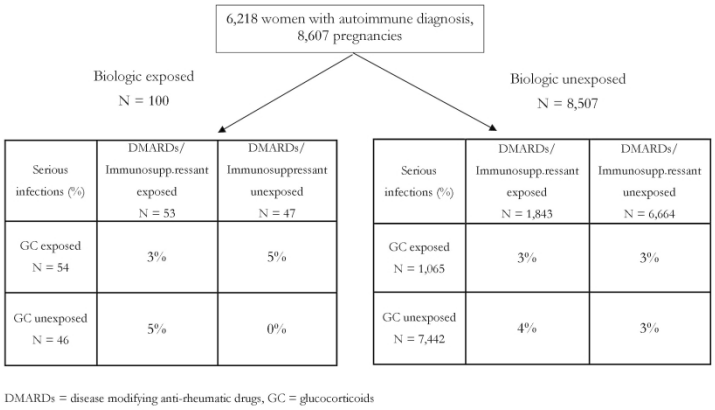



Figure 2. Rates of maternal post-partum serious infections based on drug exposure categories

279x215mm (300 x 300 DPI)

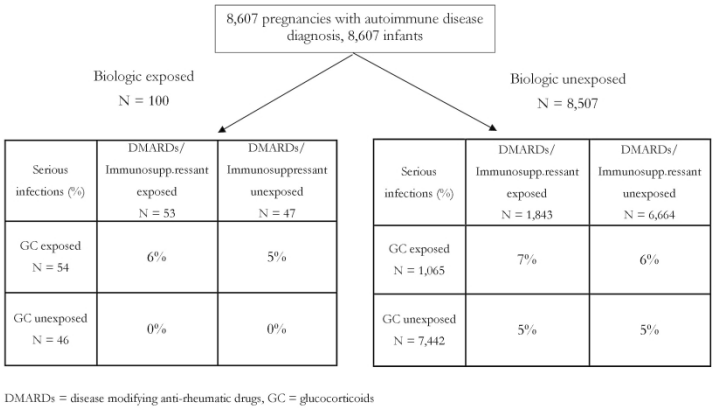



Figure 3. Rates of infant serious infections during the first year of life based on in utero drug exposure categories

279x215mm (300 x 300 DPI)

## Supplementary Materials

### Table S1. List of biologics, disease-modifying agents, immunosuppressive agents, and corticosteroids considered for inclusion

| | |
|---|---|
| Biologics | abatacept, adalimumab, alefacept, anakinra, belimumab, certolizumab pegol, etanercept, golimumab, infliximab, natalizumab, rituximab, tocilizumab, and ustekinumab. |
| Disease-modifying and immunosuppressive agents | 5-aminosalycylic acid, 6-mercaptopurine, apremilast, azathioprine, cyclophosphamide, cyclosporine, hydroxychloroquine, leflunomide, methotrexate, minocycline, mycophenolate mofetil, and sulfasalazine. |
| Corticosteroids* | Betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, prednisolone, and triamcinolone. |

* Only systemically administered agents included, excluded if route of administration is topical

### Table S2. Infections and corresponding ICD-9 and -10 codes for outcomes ascertainment

| Infection types | ICD-9 Codes | ICD-10 codes |
|---|---|---|
| Respiratory infections (acute respiratory infections, pneumonia, influenza) | 460-466; 480-488 | J00-J06, J09-J18, J20-J22 |
| Urogenital infections (cystitis, urethritis [not sexually transmitted], kidney infections, prostatitis, orchitis, epididymitis, vaginitis, other infections originating in the perinatal period) | 590, 597, 599, 601.0-601.4, 604, 616.1-616.4, 647, 670, 760.2, 771 | N30, N34, N37.0, N39.0, N41.0, N41.3, N45, N76.0, N76.2, N77, P35-P39 |
| Skin and soft tissue infections (cellulitis, impetigo, herpes virus, varicella zoster virus) | 680-686, 053, 054 | L00-L08 |
| Obstetrics-related infections* (infection of amniotic cavity, major puerperal infxn, inflammatory disease of uterus, unspec inflammatory disease of uterus, infxn of GU tract in pregnancy, maternal pyrexia during labour, generalized infxn during labour, pyrexia unknown during puerperium, septicemia, other infxn) | 658.4, 670.0, 615.0, 615.9, 646.6, 659.2, 659.3, 672.0, 038, 999.3, 041 | O41.1, O85.x, O86.x, N71.0, N71.9, O23.x, O75.2, O75.3, A40, A41 |

*Applied to maternal infections analyses only

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No | Recommendation | Page numbers |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | Page 1, title |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Page 3, abstract |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | Page 6 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | Page 7, top |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | Page 3, abstract; Pages 7-10, methods |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Pages 7, 8, data sources and study cohort |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | Page 8, study cohort and exposure definition |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | Pages 8-10, exposure, outcome and covariates |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | Pages 8-10, exposure, outcome and covariates |
| Bias | 9 | Describe any efforts to address potential sources of bias | Pages 9, 10, statistical analysis and sensitivity analysis |
| Study size | 10 | Explain how the study size was arrived at | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | Page 9, 10, covariates |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | Page 10, 11, statistical analysis |
| | | (*b*) Describe any methods used to examine subgroups and interactions | |
| | | (*c*) Explain how missing data were addressed | |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | |
| | | (*e*) Describe any sensitivity analyses | Page 10, 11, statistical analysis |

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|---|---|---|---|
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Page 11, results; Figures 2 and 3 |
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Page 11, 12, results; Table 1 |
| | | (b) Indicate number of participants with missing data for each variable of interest | Page 8, 9, methods (follow up defined in methods, there were no losses to follow up |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | Page 11-13, results; Figures 2 and 3 |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Tables 2 and 3 |
| | | (*b*) Report category boundaries when continuous variables were categorized | Pages 9-10, covariates |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | Tables 2 and 3 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | Page 13 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Pages 15, 16 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | Pages 15, 16 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | Page 16 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Page 2, end |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.