Safety of perinatal biologic use in autoimmune diseases: population-based studies of maternal and infant outcomes

by

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Abstract

Objectives: To examine biologic use before or during pregnancy among women with autoimmune inflammatory disease by: 1) Describing the patterns of use, discontinuation, and 10-year secular trends; 2) Evaluating the association between biologic exposure before or during pregnancy and adverse maternal and infant outcomes including: preterm deliveries, small-for-gestational-age (SGA) births, congenital anomalies, and serious infections; and 3) Reviewing existing literature and meta-analyzing my findings with published results.

Methods: Using provincial population-based administrative health data linked with the perinatal registry and prescription dispensations database, a cohort of women with autoimmune inflammatory disease who had at least one pregnancy during 2002-2012 was identified. Descriptive statistics, multivariable modeling, and high-dimensional propensity score (HDPS) methods were used to describe the patterns of perinatal biologic prescriptions and assess associations with outcomes of interest. Results were meta-analyzed with findings from existing literature.

Findings: 1) Perinatal biologic use has increased significantly over 10 years, comprising 5.7% of all pregnancies in this population by 2012. Most often women discontinued their biologic in the first (31%), or second (38%) trimesters, while 98% of those on treatment during the second trimester continued through to delivery. Only disease type was associated with discontinuation. 2) After applying HDPS matching, there were no associations observed between biologic use before or during pregnancy and risk of preterm deliveries (OR 1.13, 95% CI 0.67 to 1.90); SGA (OR 0.91, 95% CI 0.46 to 1.78); or congenital anomalies (OR 1.06, 95% CI 0.46 to 2.47). The theoretical concern of serious infections due to immunomodulatory effects of biologics was not observed. 3) Meta-analysis of unadjusted risk estimates showed significantly increased risks of congenital anomalies, preterm

deliveries, and low birth weight babies associated with biologic exposure. However, pooled adjusted risk estimates showed no significant associations.

Conclusions: Using novel methods to address potential confounding and pooling existing evidence, the findings from this thesis demonstrated that treatment with biologics before or during pregnancy are not associated with a number of important perinatal outcomes. These findings help patients and clinicians weigh risks and benefits of treatment options in pregnancy, and support difficult decision making around using biologics in a vulnerable population.

Lay Summary

Several types of autoimmune disease are known to affect women more commonly than men, and poorly controlled disease can lead to pregnancy complications. A newer group of highly effective medications called 'biologics' could be a suitable treatment for such diseases, except we still do not have enough information about their safety when used during pregnancy. Using 10-years of high quality healthcare data in British Columbia, I conducted a series of studies looking at womens' use of biologics during pregnancy to manage their autoimmune disease, and how safe they are. In 5.7% of women with autoimmune disease in BC who used a biologic around the time of their pregnancy, there was no sign of increased preterm deliveries, small-for-gestational-age newborns, babies with birth defects, or serious infections. These findings suggest that biologics may be safe treatments during pregnancy. This information can help women with autoimmune disease and their doctors make important treatment decisions.

Preface

This thesis comprises five research essays initiated and developed by Nicole Tsao. The author defined the research questions, designed the studies, prepared data, performed statistical analyses, interpreted results, and drafted the chapters and associated manuscripts. The co-authors of submitted or published manuscripts included several committee members who provided methodological guidance, interpretations, and critical edits of manuscript drafts. Dr. Mary De Vera also led the acquisition of data and funding.

Manuscripts related to this thesis:

Nicole W. Tsao, Larry D. Lynd, Mohsen Sadatsafavi, Gillian Hanley, Mary A. De Vera. Patterns of biologics utilization and discontinuation before and during pregnancy in women with autoimmune diseases: A population-based cohort study. Arthritis Care Res (Hoboken). 2017 Oct 3. doi: 10.1002/acr.23434. [Epub ahead of print] (published, related to Chapter 2)

Nicole W. Tsao, Eric C. Sayre, Gillian Hanley, Mohsen Sadatsafavi, Larry D. Lynd, Carlo A. Marra, Mary A. De Vera. Risk of preterm delivery and small-for-gestational-age births in women with autoimmune disease using biologics before or during pregnancy: A population-based cohort study. Ann Rheum Dis. 2018 Mar 1. pii: annrheumdis-2018-213023. doi: 10.1136/annrheumdis-2018-213023. [Epub ahead of print] (published, related to Chapter 3)

Nicole W. Tsao, Gillian E. Hanley, Larry D. Lynd, Mary A. De Vera. Risk of congenital anomalies in infants born to women with autoimmune disease using biologics before or during pregnancy: A population-based cohort study. (under peer review, related to Chapter 4)

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Studies conducted in Chapters 2 through 5 were approved by The University of British Columbia Behavioural Research Ethics Board (Certificate number: H13-02027). All inferences, opinions, and conclusions drawn in this dissertation are those of the authors, and do not reflect the opinions or policies of the Data Steward(s).

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List of Abbreviations

95% CI	95% confidence interval
aOR	adjusted odds ratio
AS	ankylosing spondylitis
BC	British Columbia
BCG	Bacillus Calmette–Guérin
BCPDR	British Columbia Perinatal Database Registry
CD	Crohn's disease
DAD	Discharge Abstract Database
DMARDs	disease modifying anti-rheumatic drugs
FcRn	Fc receptor neonatal
HDPS	high dimensional propensity score
HR	hazard ratio
IBD	inflammatory bowel disease
ICD	International Classification of Diseases
Ig	immunoglobulins
IgG	immunoglobulin type G
IL	interleukin
JIA	juvenile idiopathic arthritis
MSP	Medical Services Plan
OR	odds ratio
Ps	psoriasis
PsA	psoriatic arthritis
RA	rheumatoid arthritis
RR	relative risk
SARDs	systemic autoimmune rheumatic diseases
SLE	systemic lupus erythematosus
TNF	tumour necrosis factor
UC	ulcerative colitis

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I also want to acknowledge the invaluable support of my committee members, Professors Gillian Hanley, Mohsen Sadatsafavi, and Carlo Marra. They have each contributed instrumental input into my research, and without their insights and advice I would not have achieved the milestones of my PhD. I want to acknowledge colleagues who have helped contribute to more technical aspects of my research, Dr. Eric Sayre and Dr. Jeremy Rassen.

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My warmest gratitude goes to colleagues and friends who have been there for me through this long road, to which without their companionship and moral support it would not have been the same – Ms. Louise Gastonguay, Ms. Litsa Blanis, Dr. Natalie McCormick, Dr. Adam Raymakers, Dr. Anik Patel, and Ms. Alyssa Howren.

Dedication

To my parents, Catherine and CL, for their never ending support.

1. Introduction

1.1. Background on health problem

1.1.1. Chronic inflammatory autoimmune diseases

Chronic inflammatory autoimmune diseases include over 70 types of disorders, collectively affecting more than 5% of the population in Western countries (1). Some of the most prevalent are rheumatoid arthritis (RA), affecting 0.5-1% of the population, and inflammatory bowel disease (IBD), affecting approximately 0.5% of the population (2,3). A commonality is that nearly all autoimmune diseases have a female predominance, with more than 80% of autoimmune disease patients being women (1). This has resulted in a longstanding 'sex gap' (4), whereby females are disproportionately affected compared to males, and often with peak incidences during the reproductive years (5). A prominent example is systemic lupus erythematosus (SLE), an autoimmune disorder that affects 1 to 4 per 1,000 women, at a ratio of 9:1 women to men, with peak age of onset between 20 to 40 years (6). Rheumatoid arthritis tends to be more prevalent among women with a ratio of nearly 3:1 (7). In RA, peak onset occurs during the fourth and fifth decades of life but studies report that a substantial proportion of women between ages 16 and 40 are affected (8,9). Though less-studied than SLE and RA, ankylosing spondylitis (AS) and psoriatic disease – including psoriasis (Ps) and psoriatic arthritis (PsA) – also represent important types of autoimmune disease that occur in women of childbearing age (10,11). Inflammatory bowel disease – including Crohn's disease (CD) and ulcerative colitis (UC) – affects males and females nearly equally at a ratio of approximately 1.3:1; however, recent studies have shown that peak incidence for both is in the second to fourth decades of life, with the highest incidence among 20 to 29 year olds (12,13).

Despite the fact that the female predisposition to autoimmune diseases has been established for over a century, the underlying mechanisms of this imbalance is not well understood (1). Epidemiological and immunological evidence has implicated female sex hormones in the etiology and course of chronic inflammatory diseases, however this interaction is highly complex and research has not been able to demonstrate the exact pathways through which this occurs (14). What is known to date is that females of all ages experience significantly lower rates of infections and related mortality compared to men (15). This phenomenon appears to be due to females having a heightened inflammatory response that is advantageous toward external infectious agents, but unfavorable in immune responses against self, leading to an overall increased rate of autoimmune diseases in women (15). It is also widely accepted that the menstrual cycle, pregnancy, and menopausal status are important influencing factors of this immune response in women (14). In light of this, there is growing recognition that autoimmunity may impact every aspect of pregnancy including maternal complications and neonatal outcomes (16). As such, treatment for autoimmune diseases may be required throughout the perinatal and intrapartum periods, as evidence shows that in rheumatic diseases and in IBD, active disease at the time of conception is a predictor of adverse pregnancy outcomes (17,18). Further, the discontinuation of effective treatments after conception may lead to aggravation of disease activity during pregnancy, also increasing the risk of adverse pregnancy outcomes (19). This presents a challenge, but also a potential opportunity. Many of the traditional disease-modifying agents such as methotrexate, leflunomide, and mycophenolate mofetil, are contraindicated during pregnancy; as such, newer biologics could be a viable alternative depending on their risk-benefit profile. Given that pregnant women and infants are rarely studied in a randomized controlled trial setting, there is a reliance on population-based observational studies to characterize the safety of biologics in these special populations.

1.1.2. Role of inflammatory cytokines in autoimmune disease and in human pregnancies

During the course of normal human pregnancies, there are dramatic physiological changes that occur in order to allow for the coexistence of genetically different individuals in the same body (20). Central to this adaptation is the regulation of immune responses through cytokine production so as to protect the fetus from immunological attack. T lymphocytes (CD4+ T cells) are responsible for regulating the activity of both cell-mediated and humoral responses via T helper cells type 1 (Th1) and type 2 (Th2), respectively (Figure 1). The pathways of Th1 and Th2 reciprocally inhibit each other, and during normal pregnancies, the Th1/Th2 balance is strongly shifted toward Th2 activity as major sites of Th2 cytokine production reside in the placenta and the trophoblast (21).

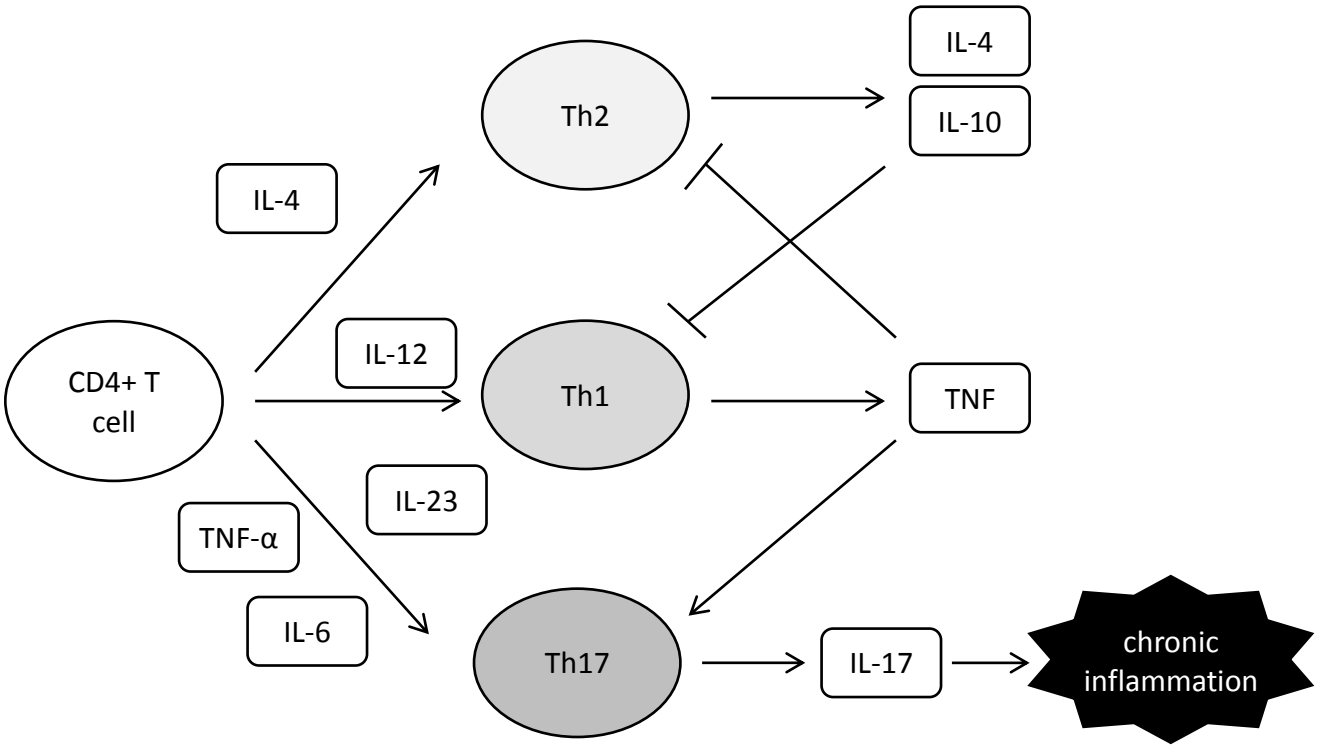


Figure 1. Schematic representation of CD4 T cell signalling via cytokine production and the relationship with chronic inflammation.
TNF = tumour necrosis factor, Th = T helper cell, IL = interleukin, arrows represent direction of activation and horizontal bars represent inhibition. Figure adapted from Straub (22)

A dominance of Th2 activity during pregnancy is essential to maintaining healthy pregnancies (Figure 2) as several pro-inflammatory cytokines in the Th1 pathway directly contribute to the production of downstream inflammatory mediators involved in parturition, such as prostaglandins and cyclooxygenases (23). An overabundance of these downstream inflammatory mediators leads to premature cervical ripening, myometrial contractions, and rupture of membranes resulting in spontaneous abortions, preterm deliveries, and fetal demise (23). However, it is important to note that inflammation is only one of many mechanisms of such adverse pregnancy outcomes, and these pathologies in their entirety are much more complex and remain not completely understood.

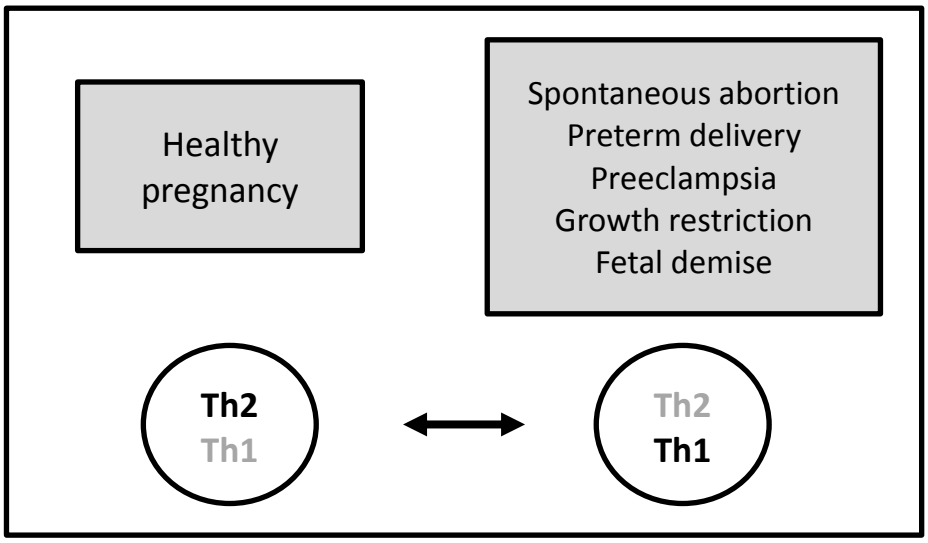


Figure 2. Th1 and Th2 balance and associated gestational pathologies.
Th1 = T helper cell type 1, Th2 = T helper cell type 2. Figure adapted from Challis et al.(23)

In diseases of autoimmunity, inflammatory cytokines in the Th1 pathway are overexpressed and play key roles in the propagation of a chronically inflamed state. Specifically, pro-inflammatory cytokines tumor necrosis factor (TNF), interleukin (IL)-6, and IL-23 activate and propagate a subset of T helper cells, Th17, which produce the potent inflammatory cytokine IL-17. These pathways comprise the underlying pathology of inflammatory autoimmune diseases and results in a shift

towards Th1 predominance, disrupting the physiology of normal healthy pregnancies. Further, many of these substances are pleiotropic, meaning that each cytokine can produce a multitude of effects making it difficult to predict what will happen when they are overexpressed or underexpressed based on shifts in Th1/Th2 balance. Nonetheless, what is known is that dysregulation in the production of different cytokines can result in the same autoimmune disease, particularly in the case of IBD or RA (Table 1). As a result, these cytokines have been exploited therapeutically as drug targets, leading to the advent of a group of drugs collectively referred to as 'biologics'. Biologics have since revolutionized the management of chronic inflammatory autoimmune diseases and altered the trajectories of these formerly progressive and debilitating conditions.

Table 1. Examples of pleiotropic inflammatory cytokines that contribute to development of various chronic inflammatory autoimmune diseases

Cytokine or Protein	**Defect**	**Manifestation**
Tumor necrosis factor	Overexpression	IBD, RA, vasculitis
Interleukin-6	Overexpression	RA
Interleukin-7	Overexpression	IBD
Interleukin-10, interleukin-10 receptor	Overexpression	IBD
Interleukin-12	Overexpression	IBD, RA
Interleukin-23/interleukin-17 pathway	Dysregulation	IBD, RA

RA = rheumatoid arthritis, IBD = inflammatory bowel disease
Adapted from Davidson and Diamond (24); Xavier & Podolsky(25); and McInnes et al.(26)

1.1.3. Biologics

Biologics are a novel class of disease-modifying drug molecules that have revolutionized the management of several chronic autoimmune inflammatory conditions (27,28). Biologics differ from synthetic chemical drugs in the sense that biologics are genetically engineered proteins derived from human genes, and grown in living systems (29). One type of biologic drugs is monoclonal antibodies which inhibit specific cytokines or cell signals in the immune system that play pivotal roles in

promoting or inhibiting inflammation. As such, these molecules have the overarching function of modulating the immune system to modify the course of autoimmune inflammatory diseases (29). Currently there are five biologics approved in the Canadian market that specifically target the cytokine TNF – infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol – collectively referred to as TNF inhibitors due to their inhibitory action on TNF activity. There are several other non-TNF inhibitor biologics, each are first-in-class, meaning that they have unique mechanisms of action (Table 2). The most common indications for treatment with biologics are RA and IBD (27,30). In British Columbia, for most biologics there are special authorization criteria patients with autoimmune disease must fulfill before the cost of these drugs can be covered by the government. These criteria depend on the specific drug, whether it is being prescribed for initial use, as a renewal, or a switch in therapy, and the criteria may change over time due to emergence of new drugs on the market, changes in the pricing of drugs, or new clinical evidence. In general, the criteria result in coverage for these drugs reserved for individuals with moderate to severe disease who have an intolerance, a contraindication, or an inadequate response to one or more traditional DMARDs or non-biologic treatments (31).

Table 2. Summary of biologics approved for use in Canada by 2018, their targets and indications

Biologic	**Target or mechanism of action**	**Indications**
Infliximab	Tumor necrosis factor alpha	RA, AS, IBD, Ps, PsA
Etanercept	Tumor necrosis factor alpha	RA, JIA, AS, Ps, PsA,
Adalimumab	Tumor necrosis factor alpha	RA, JIA, AS, Ps, PsA, IBD
Golimumab	Tumor necrosis factor alpha	RA, AS, PsA, ulcerative colitis
Certolizumab pegol	Tumor necrosis factor alpha	RA, AS, PsA
Abatacept	T cell co-stimulation inhibitor	RA, JIA
Tocilizumab	Interleukin-6	RA, GCA, JIA,
Rituximab	B cell depletor	RA, Wegener's disease
Ustekinumab	Interleukin-23/interleukin-17 pathway	Crohn's disease, Ps, PsA
Anakinra	Interleukin-1	RA
Alefacept	T cell inhibition	Ps

RA = rheumatoid arthritis, AS = ankylosing spondylitis, IBD = inflammatory bowel disease, Ps = psoriasis, PsA = psoriatic arthritis, JIA = juvenile idiopathic arthritis, GCA = giant cell arteritis

Relatively little is known about the pharmacokinetics of biologics during human pregnancies; however, since the molecules are predominantly recombinant immunoglobulin (Ig) G subtypes, much can be gleaned from the placental transport of IgGs during the pregnancy period. The human placenta appears to be impermeable to four of the five classes of Igs produced by the humoral immune system (IgA, IgM, IgE, and IgD), with the exception of IgG (32). IgG is transferred from the maternal to the fetal circulation during pregnancy and thus, comprise one of the primary sources of fetal immunity (33). IgG crosses the placenta by receptor-mediated binding of the Fcγ portion of the IgG molecule and its receptor, FcRn (Fc receptor neonatal). This complex is then transported within coated vesicles to the fetal circulation allowing the release of intact IgG into the fetal bloodstream (34,35). The FcRn is also found to have a protective effect on IgG in animal models, extending the lifespan of IgG molecules 10-fold compared to animals without FcRn (36). Detectable, and even therapeutic, levels of biologics have been confirmed in case reports of infants exposed in utero (37,38); however, the clinical impact of this on pregnancy-related outcomes has yet to be conclusively determined.

1.1.4. Adverse outcomes in pregnancy complicated by autoimmune disease

Due to the female preponderance in diseases of autoimmunity, a body of evidence on the impact of autoimmune inflammatory diseases on pregnancy-related outcomes has accumulated over the past decades. Research has demonstrated that women with autoimmune inflammatory diseases are at increased risk of developing several adverse pregnancy outcomes compared to women with similar characteristics who do not have autoimmune diseases (18,19,39–42). Here the definitions of some of these outcomes are summarized, and put into context of their relationship with diseases of

autoimmunity. These outcomes comprise the investigations that have been conducted in this dissertation.

Pre-term birth is defined as a live birth occurring before the completion of 37 weeks gestation (43). It is a leading cause of death in neonates and is an important perinatal challenge facing industrialized countries. Up to 38% of preterm births result in neonatal death (44). Preterm birth rates in Canada have increased from 6.4% in 1981 to 8.2% in 2004, according to the Public Health Agency of Canada (45). More recent estimates report that the rate of preterm births in British Columbia was around 10% in 2013 (46). In contrast, literature on women with rheumatic diseases or with IBD showed that on average the rates of preterm deliveries are approximately 80% higher than that of healthy pregnant women, with estimates ranging from 12% to 28% (19,39).

Small-for-gestational-age (SGA) is a sex-specific measure that combines both gestational age and birth weight, whereby an infant born small-for-gestational-age is one whose birth weight is below the 10th percentile for that gestational age. It is a superior measure of neonatal health than assessing prematurity (gestational age less than 37 weeks) or low birth weight (weight less than 2500 g at birth) separately. This is because a preterm neonate may have a normal weight for his or her gestational age, whereas one born at term may have an abnormal weight for his or her gestational age, as such birth weight and gestational age confound each other whereby about two-thirds of low birth weight infants are preterm (37). An SGA baby is at higher risk of complications including fetal distress, cerebral damage, long-term neurological sequelae and fetal death (47,48). In Canada, the estimated rate of SGA is around 8%, and approximately the same in British Columbia, at

7% (49,46). In those with rheumatic disease or with IBD, the rates of SGA were higher, reported to range from 10% to 17% (40,41).

Congenital anomalies or birth defects are conditions present at birth that cause structural changes in one or more parts of the body and can have adverse effects on health, development or functional ability (50). Aside from being a leading cause of infant death, accounting for more than one of every five infant deaths, babies born with birth defects have a greater chance of illness and long term disability compared to babies without birth defects (51,52). Examples of congenital anomalies include neural tube defects, orofacial defects, limb deficiency defects, and congenital heart defects. In Canada, it is estimated that congenital anomalies affect 3 to 5% of live offspring from healthy pregnancies, with a British Columbia-specific rate of approximately 4% (53). The association between autoimmune diseases and the risk of congenital anomalies has been inconclusive, with some studies suggesting there is no association and others suggesting a doubling to tripling in risk (19,39,54). Nonetheless, it is important to investigate this outcome in the context of drug safety, as the most commonly used disease-modifying drugs for autoimmune diseases have been shown to be teratogenic, including methotrexate and leflunomide (55). Understanding the relationship between biologics and teratogenicity is the first step in understanding whether it can be safely used in pregnancy.

Infections

Given that biologics target immune system function, there is widespread evidence of an association between biologics and serious infections such as tuberculosis reactivation, pneumonia, candidiasis,

sepsis, and viral infections (56–58). Types of infections identified by cohort studies to be most commonly linked to biologics exposure were predominantly respiratory infections (38%), urogenital infections (34%), skin and soft tissue infections (22%), with infectious pathogens being predominantly bacterial (75%) or viral (19%) (59–61). In a recent network meta-analysis, it was determined that there was a significant increase in serious infections in patients treated with standard-dose biologics compared to those treated with traditional disease-modifying anti-rheumatic drugs (DMARDs; OR 1.31; 95% CrI 1.09 to1.58) (62). Risk of serious infections warrants special concern in the perinatal and post-partum periods. Research shows that post-partum infections account for up to 10% of maternal deaths, and are a cause of short term morbidity and long term complications (63). For infants who may have been exposed to biologics or other immunosuppressants in utero, the risk of infections may be elevated post-partum. As pharmacokinetic studies suggest, biologics can accumulate in neonates to three times higher than that of maternal levels at term (37,38,64). After exposure to biologics in utero, these agents can be present in infants at therapeutic levels for several months after delivery, raising concerns about immunosuppression for a substantial amount of time post-partum (65).

1.1.5. Summary of evidence on the association of biologics exposure with adverse pregnancy outcomes

Since pregnant women and children are rarely represented in clinical trials, the risk of adverse perinatal outcomes due to biologic exposure has not been well characterized. At the start of my current research in 2014, little was known about the impact of biologic exposure before or during pregnancy on maternal or neonatal outcomes. Much of the data were based on case reports, registries, and prospective or retrospective non-comparative observational studies (66–69). The lack

of comparator groups renders it difficult to establish whether observed rates of these adverse outcomes are any higher than baseline rates in disease-matched groups or the general population. By the end of 2014, there were five published papers on comparative cohort or case-control studies examining adverse pregnancy outcomes in those exposed and unexposed to a biologic (70–74). Table 3 summarizes these studies and their reported results. However, evidence from comparative studies remains inconclusive, with some results showing a significant relationship between biologic use and increased risk of preterm delivery, low birth weight, and other adverse outcomes as seen in Table 3. There are several limitations to these early studies however, the first being that many studies only report the crude proportions of events by exposure group. Second, even those that do report estimates of association, the confidence intervals are large due to the studies having small sample sizes. Last, and arguably most important, is that nearly all of the studies have not employed any methods to adjust for potential confounders.

Table 3. Summary of evidence on pregnancy related outcomes in women with autoimmune diseases exposed and unexposed to biologics

Author, year	**Study type**	**Exposed N**	**Unexposed N**	**Autoimmune diseases**	**Outcomes**
Schnitzler 2011 (70)	Prospective single-centre cohort	42	78	IBD (CD, UC)	Stillbirth/spontaneous abortion (OR 1.5, 0.57 to 3.92) Preterm delivery (OR 2.38, 0.80 to 7.06) Low birth weight (OR 1.44, 0.46 to 4.46) Major malformations (OR 1.87, 0.11 to 30.8)
Verstappen 2011 (71)	Prospective cohort, registry based	71	10	RA, PsA, JIA, AS, Adult-onset Still's disease, SLE	Premature delivery (26% TNF-exposed vs. 20% unexposed) Spontaneous abortion (27% vs. 10%) Neonatal death (1.4% vs. 0%) Congenital malformations (3% vs. 0%)

Casanova 2013 (72)	Retrospective, multi-centre cohort	66	187	IBD (CD, UC)	Unfavorable global pregnancy outcome* (OR 1.62, 0.92 to 2.87)
Diav-Citrin 2014 (73)	Prospective single-centre cohort	83	86	IBD (CD, UC), RA, PsA, AS, unspecified arthritis, Behcet's disease	Miscarriage (OR 1.96, 0.64 to 5.96) Preterm delivery (23% exposed vs. 7% unexposed, p<0.001) Low birth weight (p=0.002)
Seirafi 2014 (74)	Case-control	133	99	IBD (CD, UC, unclassified)	Miscarriage (9% TNF-exposed vs. 5% unexposed) Death in utero (2% vs. 1%) Preterm delivery (17% vs. 15%) Low birth weight (16% vs. 10%) Congenital malformations (0.8% vs. 3%) Infections (2% vs. 1%)

IBD = inflammatory bowel disease, CD = Crohn's disease, UC = ulcerative colitis, OR = odds ratio, RA = rheumatoid arthritis, PsA = psoriatic arthritis, JIA = juvenile idiopathic arthritis, AS = ankylosing spondylitis, SLE = systemic lupus erythematosus, TNF = tumour necrosis factor inhibitor biologic.
*If there was a spontaneous or elective abortion, if the pregnancy ended before 37 weeks of gestational age, when obstetric complications were present, if the newborn had low birth weight, required intensive care unit admission, presented congenital malformations, or died.

Biologics are still a relatively new class of treatments for autoimmune diseases, having only been on the Canadian market over the past 20 years, but evidence on their safety in special populations is growing rapidly. Between 2014 and 2018 there has been a quadrupling of published research on this clinically important topic. However, the majority of comparative studies are only available in abstract form from conference proceedings or presentations, and most still only report crude proportions of observed events. To date, fewer than 10 studies have attempted to adjust for potential confounders such as maternal age, disease type, and concomitant medications, and due to the small sample sizes of many of these studies, only a limited number of covariates could be considered without compromising model accuracy. A comprehensive summary of all published literatures is included as a systematic review and meta-analysis in Chapter 6 of this dissertation.

