Risk of serious infections in offspring exposed in utero to ustekinumab or vedolizumab

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Abstract

Background: Chronic inflammatory diseases, including inflammatory bowel diseases (IBD), psoriasis, and psoriatic arthritis (PsA), are prevalent among women of reproductive age. For women with these conditions who plan on becoming pregnant, maintaining disease control, without harming the fetus, is of utmost concern. Traditional disease-modifying anti-rheumatic drugs (DMARDs) and some biologics, including tumour necrosis factor inhibitors (TNFi), have been relatively well studied during pregnancy. In contrast, ustekinumab and vedolizumab are newer biologics whose safety in pregnancy is unclear. They actively cross the placenta during the 2nd and 3rd trimesters, and cord blood levels can exceed maternal levels. Though biologics can increase the risk of serious infections in exposed adults, there is currently no available data on serious infections in offspring exposed in utero to ustekinumab, and only limited data for vedolizumab.

Objectives: The primary objective of this thesis was to evaluate serious infection risk in offspring exposed to ustekinumab in utero and born to mothers with chronic inflammatory diseases. The secondary objective was to evaluate serious infection risk in offspring exposed to vedolizumab.

Methods: To set the stage for my original research, I performed a structured literature review of ustekinumab use during pregnancy. Then, serious infection risk was quantified in a retrospective cohort study using US health administrative data. We identified live births among women with psoriasis, PsA, and IBD. These pregnancies were classified as being exposed to ustekinumab, vedolizumab, TNFi, other biologics, traditional DMARDs, or no drug of interest. The primary outcome was serious infection within the first year of life, defined as any infection requiring hospitalization. Multivariate logistic regression using generalized estimating equations was used to estimate the adjusted odds ratio (OR) for serious infections comparing ustekinumab to no exposure to any drug of interest. The risk of serious infection of vedolizumab exposure was assessed in a cohort restricted to women with IBD, as this is vedolizumab's only indication, using the same methods.

Results: A structured literature review of ustekinumab use during pregnancy indicated that thus far there have been no studies clearly associating this drug with an excess risk of adverse pregnancy outcomes. Our administrative data cohort identified a total of 16,130 offspring born to 14,712 mothers with chronic inflammatory diseases (including 8,507 offspring born to 7,633 women with IBD), with 52 offspring exposed to ustekinumab and 43 to vedolizumab. Crude infection risk was 3.8% (95%

confidence interval (CI) 1.1%, 13.0%) in the ustekinumab group and 2.6% (95 CI 2.3, 2.8) in the unexposed comparator. After adjusting for potential confounders, the adjusted OR for serious infection was 1.58 (95% CI 0.37, 6.84) with ustekinumab compared to no exposure. Results in the TNFi (OR 0.85 95% CI: 0.59, 1.22) and traditional DMARDs (OR 0.76 95% CI: 0.55, 1.06) groups all indicated no clear increased risk compared to no exposure. Among the offspring of women with IBD (secondary objective), the crude infection risk was 2.3% (95% CI 0.4%, 12.0%) in the vedolizumab group and 3.0% (95% CI 2.6%, 3.6%) in the no-drug comparator. After adjusting for potential confounders, the OR was 0.87 (95% CI 0.13, 6.15).

Discussion: Our structured literature review identified few studies addressing infection risk in offspring exposed to ustekinumab. To address this knowledge gap we conducted a cohort study of offspring exposed to ustekinumab and vedolizumab in utero. We were the first to use administrative health data to study this population, and did not demonstrate whether there is an increased risk of infection in offspring exposed to these drugs. We plan to repeat analyses in 2 years, so that more definitive statements can be made on the safety of ustekinumab and vedolizumab in pregnancy.

Résumé

Contexte: Les maladies inflammatoires chroniques, comme les maladies inflammatoires intestinales, le psoriasis, et l'arthrite psoriasique affectent de façon prédominante les femmes en âge de procréer. Pour les femmes atteintes de ces conditions qui veulent planifier une grossesse, il est impératif de contrôler les symptômes de la maladie sans affecter le foetus. Les agents anti-rhumatismaux modificateurs de la maladie (ARMM) traditionnels et certains agents biologiques, comme les inhibiteurs du facteur de nécrose tumorale-α (TNFi), sont relativement bien étudiés pendant la grossesse. Or, l'ustekinumab et le vedolizumab sont des nouveaux agents dont la sécurité pendant la grossesse demeure incertaine. L'ustekinumab et le vedolizumab traversent activement la placenta pendant les deuxième et troisième trimestres de la grossesse, pouvant engendrer des taux sanguins au niveau du cordon ombilical qui peuvent dépasser les niveaux sanguins maternels. Il est bien connu que les agents biologiques peuvent augmenter le risque d'infections sérieuses chez les adultes exposés. Cependant, jusqu'à maintenant, les données sur