1.1.6. Methodological challenges of existing studies

The rationale for examining the perinatal safety of a class of highly effective and revolutionary treatments for autoimmune inflammatory diseases is clear given the impact of untreated disease on pregnancy. The current knowledge gap is that the safety of biologic use during pregnancy remains inconclusive due to key methodological challenges that lead to limitations of the existing evidence. I identified, and here describe, three main areas of methodological challenge contributing to the existing knowledge gap of biologic use during pregnancy.

i) *Lack of population-based studies* – As described in the above section, at the time of conducting my research, much of the existing literature on the impact of biologic use before or during pregnancy on pregnancy outcomes were from single-centre studies, registry-based studies, or case-control studies measuring exposure through self-report or chart review. These types of study designs pose several issues relating to selection bias and information bias, resulting in potential misclassification. First and foremost, most registries only follow exposed individuals and lack a corresponding unexposed control group, and as such controls are either recruited from another registry, or from individuals presenting to different centres. Unfortunately, this approach is subject to possible selection bias as enrolment of controls is voluntary so there may be differences between exposed and unexposed groups at baseline, for example, the unexposed group may be less socioeconomically diverse, healthier, and with higher education levels, impacting the ability to generalize results to the target population (75). Second, some case-control study designs rely on patient recall in order to establish timing of

exposures. This approach is susceptible to recall bias, a type of information bias whereby a differential exists between cases and controls in their ability to accurately recall exposure information. In the context of the current study, it is important to not only establish correct exposure status but also of exposure status relative to pregnancy timing; those who had adverse outcomes (cases) may be more likely to remember drug exposure and attribute the outcome to the exposure, or those who had difficulties conceiving due to their disease activity may be able to better recollect the date of their last menstrual period (76). These types of scenarios would lead to recall bias and result in exposure misclassification, especially if there is a lack of corroborating data on subjects' prescription dispensations and pregnancy dates.

ii) *Confounding by indication* – Confounding by indication is a situation when a physicians' decision to prescribe a drug treatment to a specific patient is driven by not only the diagnosis but also other characteristics, commonly based on an evaluation of the patient's health status and prognosis, which in themselves might affect the outcome of interest (77). This results in potentially systematic differences in patients receiving a specific therapeutic regimen versus another. If these characteristics that have influenced the physicians' prescribing decision are also predictors of the outcomes of interest (i.e., patients who are preferentially prescribed a treatment are also at a higher or lower risk for the study outcome), then a confounded relationship presents (77,78). Given that autoimmune inflammatory disease activity has been shown to directly impact several outcomes of pregnancy (as described in Section 1.1.4), and that biologics tend to be a 'step-up' treatment for those with worse disease, it becomes apparent that

potential for confounding by indication is inherent to the research question at hand. Having been deemed the most persistent type of confounding (79), novel approaches must be undertaken in order to address this methodological challenge and to parse out the impact on pregnancy outcomes attributable to the drug treatment apart from the impact of the disease itself.

iii) *Rare exposures and rare outcomes* – Adverse pregnancy outcomes can be considered relatively rare, given that the estimated background rate of congenital malformations (one of the rarest pregnancy outcomes) is around 4% and preterm deliveries (one of the more prevalent outcomes) are around 10% (49,53). Generally, case control study designs are recommended for rare outcomes with incidences of less than 1 to 5 per 1000 population, and cohort study designs are considered suitable for outcomes with incidences of approximately 50 per 1000 population (80). However in studies of perinatal epidemiology, and more specifically perinatal pharmacoepidemiology, the challenge becomes not only having relatively rare outcomes but also rare exposures (80). Consider the current study, if for example the prevalence of biologic exposure during pregnancy in women with an autoimmune disease was 2%, and the outcome of interest was congenital anomalies with a prevalence of 4%, a cohort of more than 40,000 mothers with autoimmune inflammatory disease would be needed in order to detect a 50% relative increase in congenital anomalies associated with biologic exposure (80). The prevalence of autoimmune inflammatory diseases in the general population is approximately 1 to 2% and as such, it would take decades for any one study or jurisdiction to be able to accumulate a large enough sample of pregnant women with

autoimmune inflammatory disease to be very confident about their study findings. Further, in the case of rare outcomes and rare exposures, traditional covariate adjustment leads to small cell sizes, rendering individual studies with small sample sizes unable to control for important confounders (81). A practical solution to provide answers to the research questions at hand is to conduct individual studies with robust methodology and compile an accumulation of literature through meta-analytical approaches to maximize power and increase precision of the findings (82).

These major methodological challenges preclude the ability for existing knowledge on this topic to provide conclusive answers to the broad question of whether or not biologic use during pregnancy is safe. My research in this dissertation attempts to overcome the three challenges described above by using population-based linked administrative databases from the entire population of a well-defined jurisdiction, high-dimensional propensity score methods, and meta-analytical approaches to determine the relationship between biologic use before or during pregnancy and specific adverse maternal and neonatal outcomes. Here I describe the methodological approaches that have been implemented to overcome the identified challenges.

1.2. Background on approaches to methodological challenges

1.2.1. Population-based data sources and linkage

One approach to overcoming the aforementioned lack of existing population-based studies is to use high quality, population-wide data from a defined jurisdiction (BC) comprised of administrative data

holdings from: 1) Population Data BC (83–87); 2) BC PharmaNet (88); and 3) BC Perinatal Data Registry (BCPDR) (89).

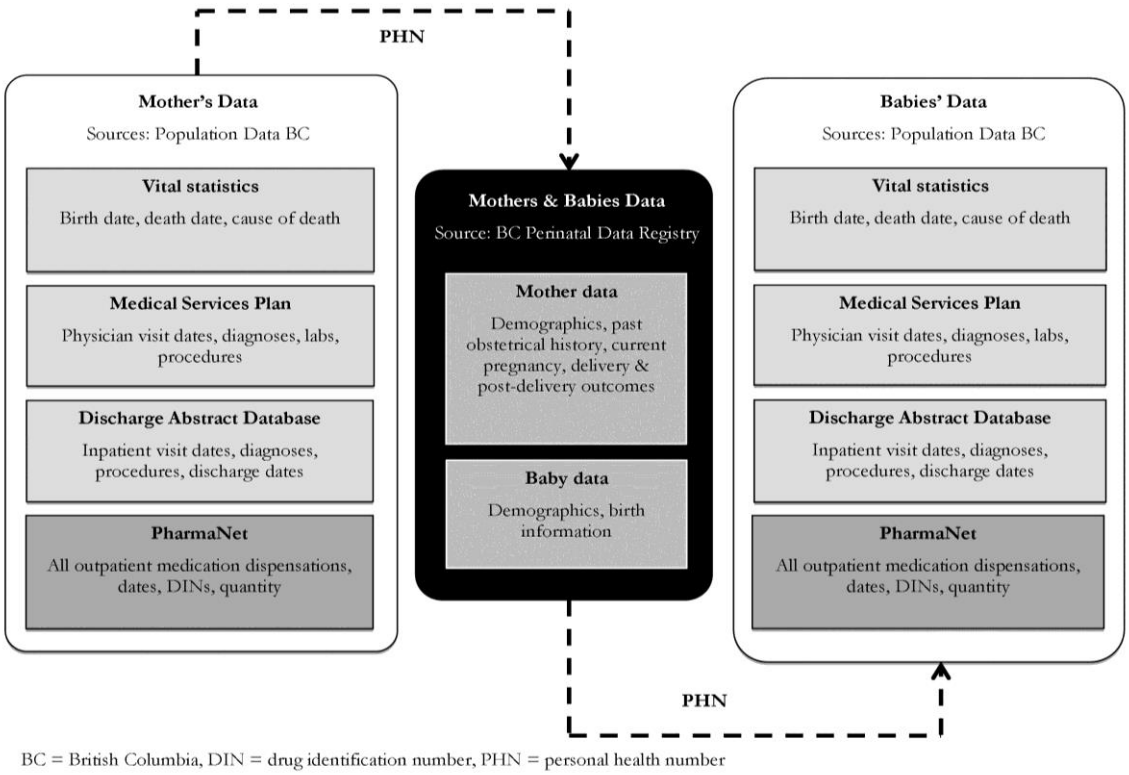
Population Data BC: Population Data BC is an extensive data resource comprising administrative data covering the entire population of BC (~4.8 million as of 2017) (90), that can be utilized for population health research. Use of the entire population base ensures the generalizability and applicability of research findings by nearly eliminating selection and information biases. From Population Data BC holdings, I used the Medical Services Plan (MSP), Discharge Abstract Database (DAD), and Vital Statistics Births and Deaths databases. The MSP database captures physician visits, dates, types of practitioners, ordering of laboratory tests and procedures, and diagnostic codes most closely related with each record, indicated through International Classification of Diseases, ninth revision (ICD-9) codes (91). The DAD captures all inpatient hospitalizations including admission date, up to 25 diagnostic fields representing the reason for admission or complications during hospitalization using ICD-9 and/or ICD-10 codes, procedure/intervention codes, and separation dates. The Vital Statistics Birth and Death databases provide information on births, including date of birth, and deaths, including date of death and underlying cause of death.

BC PharmaNet: The BC PharmaNet database captures complete information on all dispensed prescription drugs in BC, as by law, pharmacists must enter every prescription dispensed outside of hospitals in BC into this database. PharmaNet data that were utilized in my research included the drug identification number, generic name, brand name, dispensation date, dispensation quantity, dosage, and duration.

BC Perinatal Data Registry: The BCPDR contains data abstracted from obstetrical and neonatal medical records on births in BC from over 60 hospitals as well as home births attended by BC registered midwives. It captures >99% of births in BC and provides detailed information on antenatal, intrapartum and postpartum maternal and infant outcomes. Maternal data include demographics, delivery information (including mode and date of delivery, Cesarean section indication and type), post-delivery information (including post-partum infection types, antibiotic use, and cultures), information on current pregnancy (including gestational age, comorbidities, and antenatal care episodes), past obstetric history, and health behaviours. Infant data include demographics and birth outcomes including gestational age, birth length, birth weight, Apgar score, infectious agent cultures, and congenital anomalies. Validation studies have shown that the BCPDR is an accurate and comprehensive source of perinatal information in BC with >80% completion rates across all maternal variables, and >90% completion rates for neonatal variables. Validation of the BCPDR show that key variables such as maternal date of birth, date of last menstrual period, neonatal date of birth, have positive predictive values >90% (92). A unique element of the BCPDR is the availability of data on the pregnancy start date that is derived from recommended algorithms for establishing gestational age using first ultrasound and start date of last menstrual period, and newborn clinical exam (93). Given the challenges of pregnancy dating, and the importance of establishing precise timing of medication exposures during pregnancy, the availability of this information adds to the strength of the analyses of each study (94).

For the work comprising this dissertation, administrative databases described above were obtained for both mothers and babies and were linked by Population Data BC using the mothers' Personal Health Number (PHN). A schematic diagram of the data linkage is shown in

Figure 3. Altogether, these linked databases provide a comprehensive, population-wide dataset on both mothers and babies in BC, which comprised the source population for studies presented in Chapters 2 through 5 of this dissertation. An autoimmune disease cohort consisting of those with an autoimmune disease of interest (including RA, IBD, AS, Ps/PsA, SARDs, and JIA) was identified from the source population using validated algorithms with ICD-9 or 10 codes wherever possible. Validation studies were only available for RA (95), IBD (96), AS (97), Ps/PsA (98), and the same algorithm was applied for SARDs and JIA. Further details around the definitions used are presented in each chapter.



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

Figure 3. Schematic diagram of databases and linkages facilitating study analyses

1.2.2. High-dimensional propensity score methodology

The availability of large population-based healthcare databases, such as that described above, allows the conduct of real-world drug safety and effectiveness studies, which is of particular advantage for studying individuals from under-represented patient groups or those completely excluded from clinical trials, such as pregnant women and infants (99). However, pharmacoepidemiological studies using real-world data face several challenges that can compromise internal validity, including confounding by indication, and residual confounding due to unmeasured confounders (i.e., variables that were not observed or recorded, such as clinical disease severity, laboratory results, functional status, smoking status, and over-the-counter medication use) (78). One of the most important threats to internal validity, and one most relevant to the context of this body of work, is confounding by indication. As described in Section 1.1.6 – confounding by indication occurs when physicians' prescribing decisions result in potential systematic differences in patients receiving a specific therapeutic regimen, and when the factors on which the decision was based are also associated with the outcome of interest (i.e., patients who are preferentially prescribed a treatment are also at a higher or lower risk for the study outcome) (78). Propensity score methodologies are a suitable and common analytical approach to control for confounding by indication, and other types of confounding, in studies using large real-world databases (100).

An exposure propensity score, first proposed by Rosenbaum and Rubin, is a calculation commonly estimated by logistic regression of the probability (propensity) of receiving a particular treatment

(Treat = 1 versus Treat = 0) based on a number of measured covariates (X_1, X_2, X_3 … X_n) (101). The propensity score model takes the form of:

$$Logit\ (Treat = 1) = \beta_0 + \beta_1(X_1) + \beta_2(X_2) + \beta_3(X_3) \ldots + \beta_n(X_n).$$

As such, the propensity score ranges from 0 to 1 and represents the conditional probability of exposure to treatment given a set of covariates, which can be interpreted as a summary score that reflects the likelihood of being prescribed a particular treatment, given all observable characteristics. Individuals with similar estimated propensity scores will have, on average, similar chances of receiving that treatment and overall a similar covariate distribution (100). A propensity score is calculated for each subject within a cohort, irrespective of their actual treatment status. Then by matching on the propensity score a pseudo-randomization environment is created, resulting in better balance of measured covariates between exposed and unexposed subjects and improving the validity of between group comparisons (100).

The other major threat to validity is the inability to account for bias due to residual confounding from unmeasured confounders. It has been suggested that adjusting for a perfect surrogate of an unmeasured confounder is equivalent to adjusting for the confounder itself and that the degree to which a surrogate is correlated to an unmeasured confounder is proportional to the degree to which adjustment can be achieved (102,103). Further, Schneeweiss et al. proposed that often patients' health status can be indirectly described by several levels of proxy variables, which they refer to as "chains" of proxies (104). For example, the health state of a patient can be assessed through a chain of events consisting of (i) dispensation of a drug that was (ii) prescribed by a physician during a visit who (iii) made a diagnosis because the patient (iv) presented with certain symptoms. Such a chain of proxies corresponds to data captured in multiple dimensions of linked databases and comprise a

chain of events that are influenced by access to care, severity of the condition, diagnostic ability of the physician, and preference for one drug over another (105). Thus, the aim of the novel high-dimensional propensity score (HDPS), created by Schneeweiss et al. (104), is to algorithmically select a large set of measured proxy covariates from multiple dimensions of a large database which they postulate would comprise a sufficient overall proxy for relevant unobserved confounding factors.

The HDPS algorithm is a semi-automated covariate selection algorithm – available open source at http://www.drugepi.org/dope-downloads/ – for high-dimensional confounding adjustment within large population-based healthcare databases (104). The HDPS algorithm evaluates thousands of diagnostic, procedural, and prescription drug claims codes and, for each code, generates binary variables based on the frequency of occurrence for each code during a defined pre-exposure covariate assessment period (104,106). The HDPS then prioritizes or ranks each variable based on its potential for bias by assessing the variable's prevalence and univariate association with the treatment and outcome according to the Bross formula (107):

$$\frac{P_{C1}\,(RR_{CD}-1)+1}{P_{c0}\,(RR_{CD}-1)+1}$$

where P_{C_1} represents the prevalence of the binary covariate within the exposed group, P_{C_0} the prevalence of the binary covariate within the unexposed group, and RR_{CD} the relative risk for the univariate association between the binary covariate and the study outcome (107). From the ranked list of candidate covariates, investigators can then specify the number of variables to include in the HDPS model along with pre-specified variables to be forced into the model, such as maternal age (104,106). High dimensional propensity scores estimated for each subject can then be used, as traditional propensity scores, in outcomes modelling by matching on HDPS, stratifying, weighting, or

covariate adjustment (99,100). When benchmarked against randomized controlled trials, HDPS-based methods have been shown to be at least as or more robust at estimating treatment effects than using traditional propensity scores, multivariable modeling, or instrumental variable approaches (108,109). Specific details of how HDPS were implemented are available within each chapter of this dissertation that have utilized this methodology (Chapters 3 and 4).

1.2.3. Systematic review and meta-analysis

Performing a meta-analysis after a systematic review is a very commonly used methodological approach to quantitatively pool data across multiple studies (110). There are several reasons why one might conduct a meta-analysis. According to the Cochrane Handbook, these could be: 1) to increase statistical power; 2) to improve precision of estimates; 3) to answer questions not posed by individual studies; or 4) to settle controversies or generate new hypotheses (82). Based on the previously identified methodological challenges in this body of evidence, I meta-analyzed the existing literature including my own study results wherever possible, with the intent of increasing statistical power and improving the precision of the risk estimates. Details of the methods used to pool results of existing studies with results of my studies are described in detail in the systematic review and meta-analysis chapter of this dissertation (refer to Chapter 6).

1.3. Knowledge gap and specific objectives of this thesis

The current knowledge gap is that the safety of biologic use during pregnancy remains inconclusive due to key methodological challenges of the existing literature, as described. The limitations of the existing evidence preclude our ability to understand the true impact of the use of a biologic during

pregnancy by women with autoimmune inflammatory disease on important maternal and neonatal outcomes. The objectives of my research in this dissertation was to overcome the three challenges described above by using population-based linked administrative databases from the entire population of a well-defined jurisdiction, high-dimensional propensity score methods, and meta-analytical approaches. Using these methods, my specific objectives are to evaluate the safety of biologic use during pregnancy by examining their impact on the risk of adverse pregnancy outcomes including preterm deliveries, SGA births, congenital anomalies in the offspring, and serious infections in women with autoimmune inflammatory disease and their infants. Due to lack of data on spontaneous abortions and stillbirths, only specific outcomes with biological plausibility and data availability are studied. The findings from my research will not only contribute methodologically, but also clinically, to existing knowledge by providing urgently needed information on the impact of an increasingly utilized class of medications. This body of research can help inform the risk-benefit evaluation of biologics so that women with autoimmune inflammatory diseases and their healthcare providers can make informed decisions about treatment options during pregnancy. The structure of this dissertation is as follows:

Chapter 1, the current chapter, provides background information on the autoimmune diseases under study, the interaction between disease and pregnancy state, the mechanisms of action of biologics, a review of the literature, and a summary of the existing challenges and knowledge gaps. The research components of this dissertation begin from Chapter 2, consisting of a total of five analytical studies.

First, before investigating the relationship between biologic exposure and adverse pregnancy outcomes, in Chapter 2, using population-based linked administrative health data I described the patterns of use of biologics in pregnant women with autoimmune inflammatory disease in BC over a 10-year period. This included examining the secular trends of use, as well as patterns of use during the year before conception and during each trimester of pregnancy. Further, in this chapter I investigated factors associated with discontinuation of biologics with respect to pregnancy timing.

In Chapter 3, I applied HDPS to assess the risk of preterm delivery and SGA births – two related outcomes that remain as leading causes of infant morbidity and mortality (20). These two outcomes are consequences of similar underlying pathologies including overproduction of pro-inflammatory cytokines and abnormal shifts in the balance of Th1/Th2 inflammatory pathways during pregnancy due to autoimmune disease activity. Although the outcome of congenital anomalies in the offspring may not be a direct consequence of autoimmune disease, it is a common concern when considering medication use during pregnancy. As such, in Chapter 4 I investigated the relationship between exposure to biologics before and during the critical period of organogenesis and the risk of congenital anomalies in the offspring of these women.

Chapter 5 examines the risk of serious infections. 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. As such, given the known impact of the immunosuppressive effect of

biologics, it is important to examine this risk of serious infections in the context of maternal and infant health.

As evidence on the safety of biologics in pregnancy was rapidly being generated over the past few years, in Chapter 6 of this dissertation I performed a systematic review of the literature on this topic and meta-analyzed the reported results in conjunction with the findings from my research. Given that earlier studies were generally descriptive and have not considered multivariable modeling to account for potential confounders and more recent studies have begun to implement improved methodology, there is an urgent need to synthesize and incorporate these new data along with my findings, in order to compile the most precise and robust estimates possible.

The discussion, Chapter 7, connects the five studies and provides a cohesive picture of the benefits and risks of using biologics before or during pregnancy for both mothers with autoimmune inflammatory disease, and their offspring. I discuss the clinical and methodological implications of the findings of the studies presented in this dissertation, along with commentary on the strengths and limitations, and recommendations for future research directions.

2. Chapter 2: Patterns of biologics utilization and discontinuation before and during pregnancy in women with autoimmune disease[1]

2.1. Introduction

Biologic drugs have the overarching function of modulating the immune system to modify the course of certain autoimmune inflammatory diseases (29). The most common indications for treatment with biologics in autoimmune diseases are RA, IBD, and AS; other less prevalent autoimmune conditions treated with biologics include Ps, PsA, SLE and associated systemic autoimmune rheumatic diseases (SARDs) (29,30). A commonality is the longstanding 'sex gap' in these diseases of autoimmunity (4), where females are disproportionately affected compared to males, and often with peak incidences during the reproductive years (5,7,12,13).

Autoimmunity may impact every aspect of pregnancy including both maternal complications and neonatal outcomes (16). Evidence suggests that in chronic inflammatory diseases including RA and IBD, active disease at the time of conception and throughout pregnancy may be correlated with risks of adverse outcomes such as preterm delivery, small for gestational age births, and neonatal death (19,111). It is estimated that up to 50% of women with autoimmune diseases require treatment throughout pregnancy to control their disease activity and prevent adverse outcomes (55,112,113). This presents a challenge, as some of the most commonly used traditional disease-modifying agents are known teratogens; as such, biologics could be a viable treatment alternative in this population.

[1] A version of this chapter has been published: Nicole W. Tsao, Larry D. Lynd, Mohsen Sadatsafavi, Gillian Hanley, Mary A. De Vera. Patterns of biologics utilization and discontinuation before and during pregnancy in women with autoimmune diseases: A population-based cohort study. Arthritis Care Res (Hoboken). 2017 Oct 3. doi: 10.1002/acr.23434. [Epub ahead of print]

The objective of this study was to characterize the patterns of drug utilization and discontinuation in the prenatal period, and during pregnancy in women with autoimmune disease who are on a biologic.

2.2. Methods

Data sources

Population Data BC is an extensive data repository that holds individual-level, de-identified, longitudinal data on all health service use records covering the entire population of BC (~4.8 million residents as of 2017) (90), including provincially funded visits to physicians and other healthcare professionals, all medically required services provided by fee-for-service practitioners, laboratory and diagnostic procedures (x-rays, ultrasounds etc.) (83), hospital admissions and discharges (hospital separations) (87), demographics and vital statistics, since 1990 (84–86). Further, Population Data BC includes the comprehensive prescription drug database, PharmaNet, which captures all prescriptions dispensed in community pharmacies regardless of payment source, and including medications administered in infusion clinics, since 1996 (88).

These data were linked to the BCPDR (89), which contains antenatal, intrapartum, and postpartum maternal and infant data abstracted from medical records for >99% of births in BC, regardless of the place of delivery. Maternal data include demographics, delivery information, post-delivery information, characteristics of the current pregnancy, past obstetrical history, and health behaviors (including smoking status, alcohol and substance use). A unique feature of the BCPDR maternal data is the ability to calculate the precise date of conception using the final gestational age variable

which is based on information from early gestational ultrasound or the date of last menstrual period if early gestational ultrasound was unavailable. If neither field was recorded (~10% of records), gestational age was estimated from a newborn clinical exam and/or chart documentation. This method minimizes misclassification and patient recall bias as it uses the most precise estimate of gestational age available for each pregnancy. The calculated date of conception is crucial given the importance of establishing precise timing of drug exposure in the period before conception, and during pregnancy. Validation studies have shown that the BCPDR is an accurate and comprehensive source of perinatal information with over 80% completion rates for maternal variables, over 90% completion rates for neonatal variables, and positive predictive values over 90% for key variables (92).

Source population

The source population included women who had pregnancies ending in a live or still birth (defined as fetal death occurring after at least 20 weeks of gestation, or achieving a weight of at least 500 grams) 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. The source population included 449,098 pregnancies from 305,351 women over the 10-year follow up period.

Definition of autoimmune disease cohort

From the source population, I identified a cohort of women with one or more autoimmune diseases that could be treated with a biologic which included RA, IBD, Ps/PsA, AS, juvenile idiopathic arthritis

(JIA), SARDs, multiple sclerosis, and vasculitic diseases (**Error! Reference source not found.**). Each oman and their pregnancies were included if they had ICD-9/10 codes for a specific autoimmune disease in any of the diagnostic coding fields from either their physician visits data or hospital separations (**Error! Reference source not found.**), on two or more occasions at least 60 days apart nd within two years, any time prior to the date of delivery.

Definition of biologics utilization

Using dispensation dates and Canadian Drug Identity Codes for biologics in the BC PharmaNet Database, I identified women from the autoimmune diseases cohort who had at least one prescription for a biologic (Appendix A Table 1) at any point during the drug utilization period of interest – defined as one year prior to the date of conception (referred to as the preconception period), until the date of delivery of each pregnancy. A one-year preconception period was chosen in attempt to account for prolonged time to conception and reduced fecundity of women with autoimmune disease (114).

I divided the drug utilization period into three-month time windows (Figure 4), resulting in four windows during the preconception period (PC1, PC2, PC3, PC4), and three windows corresponding to trimesters of pregnancy (T1=date of conception to day 90, T2=day 91 to 180, T3=day 181 to date of delivery). Those who filled a prescription for a biologic any time during a three-month window were considered to be on treatment during that window. Discontinuation was defined as an individual having filled a prescription in a previous window but not in a subsequent window.

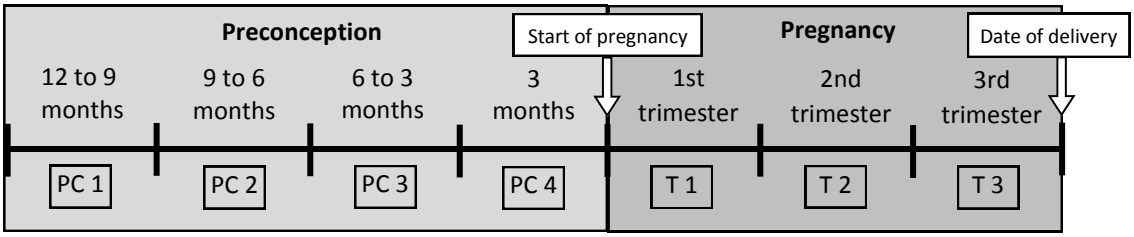


Figure 4. Schematic representation of biologic exposure windows from 12 months preconception until date of delivery

Statistical analyses

Summary statistics of demographics information were computed for women with autoimmune disease, and separately for the subgroup that had filled at least one biologic prescription anytime during the drug utilization period (PC1 to T3). Secular trends of biologic use one year before conception or during pregnancy over the 10-year study period were summarized as the annual percentages of all pregnancies in women with autoimmune disease, and tested for significance using Cochrane-Armitage Trend Test. For each drug utilization window (from PC1 to T3) patterns of biologic use was calculated as a proportion of pregnancies in women who filled a biologic prescription, among all pregnancies in women with autoimmune diseases, stratified by disease diagnosis. To assess the associations between various factors and odds of discontinuing biologics, I constructed two multivariable logistic regression models – one for the preconception period (PC1 to PC4), and the second for drug discontinuation during pregnancy (T1 to T3). I used hierarchical modeling to take into account the clustered nature of the data, namely drug utilization windows clustered within each respective pregnancy, and multiple pregnancies clustered by woman. Generalized linear models with generalized estimating equations and logit link function were used, covariance structures were examined for best model fit, and standard errors of parameter estimates

were computed with robust sandwich estimators. All analyses were performed using SAS statistical software v. 9.2.

Covariates

Covariates considered for multivariable models included maternal characteristics that may be associated with the likelihood of continuing or discontinuing biologics: maternal age at delivery; Charlson Comorbidity Index calculated over two years prior to date of conception; number of concomitant disease modifying drugs (e.g., azathioprine, methotrexate, leflunomide), immunosuppressants (e.g., cyclosporine, cyclophosphamide, mycophenolate mofetil), and glucocorticoids (refer to Appendix Table 1); and, number of hospitalizations and outpatient visits in each drug utilization window.

2.3. Results

From 8,431 pregnancies in 6,218 women with autoimmune disease between January 1st, 2002 and December 31st, 2012 in BC, there were 144 pregnancies (1.7%) from 131 women (2.1%) who filled a prescription for a biologic anytime during the drug utilization period of interest (PC1 to T3). The demographics of these women and their pregnancies are presented in Table 4. The most common autoimmune disease among this cohort were predominantly Ps, RA, and IBD; and the most commonly used biologics were TNF inhibitors infliximab, etanercept, and adalimumab.

Table 4. Demographics of women with autoimmune disease and those using a biologic before or during pregnancy (Total N=6,218 women, 8,431 pregnancies)

	Biologic users (N=131 women, 144 pregnancies)	**Biologic non-users (N=6087 women, 8287 pregnancies)**
Characteristics	**N (% of 144 pregnancies)**	**N (% of 8287 pregnancies)**
Age at delivery (mean (SD))	31.8 years (4.6)	31.8 years (5.2)
Nulliparous	80 (56)	3442 (41.5)
Cesarean section delivery	60 (42)	2780 (33.6)
Median gestational age (IQR)	38 weeks (2.2)	39 weeks (2.0)
Autoimmune disease	**N (% of 131 women[*])**	**N (% of 6087 women[*])**
Rheumatoid arthritis	67 (51)	1665 (27.4)
Inflammatory bowel disease	60 (46)	2041 (33.5)
Psoriasis	23 (18)	3315 (54.4)
Juvenile idiopathic arthritis	10 (8)	53 (0.87)
Ankylosing spondylitis	8 (6)	384 (6.3)
Multiple sclerosis	6 (5)	695 (11.4)
Systemic lupus erythematosus	-	339 (5.6)
Systemic autoimmune rheumatic diseases (including Sjogren's syndrome, systemic sclerosis, dermatomyositis, and polymyositis)	-	77 (1.3)
Vasculitic diseases (including polyarteritis nodosa, Wegener's granulomatosis, and Takayasu's disease)	-	142 (2.3)
Use of biologic preconception to delivery[†]	**N (% of 144 pregnancies[‡])**	
Infliximab	54 (38)	-
Etanercept	45 (31)	-
Adalimumab	40 (28)	-
Natalizumab	6 (4)	-
Certolizumab	< 5	-
Ustekinumab	< 5	-
Rituximab	< 5	-

Golimumab	< 5	-
Alefacept	< 5	-

*Sum of percentages exceed 100% due to some individuals having more than one diagnosis
†Anytime from 12 months prior to date of conception to date of delivery; 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

In examining the secular trends of biologic use during the drug utilization period, I found a statistically significant increase in the use of biologics in pregnant women with autoimmune disease from 2002 to 2012 ($p<0.001$; Figure 5). Despite etanercept and infliximab having been on the Canadian market since 2000 and 2001 (115), respectively, these medications were not used in this cohort until 2003. Further, there appeared to be a marked increase in biologics utilization after the approval of certolizumab and golimumab in 2009, but not due specifically to these biologics. There was a small decline in utilization from years 2010 to 2011, before increasing again thereafter. Overall, the use of biologics one year before conception or during pregnancy in women with autoimmune disease remained modest at 5.7% by 2012, the last year of observation in this study.

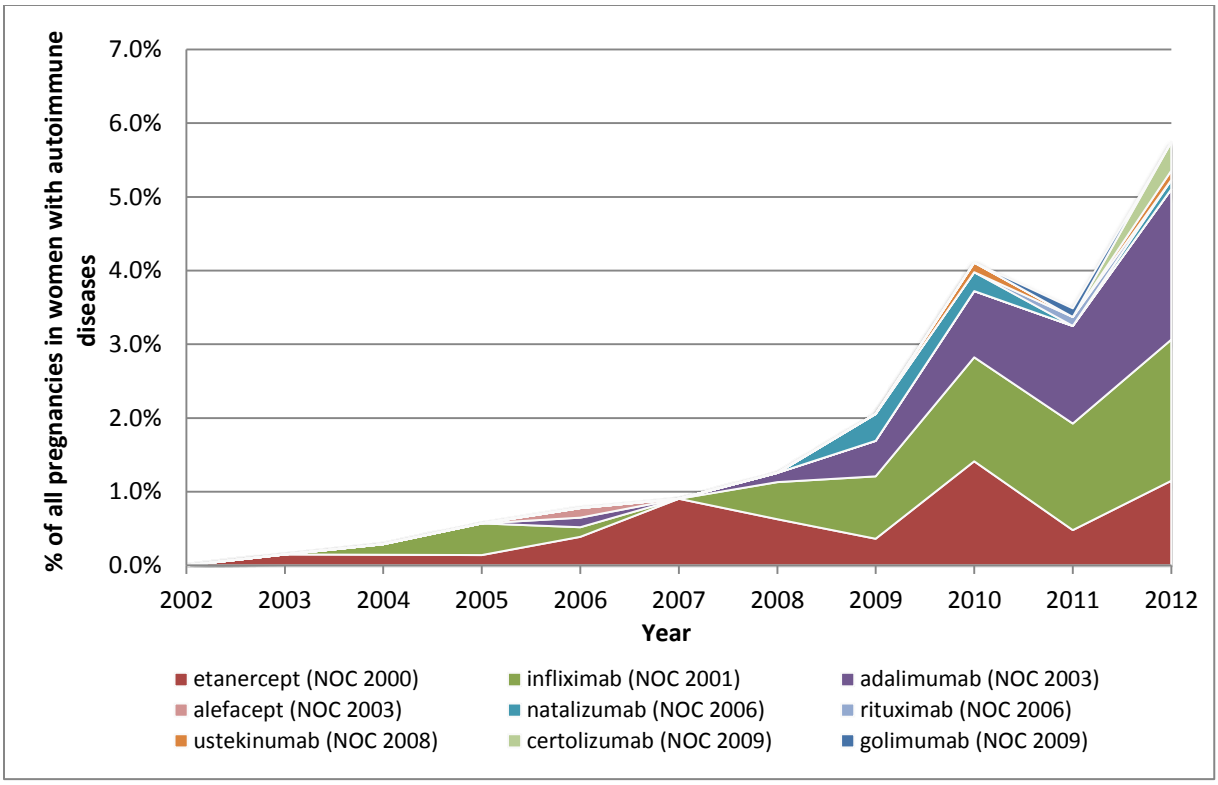


Figure 5. Secular trends of biologics use before conception or during pregnancy in women with autoimmune disease, from 2002 to 2012

NOC = Notice of Compliance from Health Canada for market authorization for autoimmune disease indications

Patterns of biologic utilization, including discontinuation and restarts are presented in Table 5. During the preconception period, use of biologics remained fairly constant; from 1.2% of all pregnancies among women with autoimmune disease in the 12 to 9 months preconception (PC1) to 1.3% in the three months preconception (PC4). With respect to new starts, the proportions ranged from 0.1% to 0.2% over the preconception period. We observed lower proportions of new starts during T1 to T3. Within the first trimester of pregnancy, 31% (34/110) of women discontinued their biologic. This trend continued with 38% (30/79) discontinuing their biologic in the second trimester while 98% (50/51) of those women who were on treatment in the second trimester continued on treatment in the third trimester.

Table 5. Patterns of biologic use one year before pregnancy and during pregnancy, in three-month windows (N, % of all pregnancies with autoimmune disease [N=8,431])

	Timing of Exposure with Respect to Pregnancy						
On Biologic	**12 to 9 months PC (PC1)**	**9 to 6 months PC (PC2)**	**6 to 3 months PC (PC3)**	**3 months PC (PC4)**	**1st T (T1)**	**2nd T (T2)**	**3rd T (T3)**
Overall	102 (1.2%)	106 (1.3%)	111 (1.3%)	110 (1.3%)	79 (1.0%)	51 (0.6%)	50 (0.6%)
Rheumatoid arthritis*	53 (0.6%)	49 (0.6%)	55 (0.7%)	51 (0.6%)	33 (0.4%)	17 (0.2%)	18 (0.2%)
Inflammatory bowel disease*	42 (0.5%)	47 (0.6%)	46 (0.6%)	48 (0.6%)	42 (0.5%)	37 (0.4%)	33 (0.4%)
Other autoimmune disease*	37 (0.4%)	37 (0.4%)	40 (0.5%)	36 (0.4%)	27 (0.3%)	12 (0.1%)	14 (0.2%)
New start/ restart†	-	15 (0.2%)	17 (0.2%)	12 (0.1%)	< 5	< 5	6 (0.1%)
Discontinued‡	-	11 (0.1%)	12 (0.1%)	13 (0.2%)	34 (0.4%)	30 (0.4%)	7 (0.1%)

PC = pre-conception; T = trimester

* Some individuals had more than one autoimmune disease; numbers do not sum to overall biologics users

† Did not fill a prescription for a biologic drug in the preceding window

‡ Filled a biologic prescription in the preceding window and no fill in current window

Given the time-dependent nature of biologic use with respect to pregnancies, and the possibility of symptom remission, I examined the association of various maternal characteristics and the odds of discontinuing biologics over two periods: 1) during the preconception period (PC1 to PC4); and 2) during pregnancy (T1 to T3). These analyses were limited to those with RA or IBD (n=127) as they represented conditions with the highest biologics use, and due to small sample sizes in other autoimmune disease categories the model algorithm did not converge.

During the preconception period (Figure 6), I did not find statistically significant associations between drug utilization windows (PC1-PC4), maternal age at delivery, having RA or IBD, or various

indicators of disease severity, with the odds of biologic discontinuation. It appears that with each additional concomitant medication, such as disease-modifying agents, immunosuppressants, or glucocorticoids, women were less likely to discontinue their biologic drug (odds ratio [OR] 0.71, 95% confidence interval [CI] 0.46 to 1.09). Though not statistically significant, the point estimate suggests that those with more concomitant drugs possibly had more severe disease, and as a result were more likely to remain on biologic treatment.

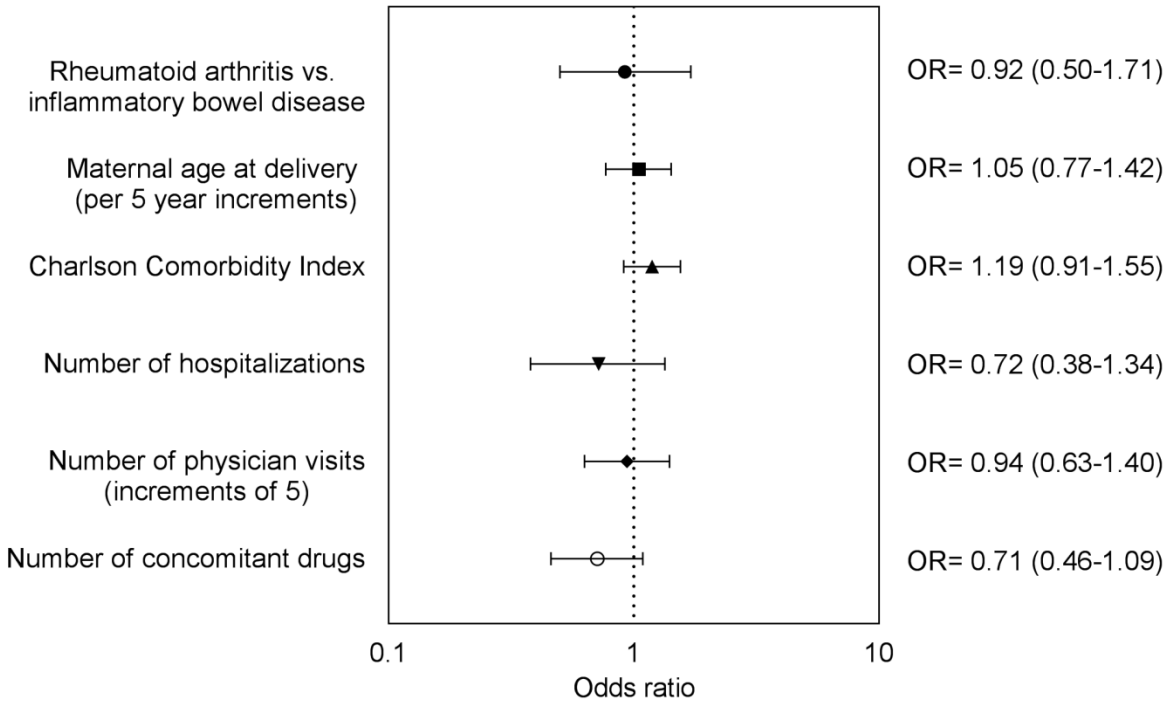


Figure 6. Odds of discontinuing biologics 12 months preconception in women with autoimmune disease (N=127)

During pregnancy (Figure 7), I also found that none of the indicators of disease severity were statistically significantly associated with the odds of discontinuing biologics. After adjusting for these covariates as well as maternal age, autoimmune disease type was independently associated with biologic discontinuation. Specifically, women with RA had three times higher odds (OR 3.40, 95% CI

1.33 to 8.71) of discontinuing biologics during pregnancy, compared to those with IBD. Biologics discontinuation also differed significantly by trimester of pregnancy. The odds of discontinuing treatment was 13 times higher (OR 13.35, 95% CI 3.57 to 49.95) in the second trimester compared to first trimester, and similarly comparing third to first trimester (OR 13.30, 95% CI 3.34 to 53.00); whereas, there was no difference in the risk of discontinuation between the second and third trimesters (OR 0.99, 95% CI 0.41 to 2.44).

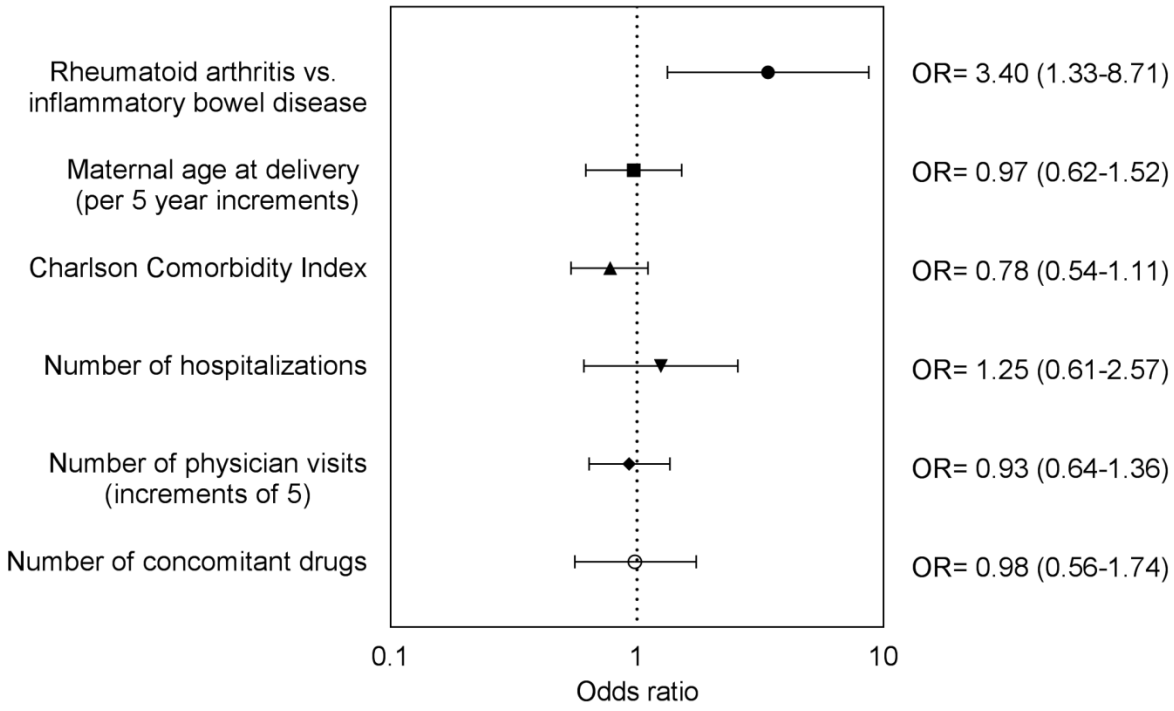


Figure 7. Odds of discontinuing biologics during pregnancy in women with autoimmune disease (N=127)

2.4. Discussion

This is the first study to characterize, at the population level, the patterns of biologics utilization and discontinuation, before conception and during pregnancy, in women with autoimmune disease. I

found that 2.3% of women with autoimmune disease had been exposed to a biologic during preconception or during pregnancy between 2002 and 2012. With respect to biologic discontinuation, I found little change before conception, while during pregnancy more than two-thirds of the women had discontinued their biologic by the third trimester. Finally, multivariable models showed that women with RA were more than three times as likely to discontinue biologics during pregnancy as compared with women with IBD, despite adjusting for various indicators of disease severity.

Despite the preponderance of autoimmune disease during childbearing years, evidence is limited on their management during pregnancy given the exclusion of pregnant women from clinical drug trials. As such, real-world observational studies such as this, which provides evidence on the increasing use of biologics in the pregnancy population, can be the only source of evidence. Secular trends in my study showed significantly increased use of biologics over the 10-year study period (2002-2012), and by 2012 biologics users comprised 5.7% of all pregnancies in this population. This was corroborated by a recent United States study by Desai et al., which found that from 2001 to 2012 the use of biologics at any time during pregnancy has increased more than three-fold (116). However, this study found much higher rates of biologic use (20.2%) compared to in the current study cohort, which is likely due to the differential access to biologics in Canada. In Canada, patients must fulfill certain criteria including failure or intolerance to first-line or combination traditional disease-modifying therapies before access to biologics are granted. Despite the differences in some of the results, Desai et al. also showed a decline in biologics use in women during year 2011. Given the data available to me, it was not possible to conclude whether there was a general decline in use or only with respect to the pregnant population. However, I speculate that one possible contributor

to this observed phenomenon was a report released in 2010 of 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 (117). Subsequently a study from the US Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry found a significant increase of infections in infants between 9 and 12 months of age whom were born to mothers with IBD receiving combination therapy with thiopurines and TNF inhibitors, relative to infants born to mothers in the unexposed group (relative risk 1.50, 95% CI 1.08 to 2.09) (118). As a result, new clinical practice guidelines from the British Society of Rheumatology, and recommendations from the American College of Rheumatology now suggest discontinuing most biologic drugs at 30 to 32 weeks gestation (75,119).

These findings show that a large proportion of women discontinued their biologic in the first (31%), and second (38%) trimesters, while those who continued to be on treatment during the second trimester mostly remained on treatment through to delivery (98%). Similar patterns were seen in Desai et al.'s RA cohort, where 33% discontinued their biologic in the first trimester, 66% in the second trimester, and 97% of those who were on treatment in the second trimester remain on treatment in the third trimester. The observed phenomenon of first trimester drug discontinuation may be in part due to earlier concerns for the association of biologics exposure with VACTERL (vertebral defects, anal atresia, cardiac defects, trachea-esophageal fistula, renal anomalies, and limb abnormalities) (120). Though this association has since been disputed (121) and subsequent systematic reviews of TNF inhibitor use in IBD have not revealed associations between biologic exposure and congenital anomalies (69,122). Indeed, the present study was the first to explore the relationships between maternal demographics, having RA versus IBD, and a number of indicators for

disease severity, with the odds of discontinuing a biologic before and during pregnancy. I found that women with RA were more than three times more likely to discontinue their biologic compared to those with IBD. One possible explanation for this is differences in clinicians' comfort level with the use of biologics in pregnant patients according to their underlying condition. Another explanation is the widely held perception that majority of RA patients experience spontaneous remission during pregnancy (123). However, recent large-scale studies in RA found that only 16-27% of women with RA achieve complete remission due to pregnancy (124,125) and often, this phenomenon is not seen until the third trimester. As such, these findings warrant two important clinical considerations, one being that a substantial proportion of women with RA may be discontinuing their biologic in early pregnancy irrespective of changes in disease severity and concomitant medication use, and two being that women with RA who were on a biologic before pregnancy discontinued their biologic in the first or second trimesters when changes in disease activity may not have manifested yet.

The main strength of this study is its population-based design and the availability of BCPDR data, one of utmost importance being a precise pregnancy start date (93). The linkage between the BCPDR with other Population Data BC databases, specifically the PharmaNet database comprised of all prescription medications dispensed in the province, provides the unique ability to establish precise patterns and impacts of drug exposures with respect to timing of pregnancies and deliveries. Given the challenges of pregnancy dating, and the importance of establishing precise timing of medication exposures during pregnancy, the availability of this information increases the validity of this study (94). However, some of my findings should be interpreted with caution as the 95% CIs of many of the estimates are very wide, and crossed the point of indifference. Due to small sample sizes, I was not able to explore differences in patterns of use of specific biologics, especially with

respect to certolizumab. Further, it is recognized that there are inherent limitations of the use of administrative data in observational studies including sub-optimal diagnostic accuracy and risk of misclassification. Uncertainty in identification of diseases in this study has been mitigated by using previously validated diagnostic codes and algorithms that have been successfully employed in similar populations with high sensitivity and specificity (126,127). Restricting the sample to women who received a biologic for several analyses (e.g., discontinuation) should have further added to the likelihood that the study sample did have the autoimmune diseases of interest.

Overall, from 2002 to 2012, there was increasing biologics utilization in the preconception and pregnancy periods of BC women with autoimmune disease, consistent with that observed in studies from other jurisdictions. These patterns showed a sharp rise in biologic use over the 10-year period, and those who used a biologic were highly likely to discontinue their treatment once pregnant. The concern highlighted by this study is that the discontinuation pattern was occurring irrespective of changes in certain indicators of disease activity and use of concomitant treatments. Future research should focus on improving our understanding of the risks and benefits of discontinuing biologics by providing evidence on the impact on fetal and maternal health. This will be critical to guiding clinical decision making in this understudied population.

3. Chapter 3: Risk of preterm delivery and small-for-gestational-age births in women with autoimmune disease using biologics before or during pregnancy[†]

3.1. Introduction

Pregnancy is a unique state of coexistence of genetically different individuals, which is possible due to dramatic shifts in maternal immune function during pregnancy, protecting the fetus from immunological attack (20). In women with chronic inflammatory disease, this interaction between autoimmunity and pregnancy becomes complex. The pathology underscoring autoimmune diseases including RA, AS, PsA, Ps, and IBD, are perpetuated mainly by the dysfunction of cytokines and chemokines regulating immune system activity, with TNF being a key cytokine in this abnormal immune response (26,128–130).

In pregnancy, TNF controls cyclooxygenases that affect blastocyst implantation, endometrial permeability, and decidualization (131), and contributes to the process of labor (132). Abnormally high levels of TNF and other cytokines have been implicated in pregnancy complications including preterm delivery, fetal growth retardation, early and unexplained spontaneous abortions, and miscarriages (132–135). As such, evidence suggests that higher autoimmune disease activity at the time of conception and during pregnancy is correlated with increased risks of adverse maternal and neonatal outcomes (19,111).

[†] A version of this chapter has been published: Nicole W. Tsao, Eric C. Sayre, Gillian Hanley, Mohsen Sadatsafavi, Larry D. Lynd, Carlo A. Marra, Mary A. De Vera. Risk of preterm delivery and small-for-gestational-age births in women with autoimmune disease using biologics before or during pregnancy: A population-based cohort study. Ann Rheum Dis. 2018 Mar 1. pii: annrheumdis-2018-213023. doi: 10.1136/annrheumdis-2018-213023. [Epub ahead of print]

Biologics work to treat autoimmune diseases by modulating the immune system by targeting key inflammatory cytokines including TNF, IL-1, IL-6, or receptors of these cytokines (136). With these medications available only within the last 15 years, their use by women during pregnancy has been growing and becoming more clinically acceptable (137) However, prior studies on this topic included only a small number of women enrolled in registries, and with comparison groups often selected from external sources; further majority of the studies have not implemented any methods to adjust for differences in baseline characteristics between groups (70,71,73,74,138). The aim of this study was to assess the risk of preterm delivery and SGA births – two related outcomes that remain as leading causes of infant morbidity and mortality (139) – in women with autoimmune disease exposed to a biologic, compared to those who were not exposed to a biologic before or during pregnancy.

3.2. Methods

Data sources

The data source comprised of healthcare administrative data from Population Data BC (140). These include all provincially-funded physician visits, laboratory tests and diagnostic procedures (x-rays, ultrasounds etc.) from the MSP database (83), hospitalizations from the DAD (87), and demographics and vital statistics since 1985 (84–86). Population Data BC also includes the comprehensive prescription drug database, PharmaNet, which captures all prescriptions dispensed in community pharmacies regardless of payment source, since 1996 (88). These data were linked to the BCPDR (89), which contains validated information on the date of conception, antenatal, intrapartum, and postpartum maternal and infant data abstracted from medical records for >99% of births in BC. Altogether, linkage of these data sources created a source population comprised of women (n=305,351) in BC who had one or more pregnancies (n=449,098) 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. Details of these data sources are described in previous work (137).

Study cohort

I created a cohort of women who had a recorded diagnosis of one or more autoimmune diseases that could be treated with a biologic, which included RA, IBD, Ps/PsA, AS, JIA, and SARDs – including SLE and other connective tissue diseases (**Error! Reference source not found.**). These were defined as having the ame ICD-9/10 code for a specific autoimmune disease from two separate physician visits that were at least 60 days apart and within two years, any time prior to the date of conception; or, having at least one hospitalization with an ICD-9/10 code for an autoimmune disease any time prior to the date of conception. Given that the unit of analysis was the individual pregnancy, each pregnancy had to satisfy the above criteria in order to be included in the analyses.

Exposure ascertainment

Using dispensation dates and Canadian Drug Identity Codes for biologics in PharmaNet, I identified pregnancies in women in the autoimmune disease cohort who had at least one prescription for a biologic at any point during the drug exposure period of interest for each study outcome. For preterm deliveries, this period was defined as three months prior to the date of conception (referred to as the preconception period) until the date of delivery or 36 weeks +6 days of gestation (i.e., one day short of 37 completed weeks of gestation), which ever came first, for each pregnancy. This was to avoid classifying pregnancies as exposed if they were exposed to a biologic on or after 37 completed weeks of

gestation in which by definition they would not be susceptible to the outcome occurring. For SGA, the exposure period was defined as three months prior to the date of conception, until the date of delivery. Disease-matched women with pregnancies that were not exposed to a biologic during the drug exposure periods of interest comprised the unexposed groups. All biologics available in BC for the treatment of autoimmune diseases of interest during the study period are listed in Appendix A Table 1.

Outcomes

The outcomes of interest were preterm delivery and SGA births. The exact date of birth for all babies born to the women in the cohort were available from the BCPDR, as well as valid gestational age estimates based on information from early gestational ultrasounds or from the date of last menstrual period if an early gestational ultrasound was not performed. If neither field was recorded, gestational age was estimated from newborn clinical exam and/or chart documentation. Preterm delivery was defined as a binary outcome of delivery occurring before 37 completed weeks of gestation, regardless of the reason. I also included infants with ICD-9/10 codes for preterm births from the MSP database or DAD. Small-for-gestational-age was defined as a newborn weighing less than the 10^{th} percentile of gestational age- and sex-specific weights for neonates in BC (141) using birth weights recorded in the BCPDR.

Statistical analysis

To minimize bias due to confounding by indication, I used a high dimensional propensity score (HDPS) algorithm that incorporated investigator-specified covariates and additional factors that acted as proxy variables for unmeasured confounders (104). The HDPS was generated using logistic regression models

and included candidate covariates that were associated with exposure and derived from four dimensions of data comprised of aforementioned data sources: 1) MSP database; 2) DAD; 3) PharmaNet; and, 4) BCPDR. Within the MSP database, DAD, and PharmaNet, only claims or codes that occurred during the 12 months prior to the date of conception for each pregnancy were assessed as candidate covariates to be included in the HDPS. I specified the HDPS algorithm to prioritize covariates across data dimensions by their potential for controlling confounding based on the bias term estimator proposed by Bross (107), meaning that the covariates must both be associated with the exposure and the outcome, to mitigate the potential for including variables that were only associated with the exposure, which may actually introduce bias into estimates (142). The top 50 empirically derived covariates for each outcome were included along with investigator-specified confounders for propensity score estimation (Appendix B Table 1 and Appendix B Table 2). For each outcome, biologic exposed pregnancies were matched with unexposed pregnancies using HDPS in a ratio of 1:5 without replacement. Match performance was evaluated using standardized mean differences in baseline characteristics of matched and unmatched cohorts.

Using logistic regression models I analyzed each study outcome among biologic exposed and unexposed women in the HDPS-matched cohort (model 1). As sensitivity analyses for each outcome, I conducted multivariable logistic regression models with deciles of HDPS included as indicator terms (model 2) and with continuous HDPS as a covariate (model 3). As sensitivity analysis for the exposure, I defined the exposure window beginning at 12 months prior to conception for both outcomes, and used HDPS matching (model 4). Using robust variance estimators to account for correlation between multiple pregnancies within the same woman did not appreciably change confidence intervals in the outcome

models, as such, all correlation structures were omitted. All analyses were conducted using SAS statistical software v.9.3 (Cary, NC, USA).

3.3. Results

From a source population of 305,351 women in BC who have had one or more pregnancies over the study period, approximately 2% had a diagnosis of one of the autoimmune diseases of interest resulting in 6,218 women with 8,607 pregnancies in the study cohort. Table 6 shows baseline characteristics for the unmatched cohorts as well as HDPS-matched cohorts for analyses of respective study outcomes. Marked imbalances between exposure groups in the distribution of autoimmune disease types, and concomitant medication use, as seen with large standardized mean differences in the unmatched cohort, were mitigated in the HDPS-matched cohorts.

Preterm delivery

The HDPS-matched cohort for analysis of preterm delivery outcomes comprised 109 women and 120 babies exposed to a biologic during three months preconception to the date of delivery, and 584 women and 600 babies unexposed to a biologic during that time (Table 6). Most of the women had a diagnosis of RA or IBD (49% and 46%, respectively) and filled prescriptions for one of three commonly prescribed TNF inhibitors (infliximab 39%, etanercept 30%, or adalimumab 25%) (Table 6). In the HDPS-matched cohort, 21 of the 120 babies (18%) exposed to a biologic preconception or during pregnancy, and 95/600 (16%) babies unexposed to a biologic, were born preterm. Table 7 shows the results of crude analyses of the association between biologic exposure and preterm delivery with an unadjusted OR of 1.64 (95% CI 1.02 to 2.63). In primary analyses, the OR for the association between biologic exposure and preterm

delivery was 1.13 (95% CI 0.67 to 1.90) (Table 7, Model 1). Sensitivity analyses involving multivariable logistic regression based on the unmatched cohort adjusting for HDPS deciles (Model 2) and continuous HDPS (Model 3), and extending the exposure window to 12 months preconception (Model 4) did not appreciably change the results. Finally, examination of the birth data showed mean gestational age at delivery was 38 weeks (range 27-43 weeks) among women exposed to a biologic and 38 weeks (range 19-43 weeks) among those unexposed (Figure 8).

Small-for-gestational-age births

The HDPS-matched cohort for analysis of SGA comprised 109 women and 120 babies exposed to a biologic during three months preconception to the date of delivery, and 585 women and 600 babies unexposed to a biologic during that time. Rheumatoid arthritis and IBD remained the most common disease types (45% and 48%, respectively), and infliximab, etanercept, and adalimumab were the most commonly prescribed biologics (Table 6). In the HDPS-matched cohort, SGA births occurred in 11/120 (9%) pregnancies in the biologic exposed group, and in 60/600 (10%) pregnancies that were in the biologic unexposed group. Table 7 shows the results of crude analyses of the association between biologic exposure and SGA with an unadjusted OR of 1.34 (95% CI 0.72 to 2.51). In primary analyses, the OR for the association between biologic exposure and SGA was 0.91 (95% CI 0.46 to 1.78) (Table 7, Model 1). Sensitivity analyses (Models 2, 3 & 4) again showed similar results. Further, examination of the Apgar scores of SGA newborns showed no appreciable differences; those exposed to a biologic had mean Apgar scores of 8.1 (SD 1.5) at 1 minute, and 9.0 (SD 1.0) at 5 minutes, and those unexposed had Apgar scores of 7.7 (SD 2.2) at 1 minute and 8.7 (SD 1.7) at 5 minutes.

Table 6. Baseline characteristics in unmatched and matched samples of biologic exposed and non-exposed pregnancies for preterm delivery and SGA analyses

	Unmatched sample overall			HDPS matched for preterm delivery analysis			HDPS matched for SGA analysis		
	Biologic exposed	**Biologic unexposed**	**SMD**	**Biologic exposed**	**Biologic unexposed**	**SMD**	**Biologic exposed**	**Biologic unexposed**	**SMD**
Current pregnancy									
Maternal age at delivery (mean (SD))	31.1	31.2	0.002	31.2	31.3	0.023	31.2	31.2	0.004
Multiparous	62 (43%)	4980 (59%)	0.309	52 (43%)	262 (44%)	0.007	52 (43%)	255 (43%)	0.017
Antenatal visits (mean (SD))	9.0	9.0	0.003	9.0	9.1	0.013	9.0	9.1	0.024
Obstetrical history									
Prior premature delivery	8 (6%)	495 (6%)	0.007	5 (4%)	28 (5%)	0.024	5 (4%)	30 (5%)	0.040
Prior spontaneous abortion	40 (28%)	2130 (25%)	0.069	37 (31%)	156 (26%)	0.107	37 (31%)	161 (27%)	0.088
Prior delivery with neonatal death	<5	52 (0.6%)	0.012	<5	7 (1%)	0.034	<5	6 (1%)	0.017
Prior stillbirth	<5	103 (1.2%)	0.072	<5	16 (3%)	0.011	<5	19 (3%)	0.040
Prior low birth weight	8 (6%)	240 (3%)	0.143	5 (4%)	24 (4%)	0.008	5 (4%)	27 (5%)	0.016
Prior anomalies	-	74 (0.9%)	0.133	<5	<5	-	<5	<5	-
Autoimmune disease type*									
Rheumatoid arthritis	67 (47%)	1733 (21%)	0.587	55 (46%)	297 (50%)	0.073	55 (46%)	272 (45%)	0.010
Inflammatory bowel disease	66 (46%)	2455 (29%)	0.335	57 (48%)	276 (46%)	0.030	57 (48%)	286 (48%)	0.003

Psoriasis/psoriatic arthritis	24 (17%)	3433 (41%)	0.535	20 (17%)	82 (14%)	0.084	20 (17%)	100 (17%)	0.000
Juvenile idiopathic arthritis	12 (8%)	89 (1%)	0.357	9 (8%)	42 (7%)	0.019	9 (8%)	33 (6%)	0.081
Systemic autoimmune rheumatic diseases	9 (6%)	1059 (13%)	0.209	7 (6%)	34 (6%)	0.007	7 (6%)	37 (6%)	0.014
Ankylosing spondylitis	8 (6%)	414 (5%)	0.037	5 (4%)	24 (4%)	0.008	5 (4%)	24 (4%)	0.008
Biologics[†‡]									
Infliximab	58 (37%)			47 (39%)			47 (39%)		
Etanercept	48 (31%)			36 (30%)			36 (30%)		
Adalimumab	40 (26%)			30 (25%)			30 (25%)		
Certolizumab	<5			<5			<5		
Ustekinumab	<5			<5			<5		
Rituximab	<5			<5			<5		
Golimumab	<5			<5			<5		
Alefacept	<5			<5			<5		
Concomitant medications									
DMARDs	81 (56%)	1693 (20%)	0.791	62 (52%)	311 (52%)	0.003	62 (52%)	314 (52%)	0.013
Glucocorticoids	66 (46%)	880 (10%)	0.854	56 (47%)	251 (42%)	0.097	56 (47%)	254 (42%)	0.087
Traditional NSAIDs	47 (33%)	2218 (26%)	0.131	35 (29%)	193 (32%)	0.065	35 (29%)	185 (31%)	0.036
Antidepressants	30 (21%)	1280 (15%)	0.146	26 (22%)	120 (20%)	0.041	26 (22%)	123 (21%)	0.029
Anxiolytics	15 (10%)	638 (8%)	0.087	12 (10%)	53 (9%)	0.040	12 (10%)	60 (10%)	0.000
COX2 NSAIDs	7 (5%)	281 (3%)	0.084	6 (5%)	31 (5%)	0.008	6 (5%)	30 (5%)	0.000

Comorbidities									
Anxiety	18 (13%)	814 (10%)	0.081	16 (13%)	76 (13%)	0.020	16 (13%)	80 (13%)	0.000
Mood disorders	12 (8%)	430 (5%)	0.139	10 (8%)	45 (8%)	0.031	10 (8%)	45 (8%)	0.031
Hospitalization at baseline	49 (34%)	2062 (24%)	0.219	40 (33%)	168 (28%)	0.116	40 (33%)	187 (31%)	0.046

HDPS = high dimensional propensity score; SMD = standardized mean difference; DMARD = disease-modifying anti-rheumatic drugs; NSAID = non-steroidal anti-inflammatory drugs; COX = cyclooxygenase. All cell sizes <5 are suppressed due to privacy restrictions of data sharing agreements.

[*]Sum of percentages exceed 100% due to some individuals having more than one diagnosis

[†]Anytime from 3 months prior to date of conception to date of delivery

[‡]Sum of percentages exceed 100% due to some pregnancies being exposed to more than one drug

Table 7. Proportion of pregnancies ending in preterm delivery or SGA based on biologic exposure group and timing of exposure

	A. Preterm Delivery		B. SGA	
	Biologic exposed	**Biologic unexposed**	**Biologic exposed**	**Biologic unexposed**
Overall	21/120 (18%)	95/600 (16%)	11/120 (9%)	60/600 (10%)
Preconception†	20/114 (18%)	96/606 (16%)	11/114 (10%)	60/606 (10%)
1st trimester	18/96 (19%)	98/624 (16%)	9/96 (9.4%)	62/624 (10%)
2nd trimester	12/55 (22%)	104/665 (16%)	5/55 (9.1%)	66/665 (10%)
3rd trimester	12/57 (21%)	104/663 (16%)	5/57 (8.8%)	66/663 (10%)
Unadjusted OR (95% CI)	1.64 (1.02 to 2.63)		1.34 (0.72 to 2.51)	
Model 1 OR (95% CI)*	1.13 (0.67 to 1.90)		0.91 (0.46 to 1.78)	
Model 2 OR (95% CI)**	1.21 (0.74 to 2.00)		1.00 (0.53 to 1.92)	
Model 3 OR (95% CI)***	0.96 (0.56 to 1.64)		1.03 (0.53 to 2.01)	
Model 4 OR (95% CI)‡	0.94 (0.56 to 1.55)		1.03 (0.56 to 1.90)	

† Defined as 3 months prior to the date of conception

*Logistic regression in matched cohort

** Multivariable logistic regression with HDPS deciles

*** Multivariable logistic regression with continuous HDPS as covariate

‡ Exposure window starting from 12 months preconception, logistic regression in HDPS matched cohort

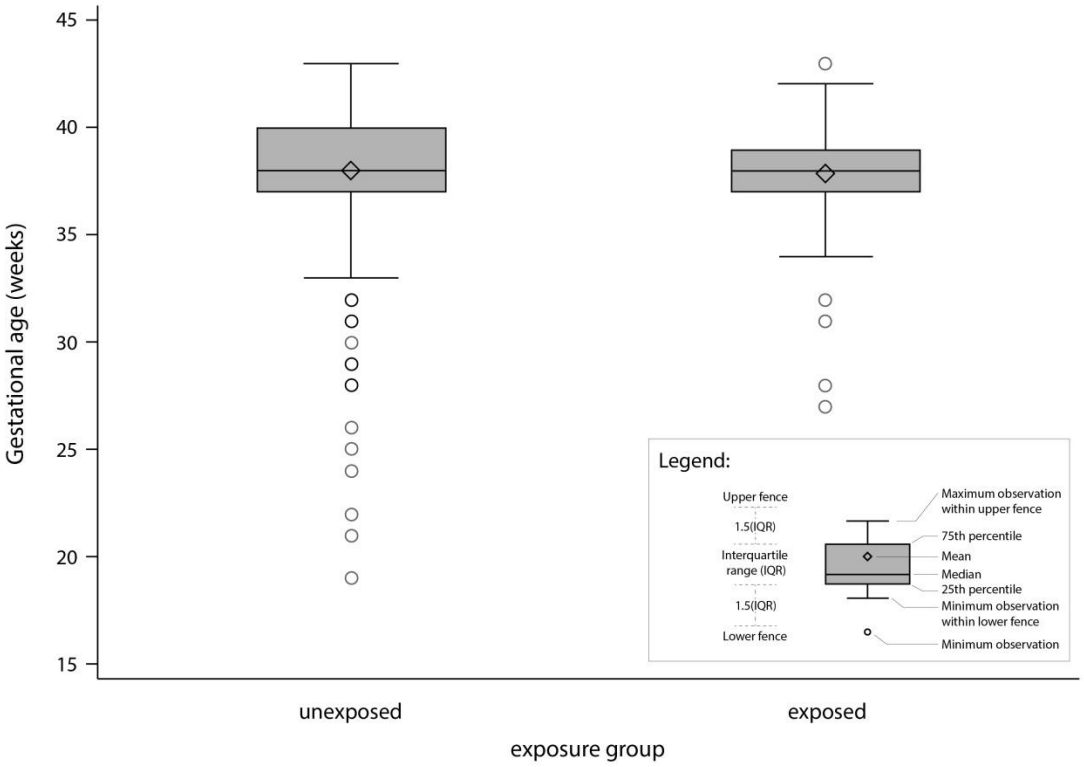


Figure 8. Distribution of gestational age by exposure group

3.4. Discussion

The objective of this study was to use population-based administrative health data with valid information on estimated date of conception and complete information on all dispensed prescriptions in BC, to evaluate the association between biologic exposure preconception, or during pregnancy, and preterm delivery or SGA births in women with autoimmune diseases. I applied HDPS matching to account for differences in baseline characteristics between women exposed and unexposed to a biologic. Prior to restricting the population using HDPS matching, I found that differences in baseline characteristics in the unmatched sample led to suggestion of an association between biologic use and the risk of preterm deliveries. However, after successful implementation of HDPS to control for confounding by indication and proxies of unmeasured confounders, I did not find an association between biologic exposure and the outcomes of interest, in primary and various sensitivity analyses. While I examined all biologics used in the cohort, TNF inhibitor biologics were the most common (94%), and as such these results mostly apply to these biologics and less so to those that are not TNF inhibitors.

Indeed the population-based setting of this study lends more generalizability to the results, and the implementation of HDPS-based methods allows for better control of confounding compared to traditional modeling methods, thus contributing to better understanding of the use of biologics in the pregnant population. With respect to the outcome of preterm delivery, several single-centre studies using maternal medical records have reported risks of preterm delivery in those exposed to a biologic during pregnancy compared to those who were not exposed, ranging from OR 2.00 (95% CI 0.19 to 20.51) to OR 2.71 (0.44 to 16.52) (70,138,143). Registry-based studies from the British Society for Rheumatology Biologics Register in RA patients, and the German registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie in IBD patients reported risk estimates of 1.42 (95% CI 0.25 to 7.73)

and 2.14 (0.10 to 44.28), respectively of preterm deliveries in women who were using a biologic before or during pregnancy (71,144). These studies have relatively small sample sizes (50-80 individuals), and have not implemented methods to adjust for the effects of the underlying disease severity or effects from measured and unmeasured confounders, as such these estimates have lower generalizability and higher uncertainty, as evidenced by the wide confidence intervals. At the time of this publication, only two studies have reported adjusted risk estimates, one abstract by Chambers (145), and one publication by Burmester (146), with data from the Organization of Teratology Information Services registry and the Adalimumab Pregnancy Exposure Registry. Chambers (total N of 722), using propensity score methods found that the adjusted hazard ratio (HR) for preterm delivery was 0.82 (95% CI 0.50 to 3.84) in pregnancies exposed to adalimumab compared to those unexposed; and Burmester (total N of 373) reported an adjusted HR for preterm delivery of 1.08 (95% CI 0.41 to 2.83) in RA patients using adalimumab during pregnancy, compared to RA patients not using adalimumab.

With respect to SGA outcome, there are fewer studies – only two to date – with conflicting findings. Using medical records from a university hospital, Schnitzler reported 6% of pregnancies exposed to infliximab ending in a very SGA birth (<5th percentile) compared to 11% of unexposed pregnancies; in contrast in my study there were no occurrences of very SGA births. Martinez, using medical records, reported that among women with IBD exposed to a biologic during pregnancy, 12.5% resulted in SGA births compared to 9% among unexposed pregnant women with IBD (70,138). These rates appeared similar to my results; however, again neither of these studies accounted for baseline differences between exposure groups. Thus, with respect to the SGA outcome among women with autoimmune disease prescribed a biologic, this study is the first to use population-based data to conduct analyses adjusted for potential confounders and proxies of unmeasured confounders using HDPS.

Strengths and limitations of this study bear discussion. High quality, high coverage, population-based databases from Population Data BC, and the linkage with the perinatal registry (BCPDR) and the prescription dispensations database (PharmaNet) provided the ability to accurately determine the timing of all medication dispensations with respect to milestone pregnancy dates, for each pregnancy in the cohort, thus minimizing potential biases caused by problems such as misclassification, patient recall bias, and selection bias. The comprehensive BCPDR data also allowed for the ascertainment of SGA using babies' gestational age and birth weights, whereas currently available research focus mainly on the outcome of low birth weight, which is itself confounded by gestational age whereby about two-thirds of low birth weight infants are preterm (147). As such, SGA is not only a more useful outcome measure, but also allowed the investigation of the impact of biologics on SGA and preterm delivery outcomes independently. Using HDPS matching is another strength which lent this study high internal validity, as it allowed for better adjustment of confounding by indication and adjustment of proxies of unmeasured confounders (104). Indeed addressing confounding by indication is of utmost importance in the population of women with autoimmune disease given the association between disease activity and adverse pregnancy outcomes (19,111), and the fact that those with higher disease activity are also more likely to be on a biologic given the current treatment pathways. The main limitation of this study remains the relatively small sample size in the matched cohorts; however the use of HDPS matching inherently prioritizes validity over precision of estimates, of which the latter can only be overcome by accumulation of further evidence or pooling of multiple databases.

Altogether, I found no association between biologic use before or during pregnancy and preterm delivery or SGA births in women with autoimmune disease, compared to those who had comparable

propensity to receive a biologic during that time but did not. As such, the findings suggest that biologics may be a safe treatment option for women with certain autoimmune diseases who, as previous research suggest, are at higher risk of adverse pregnancy outcomes due to their disease. Given that exposures and outcomes in biologic use during pregnancy remain fairly rare, relatively small samples are a continual challenge, as such my study represents an important contribution to the accumulation of evidence on the safety of the use of biologics in pregnant women, which may lead to increased prescriber comfort and patient acceptance, decreased uncertainty, and improved maternal and neonatal outcomes in this population.

4. Chapter 4: Risk of congenital anomalies in infants born to women with autoimmune disease using biologics before or during pregnancy[‡]

4.1. Introduction

Chronic inflammatory autoimmune diseases include over 70 types of disorders, collectively affecting more than 5% of the population in Western countries (1). Some of the most prevalent are RA, affecting 0.5-1% of the population, and IBD, affecting approximately 0.5% of the population (2,3). A commonality is that nearly all autoimmune diseases have a female predominance, with more than 80% of autoimmune disease patients being women, resulting in a 'sex gap' (1,4,5). In light of this, there is growing recognition that autoimmunity may impact pregnancy, including maternal complications and neonatal outcomes (16). As such, treatment for autoimmune disease may be required throughout pregnancy, as evidence shows that active disease at the time of conception and disease flares during pregnancy are both predictors of adverse outcomes (17–19). This presents a challenge given that several of the traditional disease-modifying agents and immunosuppressants are contraindicated in pregnancy, including methotrexate, leflunomide, mycophenolate mofetil, cyclophosphamide, and cyclosporine.

Disease management with biologics could be a viable alternative depending on their risk-benefit profile in pregnancy. The findings from Chapter 2 show that biologics are increasingly being used during pregnancy (137). As such, it is imperative to investigate potential adverse effects of biologics

[‡] A version of this chapter is under peer review: Nicole W. Tsao, Gillian E. Hanley, Larry D. Lynd, Mary A. De Vera. Risk of congenital anomalies in infants born to women with autoimmune disease using biologics before or during pregnancy: A population-based cohort study. Canadian Medical Association Journal

during pregnancy, including the risk of congenital anomalies. The objective of this Chapter was to conduct a population-based cohort study to assess the association between biologic use in the 90 days before pregnancy or during the period of fetal organogenesis by women with autoimmune disease, and the risk of congenital anomalies in their offspring.

4.2. Methods

Data sources

The data source for this Chapter also comes from Population Data BC (140). These include all provincially-funded physician visits, ordered laboratory tests, and diagnostic procedures (x-rays, ultrasounds etc.) from the MSP database (83), hospitalizations from the DAD (87), and demographics and vital statistics since 1985 (84–86). Population Data BC also includes the comprehensive prescription drug database, PharmaNet, which captures all outpatient dispensed prescriptions, since 1996 (88). These data were linked to the BCPDR (89), which contains data abstracted from obstetrical and neonatal medical records on nearly 100% of births in BC from over 60 acute care facilities as well as births occurring at home attended by registered midwives. These linkages allowed for the creation of the source population comprised of women in BC who had one or more pregnancies ending in a live or still birth between January 1st, 2002 and December 31st, 2012, and were continuously covered by BC's provincial health plan for at least 12 months prior to the start of pregnancy and in the 12 months following delivery. This continuous coverage requirement was to ensure all relevant data for all pregnancies in this cohort was captured. Details of these data sources are described in previous work (137,148).

Study cohort

To create the study cohort, I restricted the source population to women who had a recorded diagnosis of one or more autoimmune diseases that could be treated with a biologic, which included RA, IBD, Ps/ PsA, AS, JIA, and SARDs (**Error! Reference source not found.**). This was defined as aving the same ICD-9/10 code for a specific autoimmune disease from two separate physician visits that were at least 60 days apart and within two years, any time prior to the date of conception; or having one or more hospitalizations with an ICD-9/10 code for an autoimmune disease (137,148).

Exposure ascertainment

Using dispensation dates and Canadian Drug Identity Codes for biologics in PharmaNet, women in the autoimmune disease cohort were considered to have a pregnancy that was exposed to a biologic if they had at least one prescription for a biologic at any point during 90 days prior to the date of conception or during the first trimester. Disease-matched women with pregnancies that did not have a prescription for any biologic during the drug exposure period of interest comprised the unexposed group. The use of other non-biologic medications for autoimmune disease management was allowed for both the exposed and unexposed groups. For sensitivity analyses, the exposure period was extended to 12 months prior to the date of conception until the end of the first trimester. All biologics available in BC for the treatment of autoimmune diseases of interest during the study period are listed in Appendix A Table 1.

Outcomes

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

Statistical analysis

To minimize bias due to confounding by indication, I used an HDPS algorithm that incorporated investigator-specified covariates and additional factors that acted as proxy variables for unmeasured confounders (104). The HDPS was generated using logistic regression models with the exposure as the dependent variable. Covariates were derived from four dimensions of data comprised of aforementioned data sources: 1) MSP database; 2) DAD; 3) PharmaNet; and, 4) BCPDR. Within the MSP database, DAD, and PharmaNet, only claims or codes that occurred during the 12 months prior to the date of conception for each pregnancy were assessed as candidate covariates to be included

in the HDPS. Candidate covariates across data dimensions were prioritized by their potential for controlling confounding based on the aforementioned Bross formula (107,142). The top 50 empirically derived covariates for each outcome were included along with investigator-specified confounders for propensity score estimation (Appendix B Table 3). For each outcome, biologic exposed pregnancies were matched with unexposed pregnancies using HDPS in a ratio of 1:5 without replacement. Match performance was evaluated by comparing standardized mean differences in baseline characteristics of matched and unmatched cohorts.

Using logistic regression models I analyzed the relationship between biologic exposure and occurrence of congenital anomalies in the offspring from each pregnancy in the HDPS-matched cohort (model 1), using both the BCPDR defined outcome (congenital anomalies diagnosed at birth) and the "1-2-3" algorithm defined outcome (congenital anomalies diagnosed at birth and within the first year of life). Further sensitivity analyses were conducted using multivariable logistic regression models with deciles of HDPS included as indicator terms (model 2) and with continuous HDPS as a covariate (model 3). As sensitivity analysis for the exposure, I defined the exposure window beginning at 12 months prior to conception for both outcomes, and used HDPS matching (model 4). Following the same findings in previous chapters, I did not use generalized estimating equations with robust variance estimators to account for correlation between multiple pregnancies within the same woman, as analyses with this approach did not appreciably change estimates or confidence intervals in the outcome models. All analyses were conducted using SAS statistical software v.9.3 (Cary, NC, USA).

4.3. Results

There were 6,218 women with 8,607 pregnancies in the autoimmune disease study cohort. Table 8 shows baseline characteristics for the unmatched cohorts as well as HDPS-matched cohorts. At baseline, there were marked imbalances between exposure groups in the distribution of autoimmune disease types and concomitant medication use, as seen with large standardized mean differences in the unmatched cohort. The HDPS-matching was able to mitigate this imbalance.

Table 8. Baseline characteristics in unmatched and matched samples of biologic exposed and unexposed pregnancies for congenital anomalies analysis

	Unmatched sample overall			**HDPS matched sample**		
Maternal Characteristics	**Biologic exposed**	**Biologic unexposed**	**SMD**	**Biologic exposed**	**Biologic unexposed**	**SMD**
Current pregnancy						
Maternal age at delivery (mean (SD))	31.4 (4.7)	31.2 (5.2)	0.038	31.4 (4.7)	31.3 (5.5)	0.019
Multiparous	52 (44%)	4990 (59 %)	0.290	52 (44%)	244 (42%)	0.055
Antenatal visits (mean (SD))	9.1 (3.6)	9.0 (3.9)	0.019	9.1 (3.6)	9.0 (3.9)	0.015
Gestational hypertension	7 (6%)	645 (8%)	0.064	7 (6%)	64 (11%)	0.179
Gestational diabetes	13 (11%)	668 (8%)	0.111	13 (11%)	46 (8%)	0.111
Neighbourhood income quintiles						
5th percentile	24 (21%)	1760 (21%)	-	24 (21%)	124 (21%)	-
25th percentile	26 (22%)	1697 (20%)	-	26 (22%)	128 (22%)	-
Median (50th percentile)	21 (18%)	1841 (22%)	-	21 (18%)	128 (22%)	-
75th percentile	28 (24%)	1797 (21%)	-	28 (24%)	119 (20%)	-
95th percentile	18 (15%)	1395 (16%)	-	18 (15%)	86 (15%)	-
Hospitalization at baseline	39 (33%)	2072 (24%)	0.198	39 (33%)	181 (31%)	0.051
BMI at baseline (mean (SD))	24.6 (4.3)	24.6 (4.5)	0.005	24.6 (4.3)	24.5 (4.6)	0.036
Prior obstetrical history						
Premature delivery	5 (4%)	500 (6%)	0.074	5 (4%)	32 (5%)	0.056

Spontaneous abortion	37 (32%)	2221 (26%)	0.121	37 (32%)	156 (27%)	0.109
Delivery with neonatal death	<5	52 (1%)	0.028	<5	<5	-
Stillbirth	<5	103 (1%)	0.099	<5	13 (2%)	0.022
Low birth weight infant	5 (4%)	243 (3%)	0.076	5 (4%)	27 (5%)	0.017
Infant with anomalies	<5	74 (1%)	0.133	<5	<5	-
Autoimmune disease type*						
Inflammatory bowel disease	54 (46%)	2467 (29%)	0.359	54 (46%)	252 (43%)	0.062
Rheumatoid arthritis	55 (47%)	1745 (21%)	0.583	55 (47%)	298 (51%)	0.079
Psoriasis/psoriatic arthritis	20 (17%)	3437 (40%)	0.535	20 (17%)	95 (16%)	0.023
Juvenile idiopathic arthritis	9 (8%)	92 (1%)	0.327	9 (8%)	46 (8%)	0.006
Systemic autoimmune rheumatic diseases	7 (6%)	1061 (13%)	0.226	7 (6%)	30 (5%)	0.037
Ankylosing spondylitis	5 (4%)	417 (5%)	0.030	5 (4%)	31 (5%)	0.048
Biologics‡						
Infliximab	62 (34%)	-	-	62 (34%)	-	-
Etanercept	48 (27%)	-	-	48 (27%)	-	-
Adalimumab	45 (25%)	-	-	45 (25%)	-	-
Other biologic**	25 (14%)	-	-	25 (14%)	-	-
Concomitant medications						
DMARDs	60 (51%)	1714 (20%)	0.686	60 (51%)	307 (52%)	0.024
Glucocorticoids	55 (47%)	891 (10%)	0.882	55 (47%)	250 (43%)	0.086
Traditional NSAIDs	34 (29%)	2231 (26%)	0.062	34 (29%)	189 (32%)	0.070
COX2 NSAIDs	6 (5%)	282 (3%)	0.090	6 (5%)	31 (5%)	0.008
Antidepressants	25 (21%)	1285 (15%)	0.162	25 (21%)	117 (20%)	0.034
Anxiolytics	11 (9%)	642 (8%)	0.066	11 (9%)	54 (9%)	0.006
Comorbidities						

Anxiety	16 (14%)	816 (10%)	0.127	16 (14%)	80 (14%)	0.000
Mood disorders	10 (9%)	432 (5%)	0.138	10 (9%)	42 (7%)	0.051
Infant Characteristics	**Biologic exposed**	**Biologic unexposed**	**SMD**	**Biologic exposed**	**Biologic unexposed**	**SMD**
Female sex	63 (54%)	4515 (49%)	0.099	63 (54%)	301 (51%)	0.048
Gestational age (mean (SD))	37.9 weeks (2.3)	38.4 weeks (2.2)	0.223	37.9 weeks (2.3)	38.0 weeks (2.6)	0.031
Birth weight (mean (SD))	3200 grams (609)	3384 grams (596)	0.305	3200 grams (609)	3266 grams (665)	0.102
Apgar score at 1 minute (mean (SD))	8.1 (1.5)	8.0 (1.7)	0.072	8.1 (1.5)	7.8 (2.0)	0.176
Apgar score at 5 minutes (mean (SD))	8.9 (1.0)	9.0 (1.0)	0.036	8.9 (1.0)	8.8 (1.5)	0.108

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

*Sum of percentages exceed 100% due to some individuals having more than one diagnosis

†All cell sizes <5 are suppressed due to privacy restrictions of data sharing agreements

‡Sum of percentages exceed 100% due to some pregnancies being exposed to more than one drug

**Other biologics include: abatacept, alefacept, certolizumab pegol, golimumab, rituximab, tocilizumab, and ustekinumab

The HDPS-matched cohort included 117 pregnancies (107 women) exposed to a biologic 90 days before pregnancy or during the first trimester, and 585 HDPS-matched pregnancies (562 women) that were not exposed to a biologic during that time (Table 8). Most of the women had a diagnosis of RA or IBD (50% and 44%, respectively) and filled prescriptions for one of three commonly prescribed TNF inhibitors (infliximab 34%, etanercept 27%, or adalimumab 25%) (Table 8). There were 7/117 (6%) and 33/585 (6%) newborns that had one or more congenital anomalies at birth in the exposed and unexposed groups, respectively. Types of congenital anomalies that occurred in the biologic exposed group included: atrial septal defect, patent ductus arteriosus, other specified malformation of kidney, accessory auricle, ankyloglossia, and other specified congenital anomalies of the skin. Table 9 shows the results of crude analyses of the association between biologic exposure and congenital anomalies with an unadjusted OR of 1.09 (95% CI 0.51 to 2.36) compared to

unexposed. In the primary adjusted analysis, the OR for the association between biologic exposure and congenital anomalies was 1.06 (95%CI 0.46 to 2.47), suggesting no association (Table 9, model 1). When considering congenital anomalies at birth and during the first year of life, defined using the "1-2-3" algorithm, the proportion of congenital anomalies in the exposed group remained the same while a few more events were identified in the unexposed group, the overall results did not differ substantially (Table 9). Sensitivity analyses involving multivariable logistic regression based on the unmatched cohort adjusting for HDPS deciles (model 2) and continuous HDPS (model 3) did not appreciably change the results. Sensitivity analysis extending the exposure window to 12 months preconception (model 4) resulted in higher rates of congenital anomalies in both exposed (11/140, 8%) and unexposed groups (42/706, 6%) for the primary outcome, and in both groups for the secondary outcome (11/140, 8% and 50/706, 7%).

Table 9. Proportion of offspring with congenital anomalies identified at birth, and at birth and during the first year of life, based on timing of biologic exposure

	Congenital anomalies diagnosed at birth (defined using BCPDR)		**Congenital anomalies diagnosed at birth and during the 1st year of life (defined using "1-2-3" algorithm)**	
	Biologic exposed	**Biologic unexposed**	**Biologic exposed**	**Biologic unexposed**
Overall	7/117 (6%)	33/585 (6%)	7/117 (6%)	35/585 (6%)
3 months preconception	7/114 (6%)	46/732 (6%)	7/114 (6%)	54/732 (7%)
1st trimester	7/96 (7%)	46/750 (6%)	7/96 (7%)	54/750 (7%)
Unadjusted OR (95% CI)	1.09 (0.51 to 2.36)		0.95 (0.44 to 2.06)	
Model 1 OR (95% CI)*	1.06 (0.46 to 2.47)		1.00 (0.43 to 2.31)	
Model 2 OR (95% CI)**	1.02 (0.46 to 2.26)		0.88 (0.40 to 1.93)	

Model 3 OR (95% CI)***	1.12 (0.10 to 12.22)	1.21 (0.12 to 11.74)
Model 4 OR (95% CI)‡	1.16 (0.56 to 2.37)	1.41 (0.70 to 2.81)

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

4.4. Discussion

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

Indeed congenital anomalies are one of the most widely studied outcomes when assessing the safety of medications during pregnancy. Earlier reports raised concerns for the association of biologic exposure with VACTERL (vertebral defects, anal atresia, cardiac defects, trachea-esophageal fistula, renal anomalies, and limb) constellation of abnormalities (120). Though this association has since been disputed by Winger and Reed who drew attention to the inherent limitations of the data

source used in the earlier study, which only consisted of spontaneous adverse event reports (121). Due to the nature of the data, accumulated reports cannot be used to calculate the prevalence of anomalies or to compare risks of anomalies associated with specific drugs (121). Further, the criterion for VACTERL diagnosis requires the identification of three or more of the anomalies within a single patient, while the individually reported anomalies in their data can be regarded only as sporadic and not as a manifestation of the VACTERL constellation (121).

Due to challenges with a rare outcome, and a relatively rare exposure, no studies to date have shown a conclusive association (or lack thereof) and few have been able to adjust for potential confounders relating to autoimmune disease activity, concomitant medications, comorbidities, or obstetrical characteristics due to small sample sizes (ranging from around 50 to 250 subjects) (70–74,149,150). Even among studies with larger sample sizes that have adjusted for some potential confounders, the reported risk estimates are wide-ranging, with overlapping confidence intervals. Two published studies with particularly large sample sizes, Broms (N = 22,232) and Carman (N = 3,927) reported very divergent estimates of the association between biologic exposure before or during pregnancy and the risk of congenital anomalies as ORs were 1.32 (95%CI 0.93 to 1.87) and 0.52 (95%CI 0.13 to 2.08), respectively (151,152). There has been one abstract published by Chambers et al., which uses traditional propensity score matching to examine the association between exposure to adalimumab and risk of adverse pregnancy outcomes including congenital anomalies, with a similar sample size of 720, which reported an OR of 0.91 (95%CI 0.37 to 2.24) (145).

The main limitation of this study remains the relatively small sample size in the matched cohorts. However, the use of HDPS matching inherently prioritizes validity over precision of estimates, of which, the latter can only be overcome by accumulation of evidence drawn from studies using consistent methodological approaches or from pooling data across multiple databases. Nevertheless, a major strength of this study is the high internal validity afforded by the use of the novel methodology – HDPS – which allows for better adjustment of confounding by indication and adjustment of proxies of unmeasured confounders (104). Ensuring internal validity, and appropriate comparison of exposure groups is of utmost importance in this population of women with autoimmune disease given the association between disease activity and adverse pregnancy outcomes (19,111), and the fact that those with worse disease activity are also more likely to be on a biologic given the current treatment pathways. Further, in studies of medication safety in pregnancy and risk of congenital anomalies, the accuracy in establishing the timing of potentially harmful exposures with respect to fetal organogenesis cannot be understated. The high quality and high coverage population-based prescription dispensations database (PharmaNet), linked with the perinatal registry (BCPDR) covering nearly all births in the province, allowed me to accurately determine the timing of all medication dispensations with respect to milestone pregnancy dates. While prescription dispensation does not equate actual medication taking, these records provide the best available proxy for medication use. This dataset also provided a "gold standard" for ascertainment of the outcome, congenital anomalies at birth, as it was taken directly from chart documentation and subsequent record in the BCPDR.

These population-based data suggest that use of a biologic before pregnancy or during the first trimester is unlikely to be associated with a congenital anomaly in infants born to women with

autoimmune inflammatory disease. Given the effectiveness of biologics in controlling disease activity, and the risks of teratogenicity with certain commonly used traditional DMARDs, these findings emphasize the importance of balancing benefits and risks of treatments for patients who may be pregnant or considering pregnancy.

5. Chapter 5: Use of biologics during pregnancy and risk of serious infections in the mother and baby: A population-based cohort study[§]

5.1. Introduction

Biologics have revolutionized the management of several autoimmune chronic conditions, and are commonly used in inflammatory arthritis including RA, AS, PsA as well as IBD (27,28). Biologics are typically genetically engineered parts of, or whole, IgGs that inhibit specific components of the immune system that play pivotal roles in inflammation (29). 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 (OR 1.31; 95% credible interval 1.09 to 1.58) or in combination with traditional DMARDs (OR 1.34; 95% CI 1.09 to 1.69) compared to DMARDs alone (62).

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) (33–35). 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

[§] A version of this chapter is currently under peer review: Nicole W. Tsao, Larry D. Lynd, Mohsen Sadatsafavi, Gillian Hanley, Mary A. De Vera. Use of biologics during pregnancy and risk of serious infections in the mother and baby: A population-based cohort study. BMJ Open.

eight months (36). 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 (153). Further, detectable, and even therapeutic, levels of biologics in infant serum have been confirmed in case reports of infants exposed in utero (37,38,153). However, to date few epidemiologic studies have examined the risk of infections in women using a biologic during pregnancy, or in infants that were exposed to a biologic in utero. As such, the objectives of this chapter were to investigate the association between biologic exposure during pregnancy and serious infections in 1) mothers during the post-partum period; and 2) infants during the first year of life.

5.2. Methods

Data sources

Data for mothers and babies were obtained through Population Data BC (140). Specifically, respective data for mothers and babies comprised four linked databases including: 1) MSP database – all provincially-funded physician visits, ordered laboratory tests and diagnostic procedures (x-rays, ultrasounds etc.) (83); 2) DAD – all hospital admissions and discharges (87); and 3) PharmaNet – a comprehensive prescription drug database that captures all prescriptions dispensed in community pharmacies regardless of payment source, since 1996 (88). The BCPDR facilitated the linkage between mothers' and babies' data. The BCPDR contains data abstracted from obstetrical and neonatal medical records on >99% 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. Additionally, the BCPDR includes data on maternal postpartum readmissions up to 42 days post-delivery and baby transfers and

readmissions up to 28 days after birth (84–86,89). Details of these data sources are described in Chapter 1 and shown in a schematic diagram in Figure 3.

Study cohort

The source population comprised 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 there is complete data capture for all women and babies in this study population. I 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, Ps/PsA, AS, JIA, and SARDs (**Error! Reference source not found.**). omen were considered to have been diagnosed with one of these conditions if they had the same ICD-9/10 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 (137). Given that the unit of analysis was the 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 a biologic 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 (137). Infants born from these pregnancies were classified as being exposed to a biologic 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 Appendix A Table 1.

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 (154). 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 and codes used for identification are listed in Appendix C Table 1.

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 (155)), 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 I estimated the association between maternal exposure to a biologic during pregnancy and the risk of serious post-partum infections, and the risk of serious infant infections during the first year of life. This was done using a series of models, first as unadjusted models by treatment categories only (model 1) and then adjusted for maternal and infant characteristics according to the 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 this source population showed that accounting for correlations between multiple pregnancies within the same woman did not appreciably change effect estimates and confidence intervals (137).

As a sensitivity analysis, I estimated propensity for biologic exposure in each pregnancy using the HDPS algorithm and incorporated investigator-specified covariates and additional factors that acted as proxy variables for unmeasured confounders from the four aforementioned data dimensions (model 3) (104). 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 biologic 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).

5.3. Results

In the cohort of 6,218 women with autoimmune inflammatory disease diagnoses and 8,607 singleton pregnancies, there were 90 women exposed to a biologic during pregnancy, and 100 babies born to these women. In the biologic-exposed group, more women had IBD or RA, used at least one traditional DMARD or glucocorticoid, delivered via Cesarean section, or had gestational diabetes, anxiety, or mood

disorders. Whereas in the group not exposed to a biologic during pregnancy, more women had Ps/PsA, were multiparous, and had gestational hypertension (Table 10). A larger proportion of infants exposed to a biologic in utero were female, and those that were unexposed to a biologic tended to have more advanced gestational age and higher birth weight (Table 10).

Table 10. 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

Among women exposed to a biologic during pregnancy, occurrence of serious post-partum infections were rare, ranging from 0 to 5%, depending on concomitant exposures to traditional DMARDs or glucocorticoids (Figure 9). Serious infections that occurred in those exposed to a biologic included infection of the amniotic sac and membranes, and bacterial puerperal infections. In model 1 looking only at drug exposures, I found no independent associations between the use of a biologic (OR 0.88, 95% CI 0.27 to 2.82), DMARD (OR 0.98, 95% CI 0.68 to 1.40), or glucocorticoid (OR 1.07, 95%CI 0.64 to 1.77), with the risk of serious post-partum infection (Table 11). The results were similar when maternal factors were included (model 2), specifically, the association between biologic exposure and serious post-partum infection had an OR of 0.79 (95% CI 0.24 to 2.54), DMARD/ immunosuppressant exposure had an OR of 0.98 (95% CI 0.68 to 1.40), and glucocorticoid exposure had an OR of 1.00 (95% CI 0.60 to 1.67) (Table 11). In this model, I 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 infections; 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).

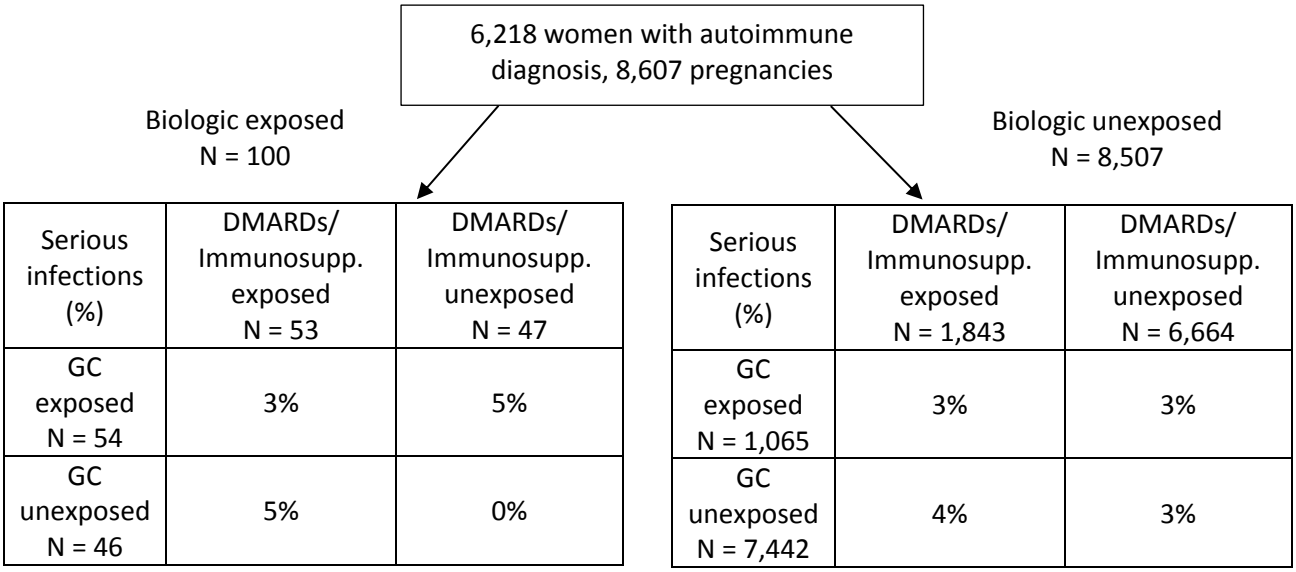


Figure 9. Rates of maternal post-partum serious infections based on drug exposure categories

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

Table 11. 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	Biologics	1.16 (0.34 to 4.14)
HDPS-matched cohort		

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

In infants exposed to a biologic in utero, proportion of serious infections ranged from 0 to 7% depending on the treatment combination used by the mother during pregnancy (Figure 10). The types of serious infections that occurred during exposed infants' first year of life were lymphadenitis, urinary tract infection, and acute bronchiolitis. In model 1 examining categories of maternal drug exposures only, I found no increased risk of serious infections in infants who were exposed to a biologic (OR 0.50, 95% CI 0.16 to 1.60), or a DMARD (OR 1.07, 95% CI 0.81 to 1.43) in utero, while glucocorticoid 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 biologic exposure had an aOR of 0.56 (95% CI 0.17 to 1.81), DMARD/immunosuppressants exposure had an OR of 1.09 (95% CI 0.81 to 1.45), and glucocorticoid exposure an OR of 1.13 (95% CI 0.77 to 1.66) (Table 12). However, I 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 12). 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).

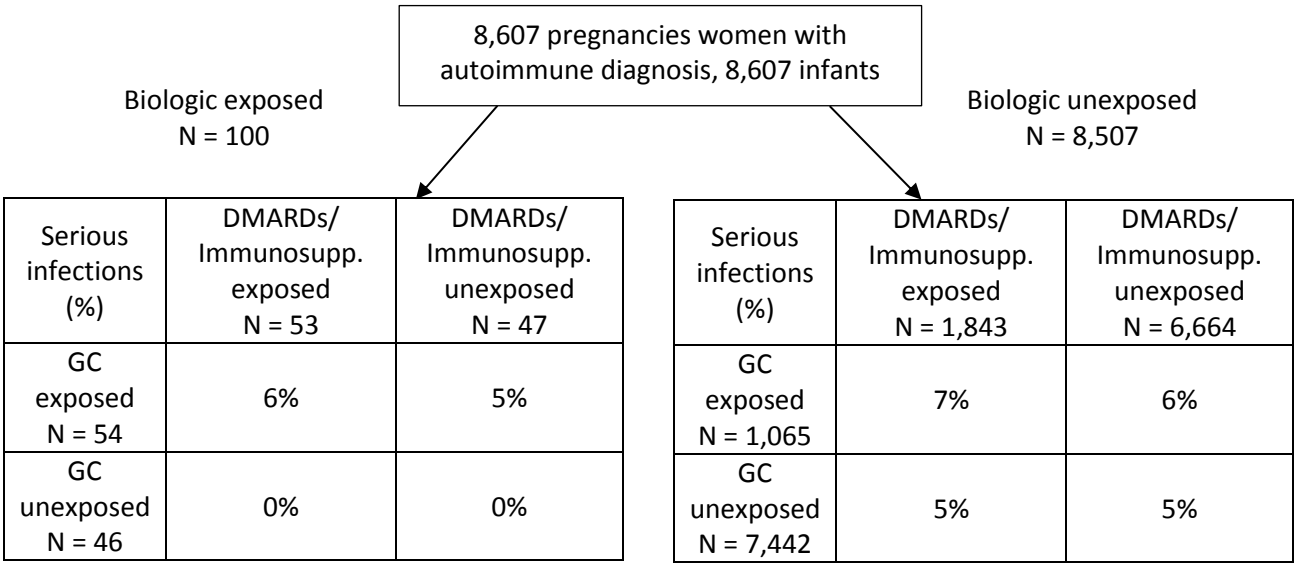


Figure 10. Proportions of infant serious infections during the first year of life based on in utero drug exposure categories

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

Table 12. 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

5.4. 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, I examined the association between exposure to a biologic 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. Overall, I found that the proportion of serious infections in all groups was low. The findings suggest that there was no difference in risk of serious post-partum infections in women who used a biologic during pregnancy versus those who did not. Similarly, I did not observe a difference in risk of serious infections during the first year of life in infants born to mothers who used a biologic during pregnancy compared to those who did not. Due to the small number of events and small sample sizes overall, a doubling to tripling in the risk of serious infections remains compatible with the upper bound of the confidence intervals of the resulting estimates. While I examined all biologics used in the cohort, TNF inhibitor biologics were the most common (94%), and as such the results mostly apply to these biologics and less so to those that are not TNF inhibitors. The results did demonstrate the association between several known factors with the increased risk of infections in mothers, including higher BMI (156) and

Cesarean section delivery (157,158); and in infants including multiparity in mothers (159) and maternal asthma diagnosis (160).

Indeed serious infections are a well-known safety concern in patients using biologics to manage their autoimmune disease, 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-biologic DMARDs and reported no meaningful increase in the risk of serious infection during pregnancy (adjusted hazard ratio 1.36, 95% CI 0.47 to 3.93) (161). However, the authors did observe that the rate of infections increased noticeably in all treatment groups as pregnancies approached term (161), thus, providing a rationale for the objective of this 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 (63). It is therefore reassuring that the current study did not show an association between biologic 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 (153). The immunosuppressive effect of TNF inhibitor accumulation is illustrated by a fatal case of disseminated BCG infection after BCG vaccination in an infant born to a mother treated with infliximab throughout her pregnancy (117). The infant received a BCG vaccination at three months of age, subsequently became ill, and died at 4.5 months of age from

disseminated infection (117). Current recommendations to stop some biologics in the third trimester are largely based on such case reports and expert opinion (119). To date, there have only been two published abstracts examining the association of biologic 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 a biologic during pregnancy (2.8%), compared to those born to women with RA not treated with a biologic (3.9%), with a relative risk [RR] of 0.71 (95% CI 0.30 to 1.71) (162). 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 a biologic in utero were not at greater risk of serious infections (HR 0.5, 95% CI 0.2 to 1.3) (163). The current study is the first to corroborate these findings using population-based data.

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 my 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 the estimates. 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 exposure, as prescription records do not equal actual intake of medications by patients. Misclassification of the outcome was also possible, 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. Further, I did not have access to data on breastfeeding practices which has been shown to be protective against infections requiring hospitalizations (164). However, my findings of other factors independently associated with serious infections, such as maternal BMI (156), Cesarean section delivery (157,158), infant gender (165), and maternal asthma diagnosis (160), are consistent with that reported in literature and thus lend validity to the results.

In conclusion, from this population-based cohort I did not observe differences in the risk of serious infections in women using or not using TNF inhibitor biologics during pregnancy or in their offspring during the first year of life. These findings are compatible with current recommendations where if indicated, biologics can be continued throughout the pregnancy (119,166). This study provides information to clinicians and women with autoimmune disease who may be considering pregnancy or those who are pregnant regarding the risks of serious infections when using a biologic.

6. Chapter 6: Maternal and neonatal outcomes associated with perinatal biologic exposure in women with autoimmune diseases: A systematic review and meta-analysis of observational studies

6.1. Introduction

Chronic autoimmune inflammatory diseases including RA, IBD, AS, Ps/PsA, SLE and associated SARDs share certain commonalities in their pathophysiology and epidemiology (29,30). The chronic and systemic nature of these diseases stem mainly from the perpetual dysfunction of key pro-inflammatory cytokines such as TNF, IL-1, and IL-6 (26,128–130). Further, there is a longstanding 'gender gap' in diseases of autoimmunity (4), where females are disproportionately affected compared to males, and often with peak incidences during the reproductive years (5,7,12,13). With growing recognition that uncontrolled disease activity around the time of conception, and disease flares during pregnancy, represent the greatest risks to maternal and infant outcomes (19,111), clinical experts in this area have called for more evidence to guide treatment decisions that balance the risks of active disease versus the risks of medications (75).

Biologics, predominantly those targeting TNF, are now increasingly used in this patient population (137). Correspondingly, adverse effects of biologic use before or during pregnancy are under scrutiny. A recent systematic review and meta-analysis by Komaki et al. of 11 studies published before November 2015 assessed the outcomes of pregnancy and neonatal complications in individuals exposed to anti-TNF agents (167). Evidence is rapidly being generated on this topic and more studies have been published in the past year than ever before. Further, earlier studies were generally descriptive and did not

incorporate multivariable modeling to account for potential confounders, which is a major limitation given the potential for confounding by disease activity or confounding by indication. More recent studies have utilized improved methodologies and thus, there is an urgent need to synthesize and incorporate these new data to continue informing the understanding of perinatal impacts of biologics. As such, my objective in this study was to identify and pool all available evidence, in conjunction with my population-based studies to assess the impact of biologic use during pregnancy on the risk of adverse maternal and neonatal outcomes in women with autoimmune inflammatory disease. Where possible, I focused on pooling both crude and adjusted results separately in order to determine whether there was a difference possibly attributable to confounding. The systematic literature review focused on comparative, observational studies that have examined women with autoimmune inflammatory diseases who have been pregnant and exposed or unexposed to a biologic around the time of pregnancy, and the association with adverse maternal or neonatal outcomes.

6.2. Methods

Search methodology

The search strategy was developed in collaboration with an information scientist, and all searches were conducted systematically by the information scientist on December 2, 2017 in the following databases: EMBASE (1980 to 2017 December 1), Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE (1946 to Present), and Cochrane Database of Systematic Reviews (2005 to November 29, 2017). The search was aimed at identifying peer-reviewed published abstracts and manuscripts related to biologic use for autoimmune disease and associated pregnancy outcomes, published from 1995 to 2017. Search terms included biologics with indications for autoimmune inflammatory diseases, and corresponding diseases, and a series of pregnancy- and infant-

related outcomes. Database-specific search terms and Medical Subject Headings (MeSH), where applicable, were used to increase relevance and precision of search results and to ensure a manageable number of items retrieved. Where subjects are less well-indexed, or had not yet been assigned subject headings, key words were added to increase recall. Records from database searches were downloaded and imported into an EndNote database to facilitate removal of duplicates. The bibliographies of published systematic reviews were also searched for additional relevant references. This literature review was performed in accordance with the PRISMA guidelines (168), the full search strategy is shown in Appendix D Table 1.

Inclusion and exclusion criteria

All records were screened for inclusion initially at the title and abstract level by one author (NT), then at the full-text level by two independent individuals. To be eligible for inclusion, studies had to fulfill the following criteria: 1) observational design (cohort study, case control, cross-sectional); 2) subjects including pregnant women with autoimmune disease (RA, SLE, JIA, PsA, AS, SARDs, and IBD, including Crohn's disease and ulcerative colitis); OR neonates/infants born to these women; 3) subjects exposed to a biologic (i.e., infliximab, adalimumab, etanercept, golimumab, certolizumab pegol, tocilizumab, abatacept, rituximab, anakinra, ustekinumab, natalizumab, alefacept, and belimumab) before or during pregnancy; OR in utero; 4) a comparator group of disease-matched unexposed subjects; and, 5) investigating and reporting of one or more outcomes of interest (preterm delivery, stillbirths, congenital anomalies, SGA and/or low birth weight, maternal infections, and infant infections). Exclusion criteria consisted of: 1) publications not in English, French, German, or Spanish. I gave consideration to both full-text publications, and abstract publications, as long as criteria for inclusion were met to ensure the

widest capture possible given that data are generally limited in this area, and new research is rapidly accumulating.

Data extraction and quality assessment

Using a data extraction form, two individuals independently extracted data from included studies in duplicate. Data extracted included study characteristics (primary author, year, study design, location, study duration, patient population) and study results (sample size, exposures, exposure time frame, outcomes reported, event rates, and effect estimates). Discrepancies were resolved through consensus. Quality assessments were done using the Newcastle-Ottawa Scale for cohort and case-control studies (169). The Newcastle-Ottawa Scale contains three domains: 1) Selection; 2) Comparability; and 3) Outcome [or Exposure for case-control], and each of the domains contains questions to assess how well the study addresses potential biases and methodological issues pertaining to that domain. The scoring system is points-based, with a maximum of 9 points awarded – 4 in Selection, 2 in Comparability, and 3 in Outcome/Exposure – for satisfying each criterion in each domain. Based on reported scoring algorithms, a study scoring above 5 is considered 'Good' quality, a score of 3 to 5 is considered 'Fair', and a score of 0 to 2 is considered 'Poor' quality (170).

Statistical analysis

Random effects meta-analyses were conducted for each respective outcome by pooling the proportions of crude events reported in each study, and where possible, by pooling reported adjusted risk estimates (e.g., ORs or HRs). Heterogeneity was assessed using the Cochrane's Q test with $p<0.1$ as indication of significant heterogeneity; and the I^2 statistic – which quantifies the percent of variability in effect

estimates that can be attributed to heterogeneity – with <25% indicating low heterogeneity, 25-75% moderate heterogeneity, and >75% high heterogeneity. Sensitivity analyses were conducted where possible by excluding studies with Newcastle-Ottawa Scales <6, indicative of studies with 'Poor' or 'Fair' quality. Funnel plots were constructed for each pooled analysis containing three or more studies, and used to assess publication bias. All statistical analyses were conducted using RevMan5 (Copenhagen, Denmark).

6.3. Results

Search results and characteristics of studies

The systematic literature search on biologic use in autoimmune disease and associated pregnancy outcomes resulted in 1,852 citations after de-duplication. After screening by title and abstracts, 1,815 citations were deemed ineligible based on the inclusion criteria (Figure 11). After full-text review, a further 16 citations were excluded, eight of these did not have an appropriate comparator group, three abstracts were older versions of other included abstracts, three studies did not report at least one outcome of interest, and two were not the appropriate study type (e.g., case series or letters to the editor). After exclusion, a total of 21 published studies were eligible for inclusion in the meta-analysis. At the time of the systematic literature review, the population-based studies from earlier chapters of my dissertation had not yet been published. As such, they are not counted here when describing the results of the systematic review.

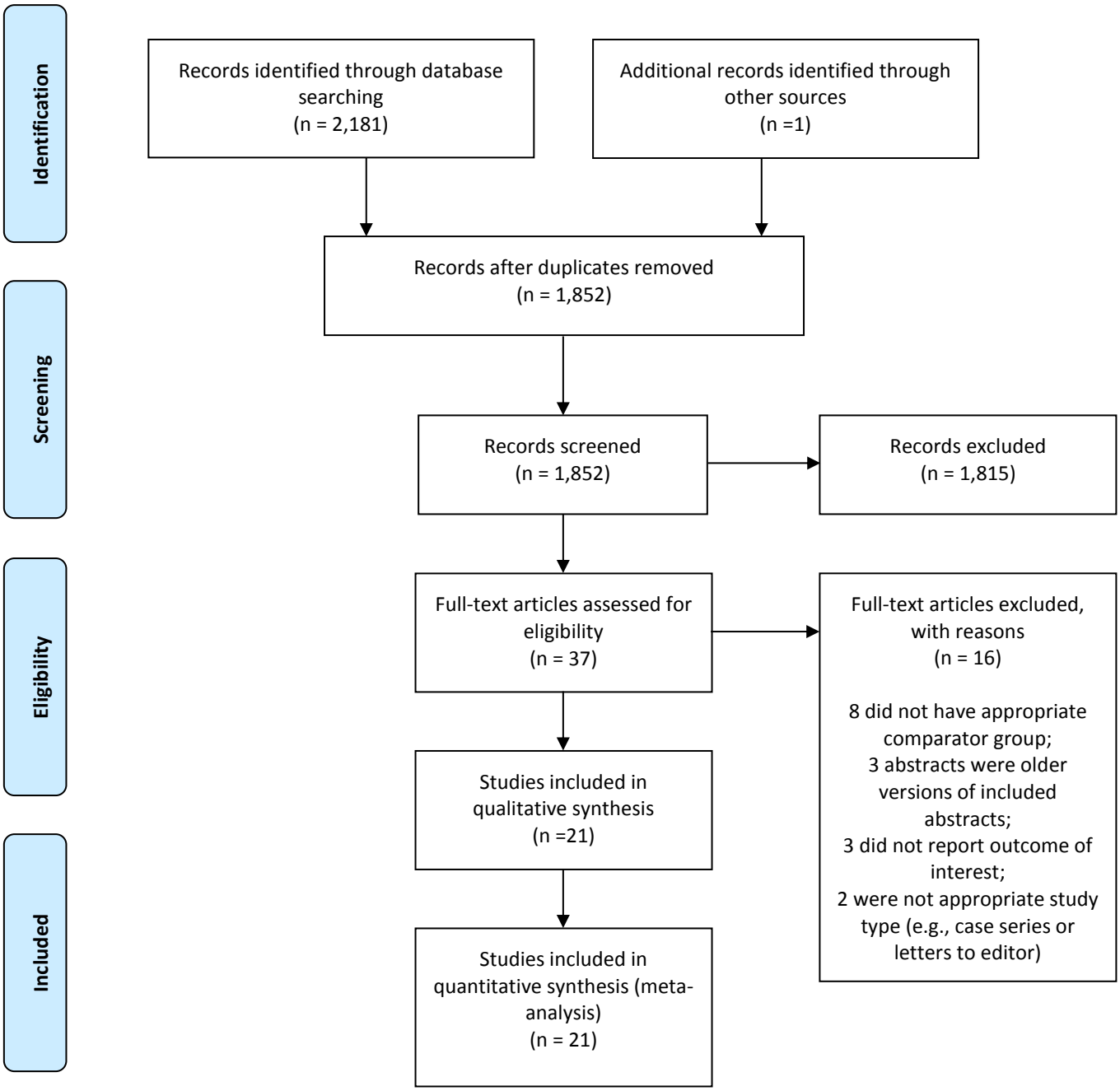


Figure 11. PRISMA flow diagram from systematic review of the literature

Overall, 21 studies published between 2011 and 2017 were identified in the systematic review and included for meta-analysis. From the published studies, there were a total of 41,558 subjects – 5,677 pregnancies exposed to a biologic and 35,881 unexposed. Study characteristics are shown in Appendix E Table 1. Nine of 21 studies were prospective and used data from registries or clinics while nine of 21 studies were retrospective and used administrative or claims data, two studies used case-control designs, and one study was cross-sectional. Overall, eight studies exclusively focused on IBD patients, eight exclusively focused on inflammatory rheumatic diseases (RA, AS, SLE, PsA, JIA, etc.), and five included a mixture of both patient populations. Of 21 included studies, 18 examined the exposure to TNF inhibitor type biologics, some focusing only on one specific drug while the majority included more than one drug within this subclass. Three of 21 studies included non-TNF inhibitor biologics however two of these did not specify the drug names. Included studies were categorized by the outcomes reported (Table 13), 15 studies reported on congenital anomalies, 14 studies reported preterm delivery rates, six studies reported on low birth weight, two studies reported on very- or small-for-gestational-age births, two studies reported on maternal infections, and four on infant infections.

With respect to study quality, I found that the mean Newcastle-Ottawa Scale score from the 21 studies was 6, indicating above fair quality, with a range from 4 to 9. However, when examining specific domains within the Newcastle-Ottawa Scale, I found that the proportion of studies with scores meeting the threshold for "good quality" were 90% in the 'Selection' domain (criteria: ≥3 points), 14% in the 'Comparability' domain (criteria: 2 points), and 86% in the 'Outcome/Exposure' domain (criteria: ≥2 points). Details on the quality assessment scores for each included study are reported in Appendix E Table 2.

Table 13. Studies included in meta-analyses and categories of outcomes reported

Outcome	Study reporting	Total N*	Crude event rates reported? (Y/N)	Risk estimates	Adjusted? (Y/N)	Newcastle-Ottawa Score
Preterm delivery						
1	Schnitzler 2011	120	Y		N	7
2	Verstappen 2011	81	Y		N	5
3	Casanova 2013	253	Y		N	6
4	Diav-Citrin 2014	169	Y		N	6
5	Giacuzzo 2014	54	Y		N	5
6	Martinez 2014	68	Y		N	6
7	Seirafi 2014	232	Y		N	9
8	Strangfeld 2015	60	Y		N	6
9	Broms 2016	22,232	Y		N	9
10	Komoto 2016	72	Y		N	4
11	Burmester 2017	154	N	HR 1.08 (0.41, 2.83)	Y	6
12	Carman 2017	3,927	Y		N	8
13	Chambers 2017	377	N	HR 0.82 (0.5, 3.84)	Y	6
14	Luu 2017	11,275	N	OR 1.22 (1.09, 1.36)	N	7
Congenital anomalies						
1	Schnitzler 2011	120	Y		N	7
2	Verstappen 2011	81	Y		N	5
3	Casanova 2013	253	Y		N	6
4	Lichtenstein 2013	187	Y		N	4
5	Diav-Citrin 2014	169	Y		N	6
6	Martinez 2014	68	Y (all 0s)		N	6
7	Seirafi 2014	232	Y		N	9
8	Chambers 2015	534	Y		N	6
9	Reggia 2015	50	Y		N	4
10	Strangfeld 2015	60	Y		N	6
11	Broms 2016	22,232	Y	OR 1.32 (0.93, 1.87)	Y	9
12	Komoto 2016	72	Y		N	4
13	Burmester 2017	154	Y	OR 0.72 (0.14, 3.70)	Y	6
14	Carman 2017	3,927	Y	OR0.52 (0.13, 2.08)	Y	8
15	Chambers 2017	377	N	OR 0.91 (0.37, 2.24)	Y	6

Low birth weight						
1	Schnitzler 2011	120	Y		N	7
2	Casanova 2013	253	Y		N	6
3	Seirafi 2014	232	Y		N	9
4	Komoto 2016	72	Y		N	4
5	Carman 2017	3,927	Y		N	8
6	Chambers 2017	377	N	OR 0.73 (0.33, 1.62)	Y	6
Stillbirths						
1	Schnitzler 2011	120	Y		N	7
2	Verstappen 2011	81	Y (all 0s)		N	5
3	Casanova 2013	253	Y		N	6
4	Diav-Citrin 2014	169	Y		N	6
5	Seirafi 2014	232	Y		N	9
Small for gestational age (SGA)	Martinez 2014	68	Y		N	6
Very SGA	Schnitzler 2011	120	Y		N	7
Maternal infections						
1	Desai 2017	4961	Y	HR 1.36 (0.47, 3.93)	Y	9
2	Luu 2017	11,275	Y	HR 1.38 (1.16, 1.66)	Y	7
Infant infections						
1	Seirafi 2014	232	Y		N	9
2	Chaparro 2016	222	N	HR 0.5 (0.2, 1.3)	Y	5
3	Vinet 2016	2,346	Y	OR 1.2 (0.6, 2.6)	Y	7
4	Chambers 2017	715	Y	RR 0.71 (0.30, 1.71)	N	5

*Not including healthy controls arm

Congenital anomalies

There were 15 studies that examined congenital anomalies in babies born to women with autoimmune disease who were exposed to a biologic before or during pregnancy (n = 3,061), compared to those who were not (n = 25,455). Only one study reported the definition used for congenital anomalies (73), which was "...structural abnormalities in the offspring that have serious medical, surgical or cosmetic consequences" and excluded genetic or cytogenetic anomalies. While 14 out of 15 studies reported the number of infants with congenital anomalies, one study was not included in the meta-analysis because there were no outcomes in either the exposed or unexposed groups (138). Pooling the crude numbers of congenital anomalies from the 13 studies resulted in an OR of 1.33 (95% CI 1.03 to 1.72) when comparing pregnancies in women with autoimmune disease exposed to a biologic (n = 1,824), to those not exposed to a biologic (n = 23,258) [Figure 12]. There did not appear to be evidence of heterogeneity across studies (Q statistic p=0.66, I^2=0%), or any evidence of publication bias based on funnel plot (Appendix F Figure 2). Based on quality assessment of the 15 studies using the Newcastle-Ottawa Scale, there were four studies with a score of 5 or lower. In sensitivity analysis, excluding these studies did not result in a substantial change, with a pooled OR of 1.39 (95% CI 1.06 to 1.80) [Appendix F Figure 2]. There were 4/15 studies that reported risk estimates of the association between biologic exposure and congenital anomalies, after adjusting for confounders (145,146,151,152). Including estimates from my work in Chapter 4 derived using HDPS matching, the pooled analysis of these adjusted risk estimates resulted in an OR of 1.16 (95% CI 0.87 to 1.56) [Figure 13]. There was no evidence of heterogeneity (Q statistic p=0.66, I^2=0%), or publication bias (Appendix F Figure 3) in this subgroup analysis. All four studies in this subgroup had Newcastle-Ottawa Scale scores above 5.

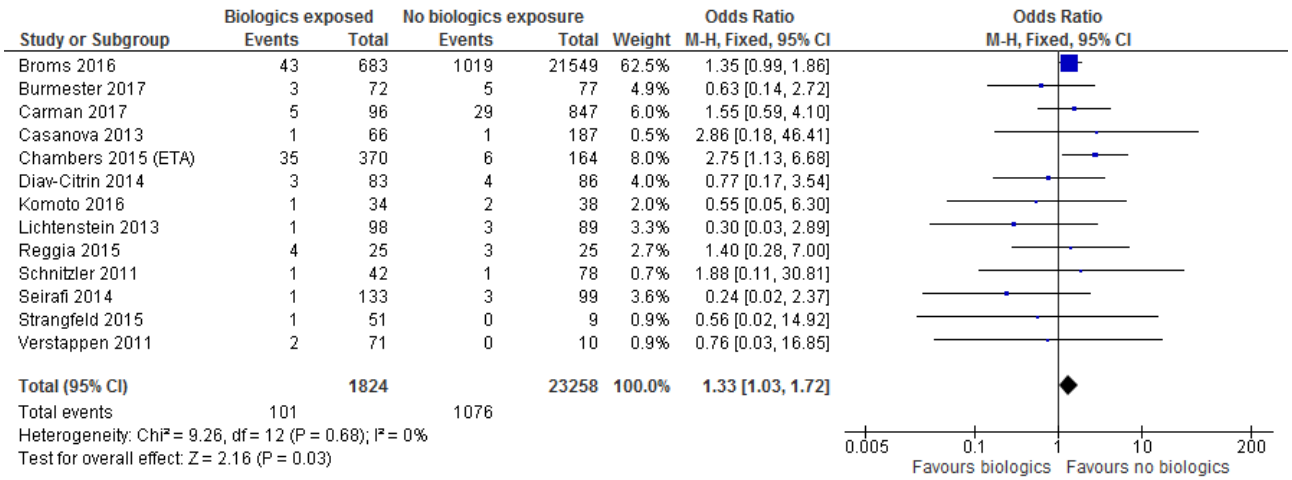


Figure 12. Results of pooled crude proportions of congenital anomalies reported by studies meeting inclusion criteria

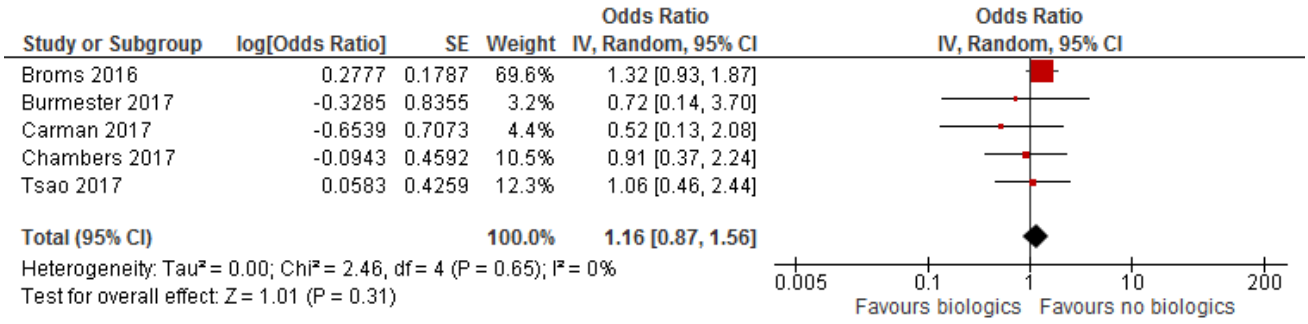


Figure 13. Results of pooled adjusted risks of congenital anomalies reported by studies meeting inclusion criteria

Preterm delivery

Fourteen studies examined preterm deliveries in women who were exposed (n = 3,977) and unexposed (n = 34,943) to a biologic before or during pregnancy, of which eleven only reported proportions of preterm deliveries by exposure group, while three reported risk estimates associated with biologic exposure. Eight out of 14 studies reported the definition for preterm delivery, six used a threshold of delivering at less than 37 weeks gestation (70,73,74,146,152,163,171), one study used

a threshold of less than 36 weeks (71), and one at less than 35 weeks (150). Despite the different definitions, pooling the crude rates of preterm deliveries from the 11 studies, the OR was 1.66 (95% CI 1.40 to 1.97) when comparing pregnancies in women with autoimmune disease exposed to a biologic (n = 1,308), to those not exposed to a biologic (n = 24,027) [Figure 14]. There was no evidence of heterogeneity across studies (Q statistic p=0.97, I^2=0%) or publication bias (Appendix F Figure 4). Based on the quality assessment of these 11 studies using the Newcastle-Ottawa scale, three studies has a score of ≤ 5 suggesting fair or poor quality. In sensitivity analysis excluding these three studies, the pooled OR did not change (OR 1.66, 95% CI 1.40 to 1.97) [Appendix F Figure 5]. Of the three studies reporting risk estimates, Luu et al. did not adjust for any confounders (171), while Chambers et al. and Burmester et al. adjusted for confounders and found the risk to be (hazard ratio, HR) 0.82 (95% CI 0.5 to 3.84) and HR 1.08 (95% CI 0.41 to 2.83), respectively (145,146). Both of these studies have Newcastle-Ottawa scores above 5, suggesting good quality. Including my work from Chapter 3 (172), on the association between biologic exposure and preterm delivery, derived using HDPS, there was a total of three studies that have risk estimates that have taken into account potential confounding. The pooled estimates from these three studies resulted in an aHR of 1.09 (95% CI 0.70 to 1.69) [Figure 15]. This subgroup analysis did not show evidence of heterogeneity across studies (Q statistic p=0.96, I^2= 0%) or publication bias (Appendix F Figure 6).

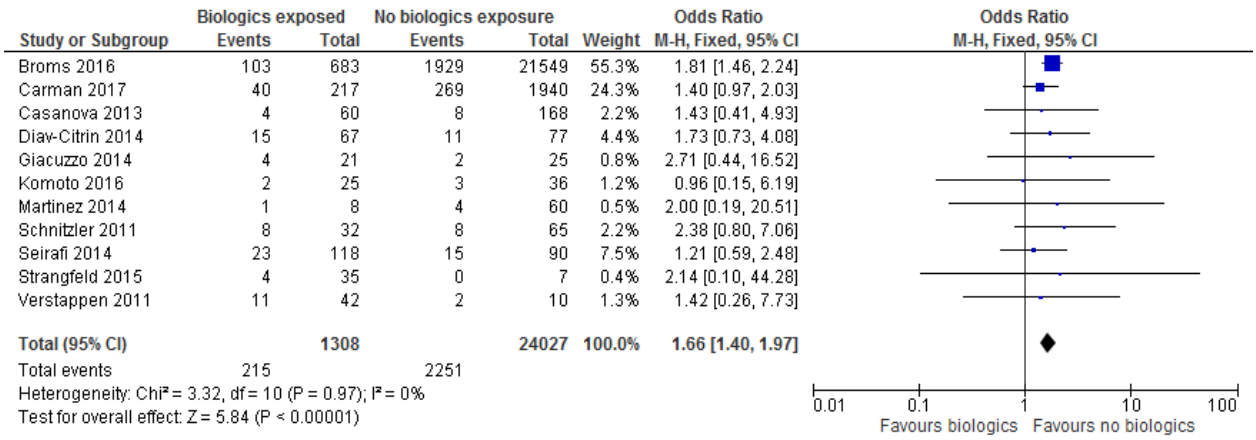


Figure 14. Results of pooled crude proportions of preterm deliveries reported by studies meeting inclusion criteria

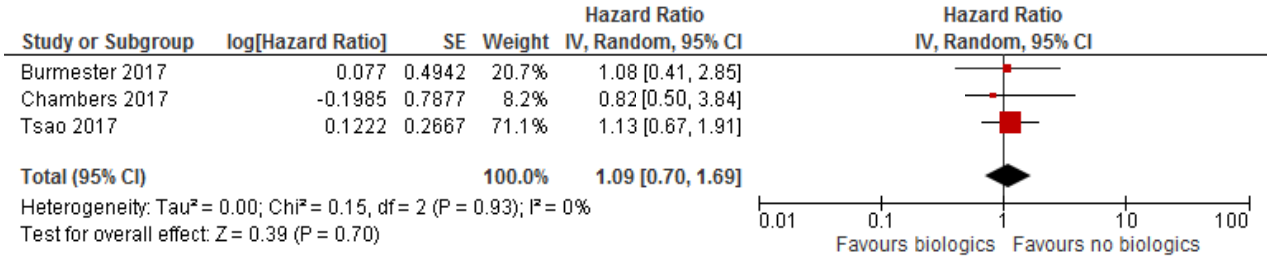


Figure 15. Results of pooled adjusted risks of preterm deliveries reported by studies meeting inclusion criteria

Low birth weight

There were six studies that reported on babies with low birth weight born to mothers who were exposed (n = 1,598) and unexposed (n = 3,383) to a biologic. Of the six studies included, five reported crude numbers of the occurrence of low birth weight, using a consistent definition of under 2,500 grams at birth. When pooling these five studies, I found that the OR for low birth weight was 1.67 (95% CI 1.21 to 2.31) in pregnancies from women exposed to a biologic (n = 452) compared to women not exposed to a biologic (n = 2,299) [Figure 16]. There was no evidence of heterogeneity in this analysis (Q statistic p=0.94, I^2=0%), or evidence of publication bias based on

funnel plot (Appendix F Figure 7). Of these five studies, one study did not meet the quality assessment threshold (150), with a Newcastle-Ottawa Scale score of 4. Excluding this study and pooling the remaining four studies did not substantially change the results, with an OR of 1.73 (95% CI 1.24 to 2.42) [Appendix F Figure 8]. Chambers et al. did not state the definition used for low birth weight in their study, however, this was the only study to adjust for potential confounders in calculating the association of biologic exposure and low birth weight, reporting an OR of 0.73 (0.33 to 1.62) in exposed versus unexposed individuals; this study had a Newcastle-Ottawa Scale score of 6 (145). Pooling of adjusted risk estimates was not possible for this outcome due to Chambers et al. being the only study that reported adjusted risks.

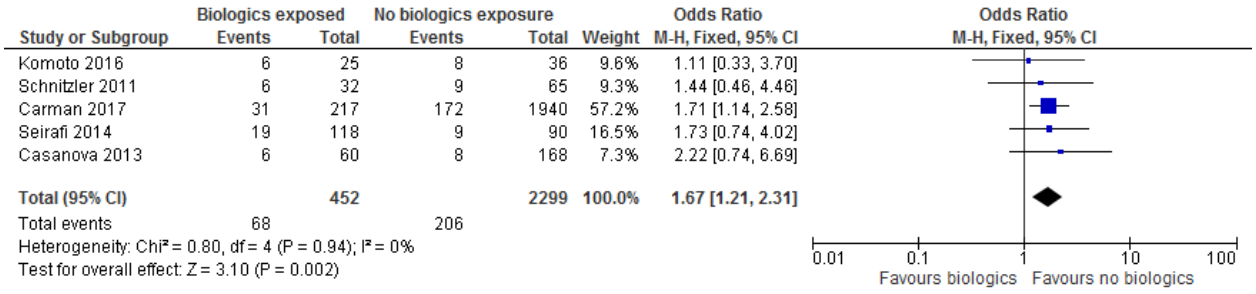


Figure 16. Results of pooled crude proportions of low birth weight outcome reported by studies meeting inclusion criteria

Stillbirths

There were five studies that reported the number of stillbirths observed from pregnant women who were exposed to a biologic during pregnancy (total N = 262) versus unexposed (total N = 361). Two of the five studies reported using the same definition for stillbirths as “pregnancy loss after 20 completed weeks gestation”, which is congruent with the definition used in Canada (173). However, there were no events reported in the study by Verstappen et al, so it was excluded from the analysis. Pooling the remaining four studies that reported crude numbers for stillbirths by exposure

group resulted in an OR of 0.75 (95% CI 0.44 to 1.29) in those exposed to a biologic versus unexposed, suggesting no association (Figure 17). However, there was some, albeit low, level of heterogeneity between studies (I^2 = 3%, Q statistic p=0.38), but little evidence of publication bias (Appendix F Figure 9). All four studies had Newcastle-Ottawa Scale scores above 5 and thus a sensitivity analysis was not conducted. No studies reported adjusted risk estimates for stillbirths.

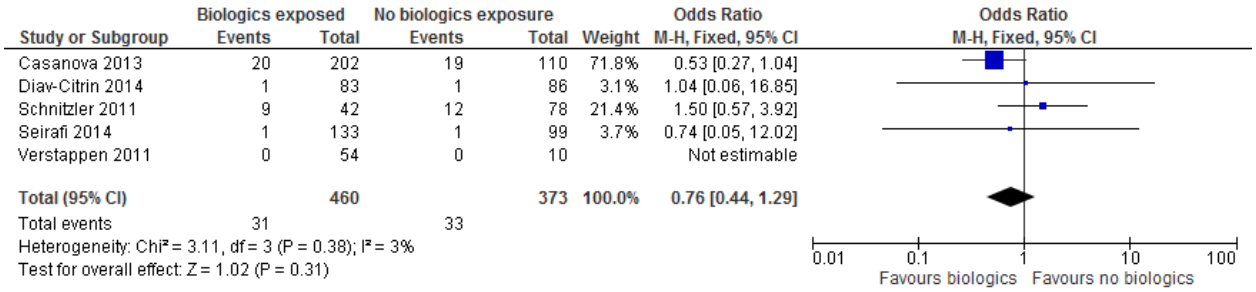


Figure 17. Results of pooled crude proportions of stillbirths reported by studies meeting inclusion criteria

Small-for-gestational-age

There were two studies identified that examined the observed proportion of SGA births associated with biologic exposure in women with autoimmune disease. Martinez et al., using a definition of less than the 10th percentile of gestational age specific weights, reported that 1/8 (12.5%) of babies born to mothers exposed to a biologic were SGA, while only 5/60 (8.3%) of babies born to mothers unexposed to a biologic were SGA (138). Using a definition of less than the 5th percentile of gestational age specific weights (i.e. very SGA), Schnitzler et al. reported that 2/32 (6.3%) of babies born to mothers exposed to a biologic were very SGA, and 7/65 (10.8%) of babies born to mothers unexposed to a biologic were very SGA (70). Given the difference in the outcome measures, I did not attempt to pool the results of these two studies, despite the fact that both were rated to have Newcastle-Ottawa Scale scores above 5. Neither study reported risk estimates, or adjusted for

potential confounding. In context of my work in Chapter 3 examining the association between biologic exposure and risk of SGA births, using HDPS matching, I found that there were 11/120 (9%) pregnancies in the exposed group and 60/600 (10%) pregnancies in the unexposed group that ended in SGA births (OR 0.91, 95%CI 0.46 to 1.78).

Maternal infections

Only two studies examined the association between biologic exposure and the risk of maternal infections. Both of these studies specifically examined intrapartum infections in women using and not using a biologic during pregnancy (161,171). Desai et al. compared serious intrapartum infections among users of a biologic compared to users of non-biologic DMARD or glucocorticoid and reported an adjusted hazard ratio [aHR] of 1.36, 95% CI 0.47 to 3.93) (161). Luu et al. also reported a positive association between biologic exposure and maternal infection (aHR 1.38; 95% CI 1.16, 1.66), adjusting for birth term, age at pregnancy start, and type of IBD; however, they did not state their definition of infection.(171). Given the difference in comparator groups used in these studies, I did not attempt to pool the risk estimates reported. However, both studies had Newcastle-Ottawa scores above 5. It is worthwhile to note that in contrast, based on my own work in Chapter 5 which examined the association between biologic exposure and risk of maternal post-partum serious infections, I found no evidence of an elevated risk (OR 0.79, 95%CI 0.24 to 2.54).

Infant infections

Four studies investigated the risk of infections in infants born to mothers using and not using a biologic before or during pregnancy and none found a significant association with biologic exposure

(74,162,163). Seirafi et al. did not describe the definition of infections in newborns but found that there were 2/133 (2%) cases in neonates born to women who were exposed to TNF inhibitors, compared to 1/99 (1%) in those unexposed (74). With respect to serious infections in infants requiring hospitalization, Vinet et al. reported an aOR of 1.2 (95% CI 0.6 to 2.6) and Chambers et al. reported a relative risk of 0.71 (95% CI 0.30 to 1.71) for serious infections during the first year of life in infants born to women who used a biologic, compared to those born to women not treated with a biologic (162). Chaparro et al. found that after a median follow up of 33 months post-partum, infants exposed toa biologic in utero did not have elevated risks of serious infections (HR 0.5, 95% CI 0.2 to 1.3) (163). Vinet et al.'s study had a Newcastle-Ottawa Scale score of 7 while the latter two studies were both rated to have Newcastle-Ottawa Scale scores of 5. My work in Chapter 5, which examined the risk of serious infant infections associated with biologic exposure in utero, showed an adjusted OR of 0.56 (95%CI 0.17 to 1.81). Despite the differences in the types of risk estimates reported (i.e., RR, HR, OR), given that the event rates are relatively rare these can be considered interchangeable and thus, I did pool the results of all five studies and found that the pooled crude risk estimate was 0.77 (95% CI 0.34 to 1.78) [Figure 18] and the pooled adjusted risk estimate was nearly the same (0.77; 95% CI 0.43 to 1.40) [Figure 19].

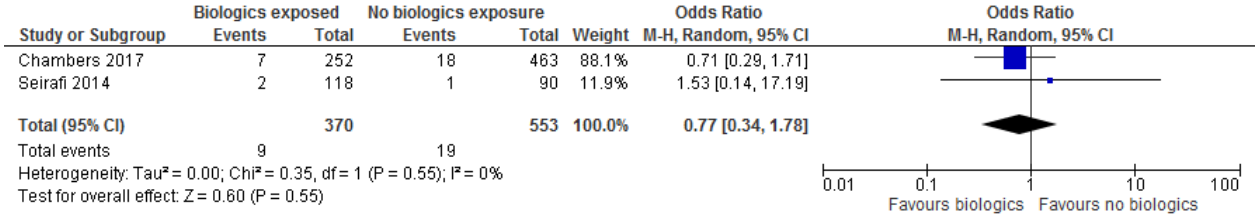


Figure 18. Results of pooled crude proportions of infant infections reported by studies meeting inclusion criteria

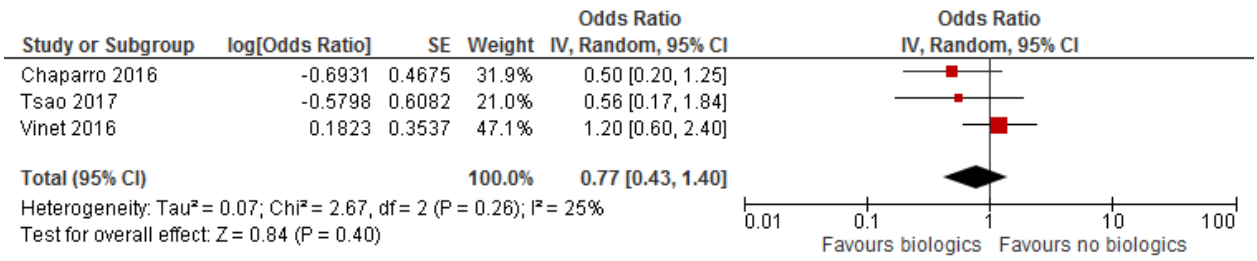


Figure 19. Results of pooled adjusted risk estimates of infant infections reported by studies meeting inclusion criteria

6.4. Discussion

I conducted a systematic literature search and meta-analysis to identify and pool all available evidence to evaluate the association between biologic use during pregnancy in women with autoimmune inflammatory disease and the risk of adverse maternal and neonatal outcomes. Outcomes evaluated in the 21 published studies meeting inclusion criteria were congenital anomalies (n = 15 studies), preterm delivery (n = 14 studies), low birth weight (n = 6 studies), stillbirths (n = 5 studies), SGA (n = 2 studies), maternal infections (n = 2 studies), and infant infections (n = 4 studies). Further, I included the results of my studies, wherever possible, which evaluated the association between biologic exposure before or during pregnancy and the risk of preterm delivery, SGA, congenital anomalies, and maternal and infant infections. When I pooled the crude number of events reported, I observed a significantly increased risk of congenital anomalies, preterm birth, and low birth weight babies associated with biologic use during pregnancy. However, due to the known association between autoimmune inflammatory disease activity and the risk of adverse pregnancy outcomes, part of the main objective was to pool risk estimates that have accounted for potential confounders in order to isolate the risk of adverse pregnancy outcomes attributable to biologics, and not the disease. As such, where available, I pooled risk estimates of biologic users compared to non-users from studies that have attempted to control for confounding

and found that risks of preterm delivery and congenital anomalies were close to null and not statistically significant.

A recent systematic review and network meta-analysis by Komaki et al. (167) searched for studies published before November 2015, and included a total of 11 that investigated the risk of adverse pregnancy and neonatal outcomes associated with immune mediated diseases (including RA, AS, IBD) and TNF inhibitor use during pregnancy. The authors did not find significant risks of several outcomes. Compared to those not using a TNF inhibitor, the OR of adverse pregnancy outcomes in those who used a TNF inhibitor during pregnancy were 1.36 (95% CI 0.84 to 2.21) for preterm birth, 1.55 (95% CI 0.89 to 2.69) for spontaneous abortion, 1.33 (95% CI 0.77 to 2.30) for low birth weight, and 1.20 (95% CI 0.89 to 1.62) for congenital anomalies including any and major anomalies (167). These conclusions were based on analyses of seven studies that have reported on the preterm delivery outcome, three studies for congenital anomalies, and three studies on low birth weight. Of the 11 studies included in Komaki's meta-analysis, 10 did not adjust for any potential confounders.

In the current study, I included twice the number of studies as was found by Komaki et al. since many were published within the past year. However, still the majority of studies reported only crude proportions of the outcomes of interest, without controlling for confounding. In the pooled analyses of crude events, I found that in women with autoimmune disease using a biologic before or during pregnancy compared to those who did not, there was a 33% increased risk of having babies with congenital anomalies (OR 1.33, 95% CI 1.03 to 1.72), a 66% increased risk of delivering prematurely (OR 1.66, 95% CI 1.40 to 1.97), and a 67% increased risk of having a low birth weight baby (OR 1.67, 95% CI 1.21 to 2.31). But more importantly, in pooled analyses of adjusted risk estimates I observed

that the association between biologic use during pregnancy compared to disease-matched pregnant women who did not use a biologic were no longer significant for congenital anomalies (aOR 1.18, 95% CI 0.88 to 1.57), and preterm delivery (aHR 1.09, 95% CI 0.70 to 1.69), suggesting that the formerly observed elevated risks may have been due to confounding by disease activity, in epidemiological terms 'confounding by indication', or confounding due to other pregnancy related factors not accounted for in previous studies. This was also the first meta-analysis to pool estimates from studies that examined the association between in utero exposure to a biologic and the risk of serious infections in infants. Despite the differences in the measure of association reported (e.g., ORs, HRs, RRs), the pooled estimates suggested no increased risk of serious infections associated with biologic exposure.

To my knowledge, this is the first meta-analysis on this topic to pool reported risk estimates from studies that have attempted to control for potential confounding. Given what is currently known about the impact of autoimmune inflammatory disease activity on pregnancy outcomes, and the place of biologic treatment in the management of moderate to severe disease, accounting for potential confounders is crucial in order to isolate the causal association between biologic use and pregnancy outcomes. Despite its importance, we are currently limited by the dearth of studies that have attempted to control for potential confounding. To ensure maximum capture of existing literature, I developed a comprehensive search strategy with an information scientist who conducted all of the database searches. From studies that met the inclusion criteria, several outcomes of interest did not have enough evidence to facilitate meta-analysis of the estimates, for example, stillbirths, small-for-gestational-age, low birth weight, and maternal infections. Another limitation is that in the identified studies, there was little standardization in the definition of the

outcomes assessed, apart from low birth weight, and many studies even did not report the definitions used. Further, there was also no standardization in the methodological approaches employed to control confounding. However, most studies were only available in abstract form, thus perhaps were not able to explain their methods in detail or to list the specific covariates included for adjustments. Unfortunately, due to this, it is not possible to determine appropriateness of the confounding adjustment and as such I was unable to gauge the extent to which confounding by indication was accounted for.

From a systematic literature review and meta-analysis pooling studies that have adjusted for confounders, I found no association between biologic use during pregnancy and the risk of congenital anomalies (aOR 1.18, 95% CI 0.88 to 1.57), or preterm deliveries (aHR 1.09, 95% CI 0.70 to 1.69), compared to disease-matched pregnant women who did not use a biologic. Further, I also did not find an association between biologic exposure in utero and the risk of serious infections requiring hospitalization in infants' first year of life (aOR 0.77, 95% CI 0.43 to 1.40). For other outcomes of interest, pooling of adjusted risk estimates was not feasible. As such, this study highlights the need for studies to do better at controlling for potential confounding, especially that related to disease activity. We also need more consistency and transparency of the selection of confounders, and the reporting of methodological approaches. It is unlikely that any single study will have a large enough sample size to provide results to a high degree of confidence. Instead, meta-analytical approaches like that employed in this study, demonstrates the importance of pooling multiple studies with comparable methodological approaches in order to arrive at a conclusive solution to determine the safety of biologic use during pregnancy.

7. Discussion and conclusion

This final chapter concludes my thesis work by summarizing the main study findings, discussing the strengths and limitations, and highlighting the clinical and methodological implications of this research.

7.1. Overview of study findings

This dissertation consisted of five studies that were progressively developed to evaluate the safety of biologics in women with autoimmune disease during pregnancy. I began with describing the perinatal patterns of utilization and discontinuation, and the secular trends of biologics treatment for autoimmune inflammatory diseases in BC. Then I examined the safety of biologic use before or during pregnancy by estimating their association with a number of adverse outcomes including preterm delivery, SGA, congenital anomalies, and maternal and infant serious infections. Finally, I pooled my findings with the existing literature via a systematic review and meta-analysis of the outcomes.

In the first study, I characterized the patterns of biologics utilization and discontinuation, before conception and during pregnancy, in women with autoimmune diseases at the population level in BC. From a source population of 305,351 women in BC who have had one or more pregnancies over the study period of 10-years from 2002 to 2012, approximately 2% had a diagnosis of one of the autoimmune diseases of interest resulting in 6,218 women with 8,607 pregnancies. From the study cohort, 2.3% of women were exposed to a biologic during 12 months preconception or during pregnancy. Secular trends showed significantly increased use of biologics over the 10-year study period, such that by 2012 biologics users comprised 5.7% of all women in this population. With

respect to discontinuation patterns, I found that a large proportion of women discontinued their biologic in the first (31%), and second (38%) trimesters, while those who continued treatment during the second trimester mostly remained on treatment through to delivery (98%).

Due to the known association between autoimmune inflammatory disease activity and the risk of adverse pregnancy outcomes, and given the high probability that women with more severe disease would be those most likely to remain on a biologic during pregnancy, my objective was to employ the most robust methods possible to account for potential measured and unmeasured confounders in order to isolate the risk of adverse pregnancy outcomes attributable to biologic use. As such, I applied HDPS methods to account for differences in baseline characteristics between women exposed and unexposed to a biologic in order to evaluate the association between biologic exposure, and preterm delivery or SGA births in women with autoimmune disease. Prior studies had shown estimates compatible with a doubling to tripling in risk of preterm deliveries associated with biologic exposure, with upper bounds of confidence intervals exceeding 40. Moreover, these studies did not adjust for any confounding. With respect to the SGA outcome, there is a dearth of evidence, with only two studies to date reporting on proportions of SGA and very SGA by exposure group. In my studies, prior to restricting the population using HDPS matching, I found that differences in baseline characteristics in the unmatched sample led to a significant association between biologic use and the risk of preterm deliveries, with an OR of 1.64 (95% CI 1.02 to 2.63); and a non-statistically significantly increased risk of SGA with an unadjusted OR of 1.34 (95% CI 0.72 to 2.51). However, after successful implementation of HDPS to control for confounding by indication and proxies of unmeasured confounders, there was no association between biologic exposure and the outcomes of interest. The OR between biologic exposure and preterm delivery became 1.13 (95% CI

0.67 to 1.90) and for SGA, became 0.91 (95% CI 0.46 to 1.78), and various sensitivity analyses did not change these results.

Using the same methods, I examined the association between exposure to a biologic before conception and during the critical period of organogenesis – the first trimester of pregnancy – with the risk of having offspring with congenital anomalies. Congenital anomalies are one of the most widely studied outcomes among questions of the safety of medications during pregnancy. Given that some of the most commonly used traditional disease-modifying agents are teratogenic, including methotrexate and leflunomide, biologics could potentially be a better alternative if their safety can be established. Earlier studies raised concerns of a possible association between biologic exposure with VACTERL constellation of anomalies, however, this suggestion has since been disputed (120). The absence of an association between biologic use and congenital anomalies of any type has been corroborated through my work using the robust method of HDPS-matching of 117 pregnancies (107 women) exposed to a biologic during 90 days before conception or during the first trimester, with 585 pregnancies (to 562 women) that were not exposed to a biologic during that time. I found that in the HDPS-matched cohort, 7/117 (6%) and 33/585 (6%) of newborns in the exposed and unexposed groups had one or more congenital anomalies at birth. In the primary adjusted analysis, the OR for the association between biologic exposure and congenital anomalies was 1.06 (95% CI 0.46-2.47), suggesting no association between biologic exposure in women with autoimmune disease and the risk of congenital anomalies in their offspring. I also examined the types of congenital anomalies that occurred in the biologic exposed group, which included: atrial septal defect, patent ductus arteriosus, other specified malformation of kidney, accessory auricle, ankyloglossia, and other specified congenital anomalies of the skin. There were no obvious patterns

with regards to these observed congenital anomalies, and as such, is indicative that the observed anomalies occurred at random rather than due to specific assaults as would be expected with drug-induced teratogenicity (e.g., thalidomide and limb defects).

In the two studies concerning perinatal outcomes, I used HDPS in attempts to account for confounding by indication and unmeasured confounders. This approach was directly in response to challenges and opportunities posed by the nature of the research questions, the nature of the data sources, and the rarity of the exposure and outcomes. There has only been four studies examining perinatal outcomes associated with biologics exposure that have adjusted for confounders, using multivariable modeling (146,151,152,174). In two of the studies (146,174), it was not reported which variables were adjusted for, and the other two studies (151,152) were only able to adjust for basic demographic characteristics such as maternal age, BMI, year of pregnancy, and disease type in one study (151). Therefore, it can be argued that the HDPS would theoretically be much more efficient at removing confounding by indication than any of the prior studies' methods simply due to the fact that it incorporates many more predictor or proxy variables, and more sophisticatedly due to the selection and prioritization algorithm that is based on both the prevalence of the predictor and strength of association with the exposure and outcome (see Page 22, Bross formula). However, it is worth acknowledging that despite these advantages, it is not possible for the HDPS method to overcome biases caused by poorly measured confounders, variables that are poor proxies for unmeasured confounders, or unmeasured confounders without available proxy variables, thus residual confounding will still always exist in the findings.

Serious infections are another well-known safety concern specifically in patients using biologics, due to their mechanism of action in attenuating or modulating the immune system through targeting inflammatory cytokines or immune cell activation. In my study, I focused on two important outcomes. First being serious post-partum infections in women with autoimmune inflammatory disease – because post-partum infections account for up to 10% of maternal deaths, and are a leading cause of short term morbidity and long term complications. Second being serious infections in infants during their first year of life – a theoretical concern stemming from pharmacokinetic studies demonstrating the exponential transport and accumulation of biologics in neonatal circulation. Despite pregnant women and infants being vulnerable populations there has been a dearth of evidence on these clinically important questions. Fortunately, my findings showed that serious infections requiring hospitalization were relatively rare, occurring in approximately 3% of 90 women exposed to biologics during pregnancy, and 100 babies born to these women. By using multivariable regression, I was able to examine not only the effect of the biologic exposure, but also of concomitant immunosuppressants such as DMARDs and glucocorticoids. I did not observe an association between biologic exposure and serious maternal post-partum infections, as the adjusted OR was 0.79 (95% CI 0.24 to 2.54). Similarly, there was no association with DMARD/ immunosuppressant use (OR 0.98, 95% CI 0.68 to 1.40), or glucocorticoid use (OR 1.00, 95% CI 0.60 to 1.67). There also was no observed association between the risk of serious infant infections and biologic exposure in utero (OR 0.56, 95% CI 0.17 to 1.81), DMARD/immunosuppressant exposure in utero (OR 1.09, 95% CI 0.81 to 1.45), or glucocorticoid exposure in utero (OR 1.13, 95% CI 0.77 to 1.66).

The final objective of this body of research was to compile my findings with all of the findings in existing literature through a systematic review and meta-analysis. Overall I found 21 studies published between 2011 and 2017 that met the inclusion criteria, altogether these comprised 5,677 pregnancies exposed to a biologic and 35,881 unexposed. Outcomes evaluated in the 21 studies were congenital anomalies (n = 15 studies), preterm delivery (n = 14 studies), low birth weight (n = 6 studies), stillbirths (n = 5 studies), small-for-gestational-age births (n = 2 studies), maternal infections (n = 2 studies), and infant infections (n = 4 studies). When I pooled the absolute numbers of events reported by these studies, I observed a significantly increased risk of congenital anomalies (OR 1.33, 95% CI 1.03 to 1.72), preterm birth (OR 1.66, 95% CI 1.40 to 1.97), and low birth weight babies (OR 1.67, 95% CI 1.21 to 2.31) associated with biologic use during pregnancy. However, in pooled analyses of adjusted risk estimates I observed that the association between biologic use during pregnancy compared to disease-matched pregnant women who did not use a biologic was no longer statistically significant for congenital anomalies (aOR 1.18, 95% CI 0.88 to 1.57), and preterm delivery (aHR 1.09, 95% CI 0.70 to 1.69), suggesting that the formerly observed elevated risks may have been due to confounding by indication, or confounding due to unmeasured factors not accounted for in previous studies. The low birth weight outcome did not have enough studies with adjusted results to facilitate pooling. These findings further substantiate the need for using novel methods such as HDPS to control both measured and unmeasured potential confounders in order to isolate the impact of biologics on these adverse outcomes during pregnancy, particularly given the relative rarity of the events.

7.2. Strengths and limitations

The aims of the studies in this dissertation set out to address three main areas identified to be critical issues in the pursuit of determining the safety of perinatal biologic use in women with autoimmune disease: i) a lack of population-based studies; ii) potential confounding by indication; and iii) rare exposures and rare outcomes. As such, the strengths of these works correspond to the methodologies used in order to address these challenges.

A fundamental strength of my work comes from the use of population-based linked databases from Population Data BC, BC PharmaNet, and BCPDR. These data are of high quality and have high coverage – with data on every legal resident in the province. These characteristics reduce the risk of information and selection biases; and increases generalizability of the results. Of particular importance for perinatal pharmacoepidemiology, is the linkage of the prescription dispensations database (PharmaNet) with the perinatal registry (BCPDR), the latter of which provided crucial information such as gestational age based on information from early gestational ultrasound or the date of last menstrual period if early gestational ultrasound was unavailable, date of delivery/baby's date of birth, birth weight, and a number of "gold standard" outcomes. The linkage of these two databases afforded the ability to accurately determine the timing of all medication dispensations with respect to milestone pregnancy dates and outcomes for each pregnancy and baby in the cohort. Three out of five studies relied on these features. For example, in Chapter 3, the BCPDR data allowed for the ascertainment of preterm deliveries and SGA using gestational age estimated through early ultrasound, baby's date of birth, and birth weights, obviating the need to identify these outcomes via diagnostic codes. Chapter 4 relied on information on the timing of biologic prescriptions being within the window of organogenesis, and the gold standard outcome of congenital anomalies recorded on chart documentation at birth. The accuracy of these data sources

and linkages cannot be understated, as it directly impacts the validity of the study findings through minimizing potential misclassification, patient recall bias, and selection bias.

The application of HDPS methods is a unique approach that strengthens these studies by improving their internal validity. Ensuring internal validity and appropriate comparison of exposure groups is of utmost importance when assessing the impact of biologic use in this population of women with autoimmune disease given the association between disease activity, adverse pregnancy outcomes (19,111), and the fact that those with worse disease activity are also more likely to be on a biologic given the current treatment pathways (confounding by indication). Propensity score-based methods are currently the most robust approach to address confounding by indication, and the HDPS takes this further by also adjusting for proxies of unmeasured potential confounders (104). This methodology was applied in two out of five studies in this dissertation, specifically where confounding by indication may pose the biggest problems. Further, an additional advantage of propensity score-based methods in the context of this particular body of work was that it was conducive to simultaneously controlling for a large number of potential confounders in the face of low numbers of events.

With rare exposures and rare outcomes being a substantial methodological challenge in existing studies on this topic, as well as in my research, I made extensive efforts to systematically review the literature and meta-analyze the results to arrive at the most accurate estimates of the risks of adverse outcomes. In Chapter 6, a major strength was the collaboration with an information scientist who conducted the database searches to ensure that all relevant literature was captured. The implementation of the Newcastle-Ottawa Scale to assess study quality, and subsequent

sensitivity analyses based on quality scores also lent more confidence to the results. Last but not least, in Chapter 6, the pooling of results from only studies that have adjusted for confounding was a unique approach in attempts to arrive at unbiased estimates of the risk of adverse pregnancy outcomes associated with biologic exposure.

Despite these extensive efforts to isolate the effect of biologics on maternal and infant outcomes, there remain several limitations with respect to the methods used in this dissertation. First and foremost, there exist well-known limitations with the use of administrative health care databases for research purposes. The information captured in these databases is primarily for the purposes of billing and are not collected for the purposes of epidemiological research. One criticism has been that these databases lack detailed clinical data that could be used to accurately measure disease severity. The purpose of the HDPS-based methodology is intended to overcome these limitations through the algorithmic selection of a large number of variables that are potential confounders or proxies for clinical disease activity and unmeasured confounders. However, there is still a reliance on the accuracy of diagnostic coding within these databases and an assumption that dispensed medications are taken as directed. Wherever possible, I used validated algorithms to ascertain diagnoses, and/or used the gold standard of outcomes recorded in the BCPDR. 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 (175).

Notwithstanding the strengths of the HDPS methodology, there are several inherent limitations to be acknowledged. For example, propensity score-based methods cannot examine multiple exposures simultaneously, due to its construction using logistic regression, unless one were to categorize exposures into mutually exclusive groups and make multiple pairwise comparisons. This was the reason for using a different methodology in the assessment of serious infections (Chapter 5), due to the possible impact of other exposures (DMARDs, immunosuppressants, and glucocorticoids) on the risk of infections. Moreover, propensity score methods also cannot account for time dependent exposures. Specific to the HDPS, there have been criticisms that its algorithmic selection of covariates based on the Bross formula, which is only able to look at each covariate's relationship with the exposure and outcome independently, disregards overall model parsimony. There are several machine learning approaches that assess overall model parsimony to various degrees, for example LASSO, random forest, and elastic net; however, simulation studies show that the HDPS performs at least as well as these methods (176).

Finally, the issue of "depletion of susceptibles" could be viewed as a limitation affecting the findings of my studies. This potential issue was identified upon examination of the patterns of use of biologics (Chapter 2), where the number of women discontinuing their biologic increased as pregnancy progressed, resulting in fewer women being exposed through to delivery. This could pose a problem with respect to the evaluation of serious infections (Chapter 5) where immunosuppression, due to maternal exposure to a biologic or accumulation of a biologic in fetal circulation, around the time of delivery may have the biggest impact on infection risks. As such, it should be noted that this could be one explanation for the low numbers of outcomes, i.e., serious infections, observed in Chapter 5. However, this issue likely did not have the same impact on the

outcomes assessed in Chapters 3 and 4, preterm delivery, SGA, and congenital anomalies respectively, because the timing corresponding to the "risk of injury" from the drug could occur any time during pregnancy.

7.3. Contributions and implications

My dissertation presents a topical and coherent body of research on the impact of biologics on the complex interplay between autoimmune disease activity and pregnancy outcomes. Given the limited research in this area, the studies comprising my thesis contribute critically needed information that addresses current knowledge gaps.

The clinical implications are straightforward. Several prior studies had contributed inconclusive evidence with respect to the association of biologics and the risk of preterm deliveries and low birth weight babies, many of which observed high ORs suggesting an elevated risk. The story was similar with respect to risk of congenital anomalies, albeit to a lesser degree. My work demonstrates that by applying robust methods to control for confounding by indication, these previously observed effects were attenuated, and this phenomenon was even more pronounced when the results from studies that did and did not adjust for confounding were pooled. This is the first time this has been demonstrated and I believe that considering the totality of this evidence, we can be fairly confident that perinatal and intrapartum biologic use does not pose a clinically meaningful threat to maternal and neonatal health. This information is pertinent for patients and clinicians who need to make important, and often difficult, decisions around weighing risks and benefits of using medications to

control autoimmune disease activity during pregnancy especially given that uncontrolled disease activity itself can lead to adverse pregnancy outcomes.

I believe that beyond the clinical contributions of this research there are also methodological contributions. Being the first study to apply the HDPS in perinatal pharmacoepidemiology using BC population-based administrative health databases, I have shown that this algorithm is applicable to the Canadian setting and implementable across multiple linked data dimensions. The approach to the meta-analysis that I undertook – namely by pooling crude results and adjusted results separately – highlights the need to examine, and perhaps standardize, the methods employed by individual studies to deal with confounding by indication. Lastly, I believe the findings also demonstrate the need to continually update these results through meta-analytical approaches given the small sample sizes of individual regional studies.

7.4. Future research directions

The series of studies in this thesis addressed specific a priori research questions and further questions have arisen through these findings that warrant additional examination. Some of these questions may not be answerable with the current data; however, they are discussed here for the purposes of future consideration.

After examining the patterns of utilization of biologics in this population, it was apparent that three specific TNF inhibitors were far more commonly used (by 94% of the exposed group) than any other biologic. This begs the question of whether the findings would differ to a meaningful extent if non-

TNF inhibitor biologics were represented. In a similar vein, the cohort consisted mostly of women with RA or IBD (together comprising approximately 90% of the cohort) and as such, we currently do not know whether the impact of biologics in subgroups of inflammatory autoimmune diseases would differ meaningfully. While I do not believe these questions can be answered with currently available data as exposures to biologics within these subcategories are simply too few to facilitate robust analyses, they are nevertheless emerging areas of interest.

In terms of outcomes of interest, through the meta-analysis I found that several outcomes of interest did not have enough existing evidence to facilitate pooling of adjusted risk estimates. Even outcomes that were pooled were based only on five or fewer studies, and it has been suggested that in meta-analyses that five or more studies are needed in order for the results to be reliable (110). As such, I believe that future works should continue to examine the impact of biologics on perinatal outcomes of interest in this population and employ methods to address confounding by indication in order to facilitate more robust future meta-analyses.

7.5. Conclusions

The work in this thesis has contributed clinically applicable and novel information on the perinatal safety of treatment with biologics in women with autoimmune inflammatory diseases by examining the patterns of utilization and their impact on several adverse maternal and neonatal outcomes. The finding that biologics are increasingly being utilized in this population demonstrates the importance of scrutinizing their safety. Using the innovative and robust HDPS methodology to address issues caused by potential confounding, I have shown that biologics do not appear to be associated with

preterm deliveries, SGA, or congenital anomalies. There also appeared to be no link between the immunosuppressive action of biologics and a risk of serious infections in either mothers or infants. Further, all of these findings were corroborated by compiling the totality of currently available evidence to provide a comprehensive picture of the perinatal effects of this highly effective class of medications. These results provide useful risk benefit information for both patients and clinicians in decision-making around treatment options for autoimmune inflammatory disease during pregnancy.

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Appendices

Appendix A: Disease codes and medications used to identify cohorts or exposures

Appendix A Table 1. Autoimmune inflammatory diseases with indication for treatment with biologics and corresponding ICD-9/10 codes

Diagnosis	**ICD-9**	**ICD-10**
Systemic Autoimmune Rheumatic Diseases		
Systemic lupus erythematosus	7100	M321, M328, M329
Scleroderma/systemic sclerosis	7101	M340, M348, M349
Sjogren's syndrome	7102	M350
Dermatomyositis	7103	M330, M331,M339
Polymyositis	7104	M332
Vasculitis		
Polyarteritis nodosa	446, 4460	M300
Wegener's Disease	4464	M313, M3130, M3131
Takayasu disease	4467	M314
Crohn's disease	555 5550, 5551, 5559	K500, K501, K508, K509
Ulcerative colitis	556 5565, 5566, 5568, 5569	K510, K512, K513, K514, K515, K518, K519
Ankylosing spondylitis	720	M450, 451, 452, 453, 454, 455, 456, 457, 458, 459
Psoriasis/Psoriatic arthritis	696 6960, 6961	L40[0-5, 8, 9]
Rheumatoid Arthritis	714 7140 71400	M05[0-9], M06[0-4, 8, 9]
JIA	7143 71430, 71431, 71432, 71433	M08[0-4, 8, 9]
Multiple sclerosis	340	G35

Appendix A Table 1. List of prescription 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

Appendix A Table 2. Congenital anomalies and corresponding ICD9/10 codes

Category	**ICD-9**	**ICD-10**
Neural tube defects		
Anencephalus & similar anomalies	740.0–740.2	Q00.0–Q00.2
Spina bifida	741.0–741.9	Q05.0–Q05.9, Q07.0
Encephalocele	742.0	Q01.0–Q01.2, Q01.8, Q01.9
Central nervous system anomalies		
Microcephalus & brain reduction	742.1–742.2	Q02, Q04.0–Q04.3
Congenital hydrocephalus	742.3	Q03.0, Q03.1, Q03.8, Q03.9
Other specified & unspecified CNS anomalies	742.4–742.9	Q04.4–Q04.6, Q04.8, Q04.9, Q06.0–Q06.4, Q06.8, Q06.9, Q07.8, Q07.9
Eye anomalies		
Anophthalmos, microphthalmos	743.0–743.1	Q11.0–Q11.2
Other eye anomalies	743.2–743.9	Q10.0–Q10.7, Q11.3, Q12.0–Q12.4, Q12.8–Q13.5, Q13.8–Q14.3, Q14.8–Q15.0, Q15.8, Q15.9

Ear face & neck anomalies		
Anomalies of ear causing impairment	744.0	Q16.0, Q16.1, Q16.3–Q16.5, Q16.9
Other ear anomalies	744.1–744.3	Q16.2, Q17.0–Q17.5, Q17.8, Q17.9
Anomalies of face & neck	744.4–744.9	Q18.0–Q18.9
Congenital heart defects		
Common truncus	745.0	Q20.0, Q21.4
Transposition of great vessels	745.1	Q20.1–Q20.3, Q20.5
Tetralogy of Fallot	745.2	Q21.3
Common ventricle	745.3	Q20.4
Ventricular septal defect	745.4	Q21.0, Q21.8
Atrial septal defect	745.5	Q21.1
Endocardial cushion defects	745.6	Q21.2
Other septal closure defects	745.7–745.9	Q21.9
Heart valve anomalies	746.0–746.6	Q22.0–Q22.5, Q23.0–Q23.3
Hypoplastic left heart syndrome	746.7	Q23.4
Other heart anomalies	746.8–746.9	Q20.6, Q20.8, Q20.9, Q22.6, Q22.8, Q22.9, Q23.8–Q24.6, Q24.8, Q24.9
Circulatory system anomalies		
Coarctation of aorta	747.1	Q25.1
Other anomalies of aorta	747.2	Q25.2–Q25.4
Pulmonary artery anomalies	747.3	Q25.5–Q25.7
Other circulatory system anomalies	747.4–747.9	Q25.8–Q26.6, Q26.8–Q27.4, Q27.8–Q28.3, Q28.8, Q28.9
Respiratory system anomalies		
Nose anomalies	748.0, 748.1	Q30.0–Q30.3, Q30.8, Q30.9
Lung agenesis & hypoplasia	748.5	Q33.2, Q33.3, Q33.6
Other respiratory system anomalies	748.2–748.4, 748.6, 748.8, 748.9	Q31.0–Q31.4, Q31.8–Q32.4, Q33.0, Q33.1, Q33.4, Q33.5, Q33.8–Q34.1, Q34.8, Q34.9
Orofacial clefts		
Cleft palate	749.0	Q35.0–Q35.9
Cleft lip	749.1	Q36, Q36.0, Q36.1, Q36.9
Cleft palate with cleft lip	749.2	Q37, Q37.0–Q37.5, Q37.8, Q37.9

Digestive system anomalies		
T-E fistula, esophageal atresia & stenosis	750.3	Q39.0–Q39.4, Q39.8
Other upper alimentary tract anomalies	750.1, 750.2, 750.4–750.9	Q38.0, Q38.2–Q38.8, Q39.5, Q39.6, Q39.9, Q40.0–Q40.3, Q40.8, Q40.9
Intestinal, anorectal atresia & stenosis	751.2	Q42.0–Q42.3, Q42.8, Q42.9
Other digestive system anomalies	751.0, 751.1, 751.3–751.9	Q41.0–Q41.2, Q41.8, Q41.9, Q43.0–Q44.7, Q45.0–Q45.3, Q45.8, Q45.9
Genital organ anomalies		
Hypospadias, epispadias	752.6	Q54.0–Q54.4, Q54.8, Q54.9, Q64.0
Other genital organ anomalies	752.0–752.5, 752.7–752.9	Q50.0–Q50.6, Q51.0–Q53.2, Q53.9, Q55.0–Q55.6, Q55.8–Q56.4
Urinary system anomalies		
Renal agenesis & dysgenesis	753.0	Q60.0–Q60.6
Cystic kidney disease	753.1	Q61.0–Q61.5, Q61.8, Q61.9
Other urinary system anomalies	753.2–753.9	Q62.0–Q62.8, Q63.0–Q63.3, Q63.8, Q63.9, Q64.1–Q64.9
Musculoskeletal anomalies		
Certain musculoskeletal anomalies	754.0–754.2, 754.4, 754.8	Q67.0–Q67.7, Q68.0–Q68.5, Q76.3
Congenital dislocation of hip	754.3	Q65.0–Q65.6, Q65.8
Clubfoot	754.5–754.7	Q66.0–Q66.9
Polydactyly, syndactyly	755.0–755.1	Q69.0–Q69.2, Q69.9–Q70.4, Q70.9
Limb deficiency defects	755.2–755.4	Q71.0–Q71.4, Q71.5, Q71.8–Q73.1, Q73.8
Other, unspecified limb anomalies	755.5–755.9	Q65.9, Q68.8, Q71.6, Q74.0–Q74.3, Q74.8, Q74.9
Anomalies of abdominal wall	756.7	Q79.2–Q79.5
Other musculoskeletal anomalies	756.0–756.6, 756.8, 756.9	Q67.8, Q75.0–Q75.5, Q75.8–Q76.2, Q76.4–Q78.6, Q78.8–Q79.1, Q79.6, Q79.8, Q79.9

Anomalies of integument	757.0–757.9	Q80.0–Q80.4, Q80.8–Q81.2, Q81.8–Q82.5, Q82.8–Q83.3, Q83.8–Q84.6, Q84.8, Q84.9
Down syndrome	758.0	Q90.0–Q90.2, Q90.9
Other & unspecified anomalies	758.9, 759.0–759.9	Q85.0, Q85.1, Q85.8–Q86.2, Q86.8, Q87.0– Q87.5, Q87.8, Q89.0–Q89.4, Q89.7–Q89.9, Q99.8, Q99.9

Appendix B: High dimensional propensity score algorithm selected covariates, by outcome

Appendix B Table 1. Data dimensions and covariates empirically selected using HDPS algorithm for preterm delivery outcome analysis

Dimension	Code	Frequency of occurrence	Item
PharmaNet prescriptions database	2163926	Once	Tylenol 3
PharmaNet prescriptions database	312770	Frequent	prednisone
PharmaNet prescriptions database	312770	Once	prednisone
PharmaNet prescriptions database	312770	Sporadic	prednisone
PharmaNet prescriptions database	608882	Frequent	Emtec 30
PharmaNet prescriptions database	545066	Once	metronidazole
PharmaNet prescriptions database	2041464	Frequent	lorazepam
PharmaNet prescriptions database	2041464	Once	lorazepam
PharmaNet prescriptions database	426849	Frequent	folic acid 5 mg
PharmaNet prescriptions database	426849	Once	folic acid 5 mg
PharmaNet prescriptions database	426849	Sporadic	folic acid 5 mg
PharmaNet prescriptions database	2242907	Frequent	azathioprine
PharmaNet prescriptions database	2242907	Once	azathioprine
PharmaNet prescriptions database	2242907	Sporadic	azathioprine

PharmaNet prescriptions database	2246691	Frequent	hydroxychloroquine
PharmaNet prescriptions database	2246691	Once	hydroxychloroquine
PharmaNet prescriptions database	2246691	Sporadic	hydroxychloroquine
Medical Services Plan database	787	Frequent	symptoms involving digestive system (includes N/V, heartburn, dysphagia, flatulence/gas, peristalsis, incontinence, abnormal feces, and other
Medical Services Plan database	787	Once	symptoms involving digestive system (includes N/V, heartburn, dysphagia, flatulence/gas, peristalsis, incontinence, abnormal feces, and other
Medical Services Plan database	787	Sporadic	symptoms involving digestive system (includes N/V, heartburn, dysphagia, flatulence/gas, peristalsis, incontinence, abnormal feces, and other
Medical Services Plan database	01L	Once	laboratory
Medical Services Plan database	01L	Sporadic	laboratory
Medical Services Plan database	626	Once	disorders of menstruation and other abnormal bleeding from female genital tract
Medical Services Plan database	30B	Once	prenatal care
Medical Services Plan database	01X	Frequent	xray
Medical Services Plan database	01X	Once	xray
Medical Services Plan database	01X	Sporadic	xray

Medical Services Plan database	02A	Frequent	abdominal swelling not otherwise specified or abdominal pain
Medical Services Plan database	02A	Once	abdominal swelling not otherwise specified or abdominal pain
Medical Services Plan database	02A	Sporadic	abdominal swelling not otherwise specified or abdominal pain
Medical Services Plan database	01X0	Frequent	xray
Medical Services Plan database	311	Once	depressive disorder, not elsewhere classified
Medical Services Plan database	311	Sporadic	depressive disorder, not elsewhere classified
Medical Services Plan database	786	Sporadic	symptoms involving respiratory system and other chest symptoms
Medical Services Plan database	714	Frequent	rheumatoid arthritis and other inflammatory polyarthropathies
Medical Services Plan database	714	Once	rheumatoid arthritis and other inflammatory polyarthropathies
Medical Services Plan database	714	Sporadic	rheumatoid arthritis and other inflammatory polyarthropathies
Medical Services Plan database	789	Once	other symptoms involving abdomen and pelvis
Medical Services Plan database	628	Sporadic	infertility, female
Medical Services Plan database	788	Once	symptoms involving urinary system
Hospitalizations database	K512	Once	ulcerative colitis
Hospitalizations database	K500	Once	Crohn's of small intestine
Hospitalizations database	K501	Once	Crohn's of large intestine
Hospitalizations database	K509	Once	Crohn's disease unspecified
Hospitalizations database	Z098	Once	follow up encounter
Hospitalizations database	K512	Frequent	ulcerative colitis
Hospitalizations database	K500	Frequent	Crohn's of small intestine

Hospitalizations database	K501	Frequent	Crohn's of large intestine
Hospitalizations database	K509	Frequent	Crohn's disease unspecified
Hospitalizations database	Z098	Frequent	follow up encounter

Appendix B Table 2. Data dimensions and covariates empirically selected using HDPS algorithm for SGA outcome analysis

Dimension	**Code**	**Frequency of occurrence**	**Item**
PharmaNet prescriptions database	1997580	Frequent	mesalazine
PharmaNet prescriptions database	2028700	Frequent	Tri-cyclen 21
PharmaNet prescriptions database	893722	Once	clomiphene citrate
PharmaNet prescriptions database	893722	Sporadic	clomiphene citrate
PharmaNet prescriptions database	312770	Frequent	prednisone
PharmaNet prescriptions database	312770	Once	prednisone
PharmaNet prescriptions database	312770	Sporadic	prednisone
PharmaNet prescriptions database	2236974	Once	Alesse-21
PharmaNet prescriptions database	608882	Frequent	Emtec-30
PharmaNet prescriptions database	545066	Once	metronidazole
PharmaNet prescriptions database	2236975	Frequent	Alesse-28
PharmaNet prescriptions database	2041464	Frequent	lorazepam
PharmaNet prescriptions database	2041464	Once	lorazepam
PharmaNet prescriptions database	426849	Frequent	folic acid 5 mg

PharmaNet prescriptions database	426849	Once	folic acid 5 mg
PharmaNet prescriptions database	37605	Once	Micronor 28
PharmaNet prescriptions database	2242907	Frequent	azathioprine
PharmaNet prescriptions database	2242907	Once	azathioprine
PharmaNet prescriptions database	2244914	Once	salbutamol
PharmaNet prescriptions database	2244756	Once	clarithromycin
PharmaNet prescriptions database	2246691	Frequent	hydroxychloroquine
PharmaNet prescriptions database	2246691	Once	hydroxychloroquine
PharmaNet prescriptions database	2246691	Sporadic	hydroxychloroquine
Medical Services Plan database	787	Frequent	symptoms involving digestive system (includes N/V, heartburn, dysphagia, flatulence/gas, peristalsis, incontinence, abnormal feces, and other
Medical Services Plan database	01L	Sporadic	laboratory
Medical Services Plan database	30B	Frequent	prenatal care
Medical Services Plan database	30B	Once	prenatal care
Medical Services Plan database	30B	Sporadic	prenatal care
Medical Services Plan database	01X	Sporadic	xray
Medical Services Plan database	02A	Frequent	abdominal swelling not otherwise specified or abdominal pain
Medical Services Plan database	02A	Once	abdominal swelling not otherwise specified or abdominal pain
Medical Services Plan database	02A	Sporadic	abdominal swelling not otherwise specified or abdominal pain

Medical Services Plan database	311	Once	depressive disorder, not elsewhere classified
Medical Services Plan database	311	Sporadic	depressive disorder, not elsewhere classified
Medical Services Plan database	786	Sporadic	symptoms involving respiratory system and other chest symptoms
Medical Services Plan database	714	Once	rheumatoid arthritis and other inflammatory polyarthropathies
Medical Services Plan database	714	Sporadic	rheumatoid arthritis and other inflammatory polyarthropathies
Medical Services Plan database	789	Once	other symptoms involving abdomen and pelvis
Hospitalizations database	O021	Once	missed abortion
Hospitalizations database	O034	Once	incomplete spontaneous abortion without complication
Hospitalizations database	N979	Once	infertility, female
Hospitalizations database	K508	Once	Crohn's of small and large intestine
Hospitalizations database	K500	Once	Crohn's of small intestine
Hospitalizations database	K501	Once	Crohn's of large intestine
Hospitalizations database	O021	Sporadic	missed abortion
Hospitalizations database	O034	Sporadic	incomplete spontaneous abortion without complication
Hospitalizations database	N979	Sporadic	infertility, female
Hospitalizations database	K508	Frequent	Crohn's of small and large intestine
Hospitalizations database	K500	Frequent	Crohn's of small intestine
Hospitalizations database	K501	Frequent	Crohn's of large intestine

Appendix B Table 3. Data dimensions and covariates empirically selected using HDPS algorithm for congenital anomaly outcome analysis

Dimension	**Code**	**Frequency of occurrence**	**Item**
PharmaNet prescriptions database	2163926	Frequent	Tylenol 3
PharmaNet prescriptions database	2163926	Once	Tylenol 3
PharmaNet prescriptions	2238465	Once	mometasone furoate nasal spray

database			
PharmaNet prescriptions database	2244914	Once	salbutamol inhaler
PharmaNet prescriptions database	893722	Frequent	clomiphene citrate
PharmaNet prescriptions database	893722	Sporadic	clomiphene citrate
PharmaNet prescriptions database	893722	Once	clomiphene citrate
PharmaNet prescriptions database	312770	Frequent	prednisone
PharmaNet prescriptions database	312770	Once	prednisone
PharmaNet prescriptions database	2041464	Frequent	lorazepam
PharmaNet prescriptions database	2041464	Once	lorazepam
PharmaNet prescriptions database	426849	Frequent	folic acid 5 mg
PharmaNet prescriptions database	426849	Sporadic	folic acid 5 mg
PharmaNet prescriptions database	2242907	Frequent	azathioprine
PharmaNet prescriptions database	2242907	Once	azathioprine
PharmaNet prescriptions database	2242907	Sporadic	azathioprine
PharmaNet prescriptions database	2246691	Sporadic	hydroxychloroquine
Medical Services Plan database	787	Frequent	symptoms involving digestive system (includes N/V, heartburn, dysphagia, flatulence/gas, peristalsis, incontinence, abnormal feces, and other
Medical Services Plan database	787	Sporadic	symptoms involving digestive system (includes N/V, heartburn, dysphagia, flatulence/gas, peristalsis, incontinence, abnormal feces, and other
Medical Services Plan	01L	Once	laboratory

database			
Medical Services Plan database	01L	Sporadic	laboratory
Medical Services Plan database	780	Frequent	general symptoms
Medical Services Plan database	30B	Once	prenatal care
Medical Services Plan database	01X	Frequent	xray
Medical Services Plan database	01X	Once	xray
Medical Services Plan database	01X	Sporadic	xray
Medical Services Plan database	02A	Once	abdominal swelling not otherwise specified or abdominal pain
Medical Services Plan database	02A	Sporadic	abdominal swelling not otherwise specified or abdominal pain
Medical Services Plan database	50B	Frequent	anxiety/depression
Medical Services Plan database	311	Once	depressive disorder, not elsewhere classified
Medical Services Plan database	781	Once	symptoms involving nervous and musculoskeletal systems
Medical Services Plan database	714	Frequent	rheumatoid arthritis and other inflammatory polyarthropathies
Medical Services Plan database	714	Once	rheumatoid arthritis and other inflammatory polyarthropathies
Medical Services Plan database	714	Sporadic	rheumatoid arthritis and other inflammatory polyarthropathies
Medical Services Plan database	788	Once	symptoms involving urinary system
Medical Services Plan database	611	Sporadic	other disorders of breast
Hospitalizations database	K512	Once	ulcerative colitis
Hospitalizations database	O034	Once	incomplete spontaneous abortion without complication
Hospitalizations database	K500	Once	Crohn's of small intestine
Hospitalizations database	K501	Once	Crohn's of large intestine

Hospitalizations database	K508	Once	Crohn's disease of both large and small intestine
Hospitalizations database	R1030	Once	lower abdominal pain, unspecified
Hospitalizations database	Z098	Once	follow up encounter
Hospitalizations database	K512	Sporadic	ulcerative colitis
Hospitalizations database	O034	Sporadic	incomplete spontaneous abortion without complication
Hospitalizations database	K500	Sporadic	Crohn's of small intestine
Hospitalizations database	K501	Sporadic	Crohn's of large intestine
Hospitalizations database	K508	Sporadic	Crohn's disease of both large and small intestine
Hospitalizations database	R1030	Sporadic	lower abdominal pain, unspecified
Hospitalizations database	Z098	Sporadic	follow up encounter

Appendix C: Infection types and diagnostic codes

Appendix C Table 1. Infections and corresponding ICD-9 and -10 codes for outcomes ascertainment in Chapter 5

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 infection, inflammatory disease of uterus, unspecified inflammatory disease of uterus, infection of GU tract in pregnancy, maternal pyrexia during labour, generalized infection during labour, pyrexia unknown during puerperium, septicemia, other infection)	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

Appendix D: Systematic review search strategy

Databases searched: Cochrane Database of Systematic Reviews 2005 to November 29, 2017, Embase 1980 to 2017 December 1, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search conducted on: December 2, 2017

Appendix D Table 1. Systematic review search strategy

1	Infliximab/ or B72HH48FLU.rn. or (Infliximab or "Mab cA2" or "Monoclonal Antibody cA2" or Remicade or avakine or flixabi or revellex).ti,ab.	56252
2	Adalimumab/ or FYS6T7F842.rn. or (Adalimumab or "D2E7 Antibody" or Humira or trudexa or "monoclonal antibody D2E7").ti,ab.	33136
3	Etanercept/ or OP401G7OJC.rn. or (Etanercept or "TNF Receptor Type II IgG Fusion Protein" or "Enbrel" or "TNFR Fc Fusion Protein" or "TNR001" or "TNR 001" or "TNT Receptor Fusion Protein" or "TNTR-Fc" or benepali or embrel).ti,ab.	35671
4	91X1KLU43E.rn. or (golimumab or Simponi).ti,ab.	3404
5	Certolizumab Pegol/ or UMD07X179E.rn. or ("Certolizumab Pegol*" or "Cimzia*" or "CDP870" or "CDP870s" or "CDP 870" or "CDP 870s").ti,ab.	5768
6	I031V2H011.rn. or (tocilizumab or atlizumab or Actemra or roactemra).ti,ab.	7221
7	Abatacept/ or 7D0YB67S97.rn. or (Abatacept or Belatacept or "BMS224818" or "BMS 224818" or "LEA29Y" or "Nulojix" or "Orencia" or "BMS 188667" or "BMS188667" or "CTLA-4-Ig" or "CTLA4-Ig" or "CTLA4-Fc" or "Cytotoxic T Lymphocyte associated Antigen 4 immunoglobulin").ti,ab.	12724
8	Rituximab/ or 4F4X42SYQ6.rn. or (Rituximab or Mabthera or "IDEC C2B8" or "IDECC2B8" or "GP2013" or Rituxan or reditux or rituxin).ti,ab.	85287
9	"Interleukin 1 Receptor Antagonist Protein"/ or D053590.rn. or (Anakinra or "IL1 Febrile Inhibitor" or "IL-1Ra" or "Urine Derived IL1 Inhibitor" or "Urine IL-1 Inhibitor" or "Urine Interleukin 1 Inhibitor" or Antril or Kineret or "recombinant interleukin 1 receptor antagonist" or "recombinant interleukin 1 receptor blocker" or "recombinant interleukin 1 receptor blocking agent").ti,ab.	23525
10	Ustekinumab/ or FU77B4U5Z0.rn. or (Ustekinumab or Stelara or "CNTO 1275"	5377

	or "CNTO127").ti,ab.	
11	ELK3V90G6C.rn. or (alefacept or "LFA-3 IgG1 fusion protein" or "LFA-3 IgG 1 fusion protein" or Amevive or LAFA3TIP).ti,ab.	1000
12	73B0K5S26A.rn. or (belimumab or "LymphoStat-B" or benlysta).ti,ab.	1351
13	"Tumor Necrosis Factor-alpha"/ or "tumor necrosis factor"/ or ("Tumor Necrosis Factor alpha" or "Tumour Necrosis Factor alpha" or TNFalpha or "TNF alpha" or Cachectin or cachetin).ti,ab.	513824
14	(biologics or "biological agent*").ti,ab.	32463
15	or/1-14 [BIOLOGICS BROAD]	692173
16	exp Pregnancy/ or exp Pregnancy Complications/ or pregnancy complication/ or (pregnanc* or pregnant).ti,ab.	1860333
17	"prenatal exposure*".ti,ab.	13462
18	or/16-17 [PREGNANCY]	1863745
19	exp Infant/	2084914
20	(infant or infants or infancy or baby or babies or newborn or newborns or neonate or neonates or neonatal).ti,ab.	1400478
21	or/19-20 [NEONATAL]	2621007
22	18 or 21 [PREGNANCY/NEONATAL]	4005467
23	15 and 22 [BIOLOGICS BROAD + PREGNANCY/NEONATAL]	29758
24	exp "Arthritis, Rheumatoid"/	290364
25	exp rheumatoid arthritis/	290364
26	(rheumatoid arthritis or inflammatory arthritis or rheumatic arthritis or Caplan Syndrome or "Caplan's Syndrome" or Caplans Syndrome or Felty Syndrome or "Felty's Syndrome" or Rheumatoid Nodul* or Rheumatoid Vasculitis or Rheumatoid Vasculitides or "Sjogren's Syndrome" or Sjogrens Syndrome or Sjogren Syndrome or "Sjogren's disease" or "Sjogrens disease" or "Sjogren disease" or Sicca Syndrome or "Adult-Onset Still's Disease" or Adult-Onset Still Disease).ti,ab.	272719
27	(arthritis deformans or arthrosis deformans or beauvais disease or chronic polyarthritis or chronic progressive poly arthritis or chronic progressive polyarthritis or primary chronic polyarthritis or rheumarthritis or rheumatic	3851

	polyarthritis).ti,ab.	
28	or/24-27 [RA]	363039
29	"Lupus Erythematosus, Systemic"/	89964
30	Lupus Nephritis/	10310
31	lupus erythematosus nephritis/	12895
32	"Lupus Vasculitis, Central Nervous System"/	2228
33	(Systemic Lupus Erythematosus or Lupus Erythematosus Disseminatus).ti,ab.	106750
34	(disseminated lupus or erythematodes visceralis or lupovisceritis or lupus erythematodes disseminatus or lupus erythematosus disseminatus or lupus erythematosus visceralis or systemic lupus erythematodes or systemic lupus erythematosis or systemic lupus erythematous).ti,ab.	4954
35	(Lupus Nephritis or Lupus Glomerulonephritis or lupus nephritides or lupus glomerulonephritides).ti,ab.	18115
36	(lupoid nephritis or lupus kidney or lupus nephropathy).ti,ab.	648
37	(Central Nervous System Lupus Vasculitis or Central Nervous System Lupus or Lupus Meningoencephalitis or Lupus Meningoencephalitides).ti,ab.	228
38	sle.ti,ab.	78075
39	38 not (lupus or autoimmun* or auto immun* or rheum* or connective).ti,ab. [ELIMINATES MOST NON-RELEVANT ITEMS]	7102
40	38 not 39	70973
41	or/29-37,40 [SLE]	158825
42	"Scleroderma, Systemic"/ or Dermatomyositis/ or Polymyositis/ or Wegener Granulomatosis/ or Giant Cell Arteritis/ or Takayasu Arteritis/ or Polyarteritis Nodosa/	102579
43	exp systemic sclerosis/ or aorta arch syndrome/	53036
44	("systemic sclerosis" or "systemic scleroderma" or " SARDS" or "systemic autoimmune rheumatic disease*" or "dermatomyositides" or "dermatopolymyositis" or "dermatopolymyositides" or "polymyositis dermatomyositis" or "polymyositis" or "multiple myositis" or "multiple myositides" or "wegener's disease" or "wegeners disease" or "Wegener's granulomatosis" or "Wegeners granulomatosis" or "giant cell arteritis" or	105327

	"giant cell arteritides" or "Horton's disease" or "Hortons disease" or "Horton disease" or "giant cell arteritis" or "giant cell arteritis" or "temporal arteritis" or "temporal arteritides" or "giant cell aortitis" or "giant cell aortitides" or "cranial arteritis" or "cranial arteritides" or " Takayasu's arteritis" or " Takayasus arteritis" or " Takayasu arteritis" or " Takayasu's disease" or " Takayasus disease" or " Takayasu disease" or " Takayasu's syndrome" or " Takayasus syndrome" or " Takayasu syndrome" or "pulseless disease" or "young female ateritis" or "aortitis syndrome" or "polyarteritis nodosa" or "periartreritis nodosa" or "necrotizing arteritis" or "necrotising arteritis" or "necrotizing arteritides" or "necrotising arteritides" or "essential polyarteritis" or "essential polyarteritides" or polyarthritis).ti,ab.	
45	("generalized scleroderma" or "generaliz]sed scleroderma" or "progressive scleroderma" or dermatomucomysitis or dermatomyositides or "petges clegat syndrom" or poikilodermatomyositis or "wegner hepp unverrricht disease" or fibromyositis or inomyositis or klinger wegener syndrome or morbus wegener or necrotizing respiratory granulomatosis or pneumogenic granulomatosis or wegener granuloma or egener klinger churg syndrome or wegener klinger granulomatosis or giant cell arteriitis or aorta arch syndrome* or anonymous artery occlusion or arteritis brachiocephalica or brachiocephalic arteritis or brachiocephalic artery occlusion or brachiocephalic ischemia or brachiocephalic trunk occlusion or brachiocephalic vascular occlusion or innominate arterial ligation or innominate artery ligation or innominate artery occlusion or martorell syndrome or reversed coarctation or takayasu arteriopathy or takayasu ohnishi syndrome or arteritis nodosa or kussmaul maler disease or kussmaul syndrome or nodular periarteritis or nodular polyarteritis or panarteriitis nodosa or panarteritis nodosa or periarterial fibrosis or periarteriitis nodosa or periarteritis nodosa or poliarteritis nodosa or polyarteriitis nodosa or polyarthritis nodosa).ti,ab.	4301
46	or/42-45 [SLE/SARDS]	153653
47	(juvenile idiopathic arthritis or systemic juvenile rheumatoid arthritis).ti,ab.	13260
48	juvenile rheumatoid arthritis/	28200
49	(arthritis deformans juvenilis or chauffard still disease or chauffard syndrome or chronic juvenile arthritis or juvenile arthritis deformans or juvenile arthropathy or juvenile chronic arthritis or juvenile idiopathic arthritis or juvenile polyarthritis or juvenile rheumatoid polyarthritis or Stiel disease or Still Chauffard disease or Still disease or Still syndrome).ti,ab.	16586
50	juvenile arthritis.ti,ab.	2120
51	or/47-50 [JUV IDIOPATHIC ARTHRITIS]	31673
52	"Spondylitis, Ankylosing"/	24667

53	ankylosing spondylitis/	38737
54	("ankylosing spondylitis" or "ankylosing spondyloarthritis" or "ankylosing spondyloarthritides" or "Bechterew's disease" or "Bechterews disease" or "Bechterew disease" or " Marie-Struempell's disease" or " Marie-Struempells disease" or " Marie-Struempell disease" or "spondyloarthritis ankylopoietica" or "rheumatoid spondylitis").ti,ab.	32842
55	(ankylating spondylitis or ankylopoietic spondylarthritis or ankylopoietic spondylitis or ankylosing spine or ankylosing spondylarthrosis or ankylosis spondylitis or ankylotic spondylitis or bekhterev disease or morbus bechterew or spinal ankylosis or spine ankylosis or spondylarthritis ankylopoietica or spondylarthritis ankylosans or spondylarthrosis ankylopoietica or spondylitis ankylopoetica or spondylitis ankylopoietica or spondyloarthritis ankylopoietica or vertebral ankylosis).ti,ab.	585
56	or/52-55 [ANKYL SPONDYLITIS]	44998
57	"Arthritis, Psoriatic"/	11680
58	psoriatic arthritis/	22739
59	("psoriatic arthritis" or "psoriasis arthropathica" or "psoriatic arthropathy" or "psoriatic arthropathies" or "arthritic psoriasis").ti,ab.	21372
60	(alibert bazin disease or arthropathic psoriasis or psoriasis arthropathica or psoriasis pustulosa arthropathica or psoriatic arthropathy or psoriatic polyarthritis or psoriatic rheumatism or psoriatic rheumatoid arthritis).ti,ab.	1244
61	or/57-60 [PSORIATIC ARTHRITIS]	27984
62	Rheumatology/	65658
63	rheumat*.ti,ab.	402111
64	62 or 63 [RA BROAD]	425015
65	or/28,41,46,51,56,61,64 [ALL INFLAM ARTHRITIS BROAD]	788889
66	Connective Tissue Diseases/ or connective tissue disease/ or Mixed Connective Tissue Disease/ or Weill-Marchesani Syndrome/	25994
67	("connective tissue disease*" or "connective tissue disorder*" or "Sharp Syndrome" or MCTD or "Weill Marchesani Syndrome" or "Marchesani Syndrome" or "Marchesani Weill Syndrome").ti,ab.	30538
68	66 or 67 [CONNECTIVE TISSUE DISEASE]	41582

69	exp Inflammatory Bowel Diseases/ or exp inflammatory bowel disease/	196508
70	("inflammatory bowel disease" or "Crohn's Enteritis" or "Regional Enteritis" or "Crohn's Disease" or "Crohns Disease" or "Crohn Disease" or "Granulomatous Enteritis" or Ileocolitis or "Granulomatous Colitis" or "Terminal Ileitis" or "Regional Ileitides" or "Regional Ileitis" or "Idiopathic Proctocolitis" or "Ulcerative Colitis" or "Colitis Gravis").ti,ab.	204581
71	69 or 70 [IBD]	244165
72	exp Autoimmune Diseases/ or exp autoimmune disease/	981863
73	("autoimmune disease*" or "autoimmune disorder*").ti,ab.	151234
74	72 or 73 [AUTOIMMUNE DISEASE BROAD]	1037388
75	or/65,68,71,74 [ALL CONDITIONS WITH RA BROAD]	1545848
76	15 and 22 and 75 [BIOLOGICS BROAD + PREGNANCY/NEONATAL + ALL CONDITIONS WITH RA BROAD]	4536
77	Premature Birth/ or "Infant, Premature"/ or "Infant, Extremely Premature"/ or Stillbirth/ or Pregnancy Outcome/	251989
78	(premature or pre-mature or preterm or pre-term or stillbirth*).ti,ab.	387504
79	77 or 78 [MATERNAL OUTCOMES]	507213
80	exp "Congenital Abnormalities"/ or exp "congenital malformation"/ or ("congenital malformation*" or "congenital defect" or " congenital defects*" or "birth defect" or "birth defects*" or deformity or deformities or "congenital abnormalit*" or "congenital anomaly" or "congenital anomalies" or "development anomaly" or "development anomalies").ti,ab.	1896152
81	("fetal malformation*" or "fetal abnormalit*" or "fetal defect" or "fetal defects" or "fetal anomaliy" or "fetal anomalies").ti,ab.	11832
82	exp " Infant, Low Birth Weight "/ or exp "low birth weight"/ or ("small for gestational age " or "small for date infant*" or "low birth weight" or "low birthweight" or "neonatal underweight").ti,ab.	113012
83	or/80-82 [NEONATAL OUTCOMES]	1997201
84	exp Infection/ or (infection or infections).ti,ab. [INFECTION]	5059666
85	or/79,83-84 [ALL OUTCOMES]	7218052
86	15 and 22 and 75 and 85 [BIOLOGICS BROAD + PREGNANCY/NEONATAL + ALL	2232

CONDITIONS WITH RA BROAD + ALL OUTCOMES]

87	limit 86 to yr="1995 -Current"	2224
88	(English or French or German or Spanish).lg.	54658089
89	87 and 88 EBM Reviews - Cochrane Database of Systematic Reviews <2005 to November 29, 2017> Embase <1980 to 2017 December 01> Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>	21810 1822 359
90	remove duplicates from 89 EBM Reviews - Cochrane Database of Systematic Reviews <2005 to November 29, 2017> Embase <1980 to 2017 December 01> Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>	18560 1535 321
91	90 use ppez [MEDLINE]	321
92	90 use emezd [EMBASE]	1535

Appendix E: Characteristics and quality assessment results of studies meeting inclusion criteria from systematic literature review

Appendix E Table 1. Characteristics of included studies

Author	Year	Country	Type of Study	Study Period	Autoimmune diseases	Exposure	Exposure time frame	Total cohort N	Exposed group N	Disease-matched unexposed group N
Schnitzler et al.	2011	Belgium	Prospective, cohort, single-centre study	1994-2007	IBD (CD, UC)	TNFi	90 days preconception until delivery	176	42	78
Verstappen et al.	2011	UK	Prospective, cohort, registry based	NR	RA, PsA, JIA, AS, SLE, Adult-onset Still's disease	TNFi	30 days preconception until delivery	81	71	10
Casanova et al.	2013	Spain	Retrospective, cohort, multi-centre study	NR	IBD (CD, UC)	TNFi	90 days preconception until delivery	571	66	187
Lichtenstein et al.	2013	USA and Canada	Prospective, cohort, registry based	1999-2012	CD	infliximab	NR	187	98	89
Diav-Citrin et al.	2014	Israel	Prospective, cohort	2002-2011	IBD (CD, UC), RA, AS, PsA, Behcet's disease	TNFi	90 days preconception until 90 days during pregnancy	510	83	86
Giacuzzo et al.	2014	Italy	Prospective, cohort, single-	2006-2013	RA, AS, PsA, JIA, undifferentia	Biologics (TNFi and rituximab)	90 days preconception until delivery	54	26	28

			centre study		ted spondyloarthritis					
Martinez et al.	2014	Spain	Retrospective, cohort	2009-2013	IBD (CD, UC)	TNFi	"before pregnancy" until delivery	68	8	60
Seirafi et al.	2014	France and Belgium	Retrospective, cohort	2009-2010	IBD (CD, UC, unclassified)	TNFi	90 days preconception until delivery	232	133	99
Chambers et al.	2015	USA and Canada	Prospective, cohort, registry based	2005-2012	NR	etanercept	During pregnancy	534	370	164
Reggia et al.	2015	Italy	Case-control	NR	RA, PsA, AS	TNFi	During pregnancy	50	25	25
Strangfeld et al.	2015	Germany	Retrospective, cohort, registry based	?-2014	RA	Biologics	Unclear "at conception"	60	51	9
Broms et al.	2016	Denmark and Sweden	Retrospective, cohort, population based	2004-2012	IBD (CD, UC), RA, AS, PsO, PsA	TNFi	90 days preconception until 90 days during pregnancy	1272424	683	21549
Chaparro et al.	2016	European countries	Retrospective, cohort, multi-centre study	NR	IBD (CD, UC)	TNFi	90 days preconception until delivery	222	105	117
Komoto et al.	2016	Japan	Cross-Sectional Study	2008-2014	IBD (CD, UC)	TNFi	NR	72	34	38

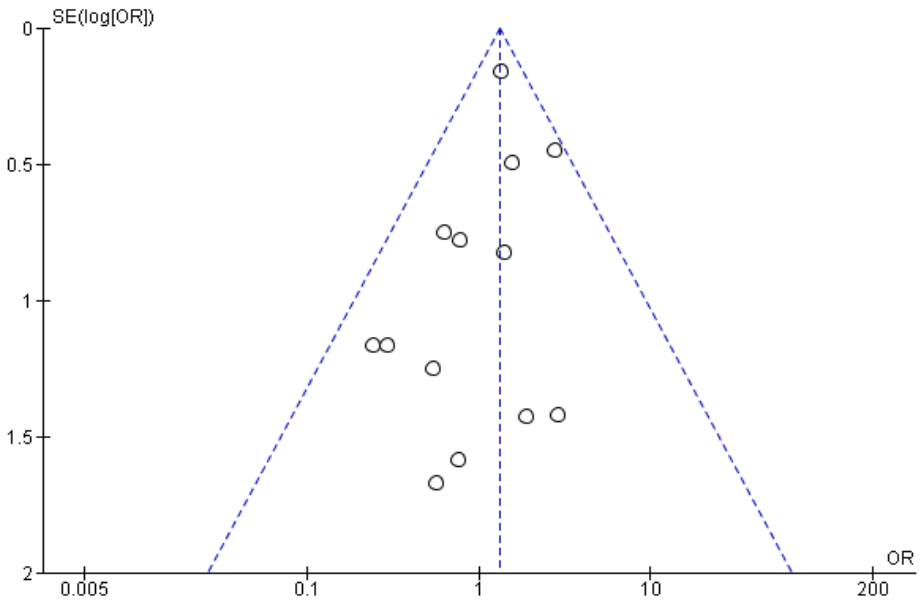
Vinet et al.	2016		Retrospective	2011-2014	RA	TNFi	12 weeks preconception until delivery	2346	290	2056
Burmester et al.	2017	USA and Canada	Prospective, cohort, registry based	2004-2013	RA	Adalimumab	During pregnancy	373	74	80
Carman et al.	2017	USA	Retrospective, cohort, population based	1995-2012	Chronic Inflammatory Arthritis (cIA) or PsO	etanercept	During pregnancy	4883	1066	2861
Chambers et al.	2017	USA and Canada	Prospective, cohort, registry based	2004-2014	RA, CD	Adalimumab	NR	602	257	120
Chambers et al.	2017	USA and Canada	Prospective, cohort, registry based	2004-2016	RA	Biologics	During pregnancy	1184	252	463
Desai et al.	2017	USA	Retrospective, cohort, population based	2001-2015	RA, SLE, AS, PsA, IBD (CD, UC)	TNFi	During pregnancy	4961	776	4185
Luu et al.	2017	France	Retrospective, cohort, population based	2011-2014	IBD (CD, UC)	TNFi	During pregnancy	11275	1457	9818

Appendix E Table 2. Quality assessment of included studies using Newcastle-Ottawa Scale

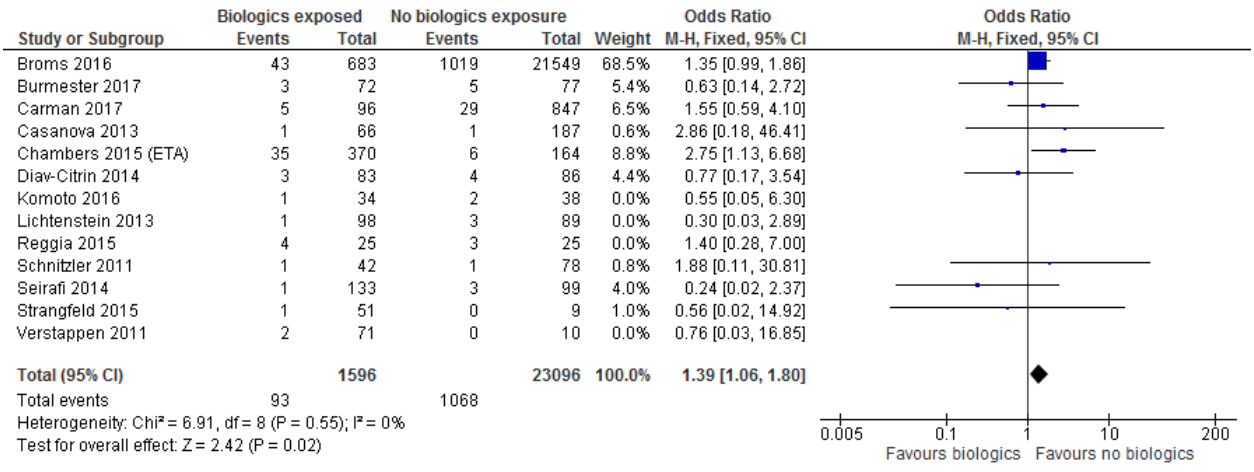
	Selection Domain				Comparability Domain	Outcome Domain			
Author	**Representativeness of exposed group**	**Selection of non-exposed group**	**Ascertainment of exposure**	**Outcome not present at start**	**Comparability**	**Assessment of outcome**	**Follow-up length**	**Adequate follow-up of cohort**	**Total score (max 9)**
Schnitzler et al.	*	*	*	*	-	*	*	*	7
Verstappen et al.	*	-	*	*	-	-	*	*	5
Casanova et al.	*	*	*	*	*	-	-	*	6
Lichtenstein et al.	*	*	-	*	-	-	*	-	4
Diav-Citrin et al.	*	*	-	*	-	*	*	*	6
Giacuzzo et al.	*	*	-	*	-	-	*	*	5
Martinez et al.	*	*	*	*	-	-	*	*	6
Seirafi et al.	*	*	*	*	* *	*	*	*	9
Chambers et al.	*	*	*	*	-	-	*	*	6
Reggia et al.	*	*	-	-	-	-	*	*	4
Strangfeld et al.	*	*	*	*	-	-	*	*	6
Broms et al.	*	*	*	*	* *	*	*	*	9
Chaparro et al.	*	-	-	*	-	*	*	*	5

Komoto et al.	*	*	*	*	-	-	-	-	4
Vinet et al.	*	*	*	*	-	*	*	*	7
Burmester et al.	*	*	*	*	-	-	*	*	6
Carman et al.	*	*	*	*	*	*	*	*	8
Chambers et al.	*	*	-	*	*	-	*	*	6
Chambers et al. (infections)	*	*	*	-	-	-	*	*	5
Desai et al.	*	*	*	*	* *	*	*	*	9
Luu et al.	*	*	*	-	*	*	*	*	7

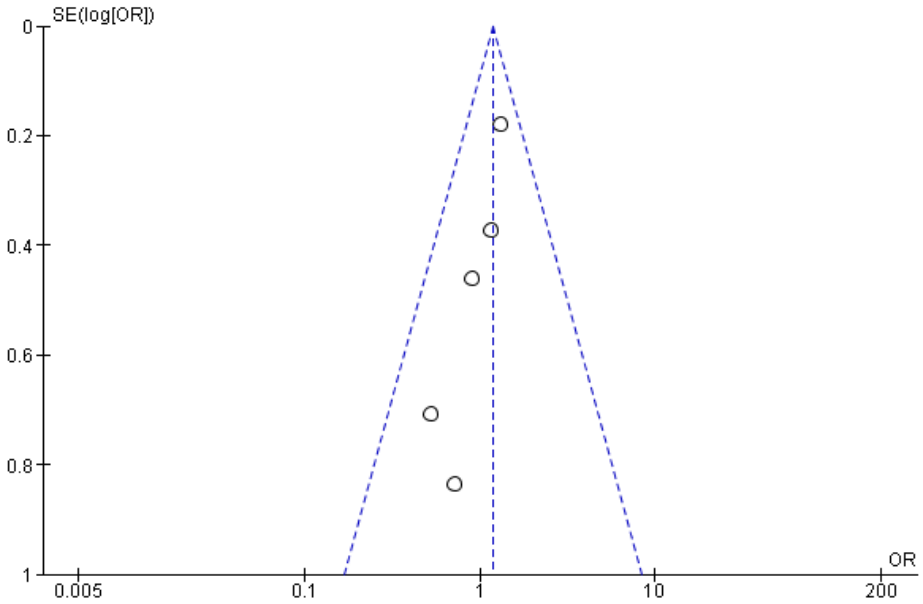
Appendix F: Results of sensitivity analyses and publication bias assessment in meta-analysis of adverse pregnancy outcomes associated with biologics exposure



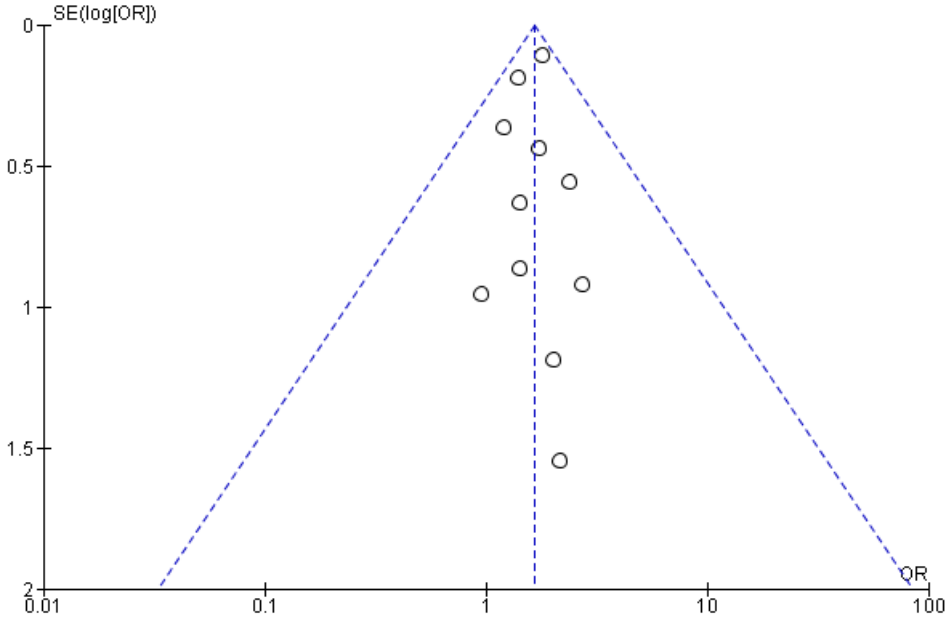
Appendix F Figure 1. Funnel plot assessment of publication bias in meta-analysis of studies reporting on crude proportions of congenital anomaly outcome associated with biologic exposure



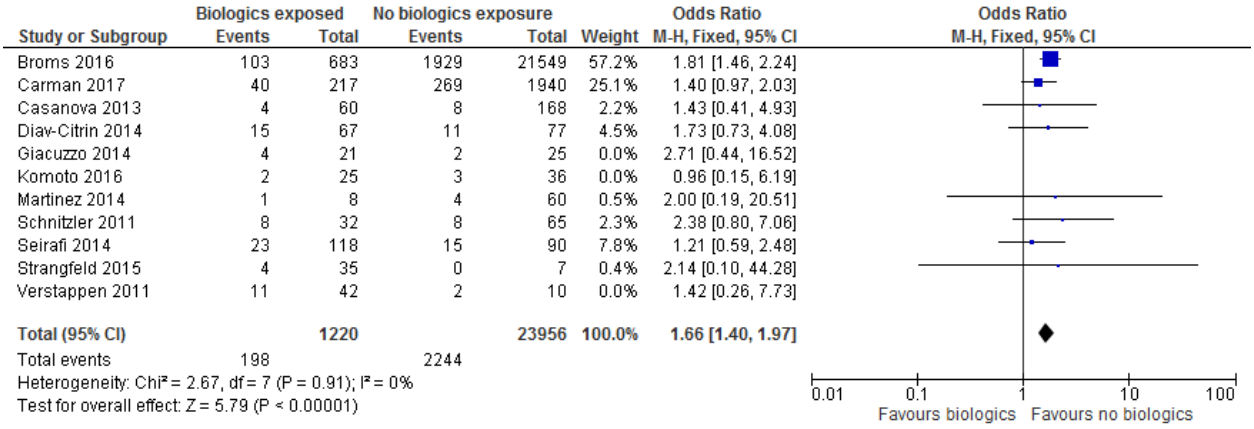
Appendix F Figure 2. Sensitivity analysis of pooled crude proportions of congenital anomalies based on Newcastle-Ottawa Scale (excluding studies with quality score <6)



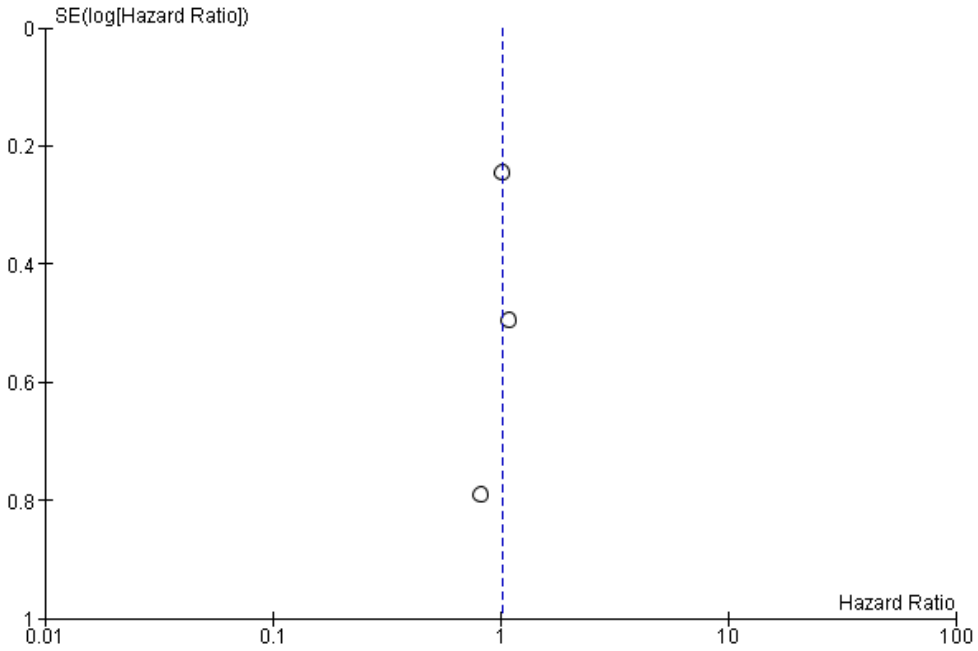
Appendix F Figure 3. Funnel plot assessment of publication bias in meta-analysis of studies reporting on adjusted risks of congenital anomaly outcome associated with biologic exposure



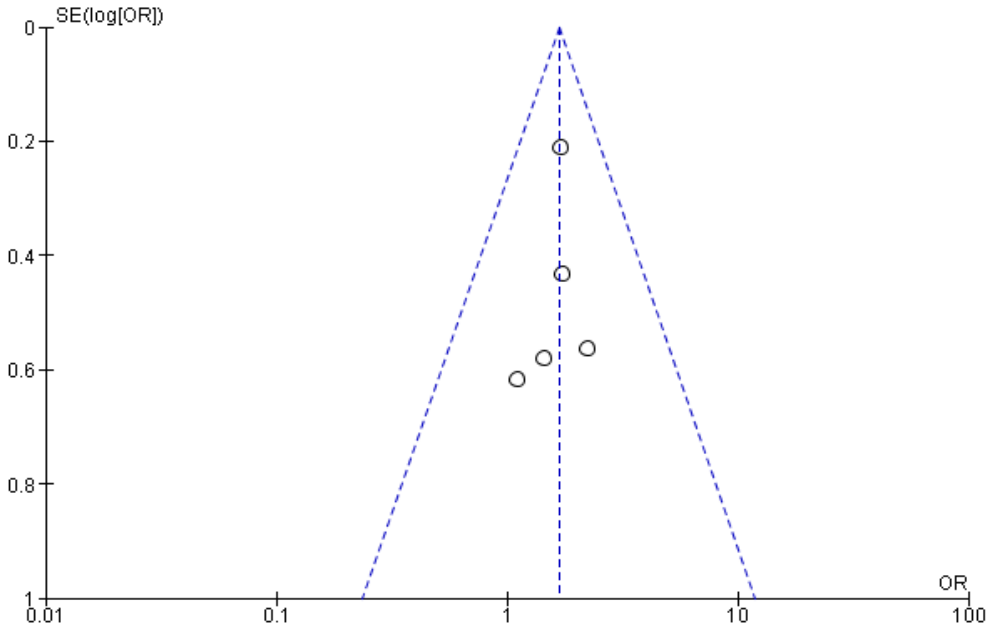
Appendix F Figure 4. Funnel plot assessment of publication bias in meta-analysis of studies reporting on crude proportions of preterm delivery outcome associated with biologic exposure



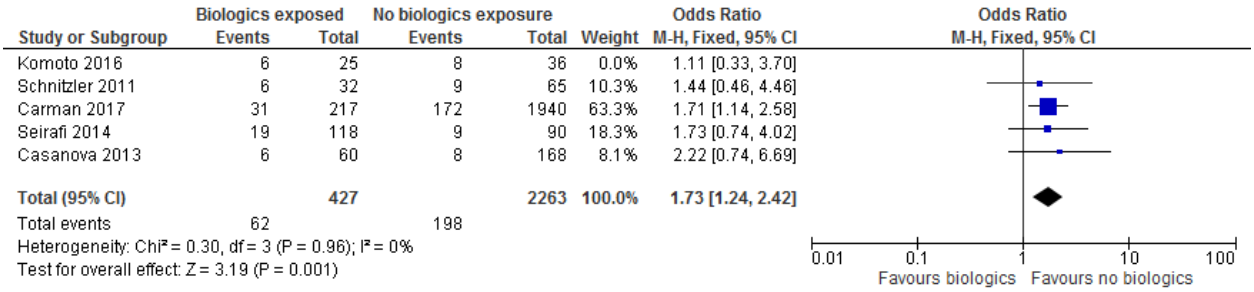
Appendix F Figure 5. Sensitivity analysis of pooled crude proportions of preterm deliveries based on Newcastle-Ottawa Scale (excluding studies with quality score <6)



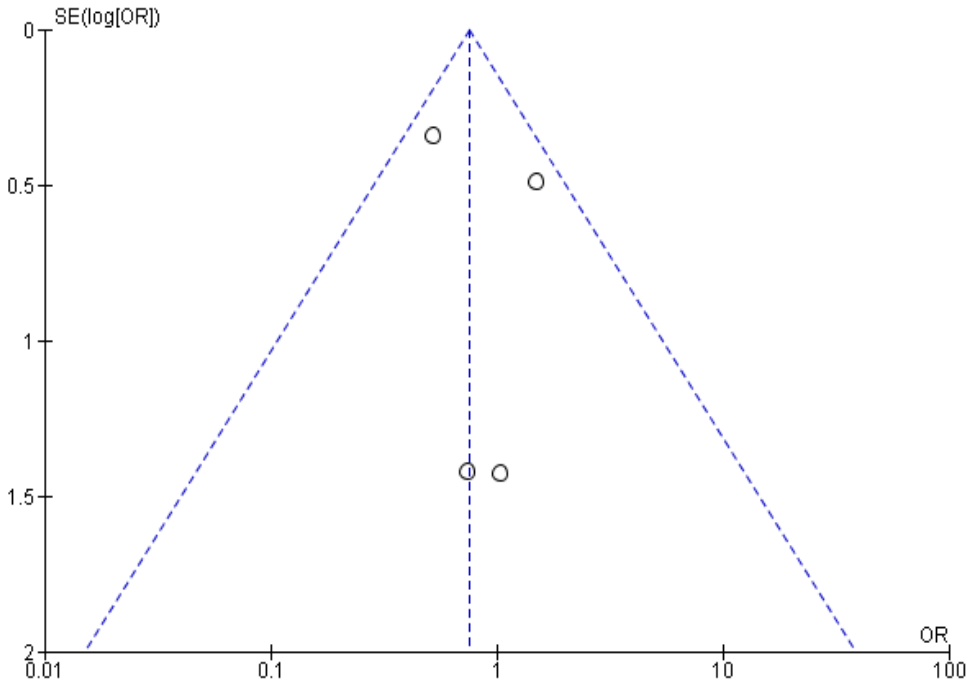
Appendix F Figure 6. Funnel plot assessment of publication bias in meta-analysis of studies reporting on adjusted risks of preterm delivery outcome associated with biologic exposure



Appendix F Figure 7. Funnel plot assessment of publication bias in meta-analysis of studies reporting on crude proportions of low birth weight outcome associated with biologic exposure



Appendix F Figure 8. Sensitivity analysis of pooled crude proportions of low birth weight newborns based on Newcastle-Ottawa Scale (excluding studies with quality score <6)



Appendix F Figure 9. Funnel plot assessment of publication bias in meta-analysis of studies reporting on crude proportions of stillbirth outcome associated with biologic exposure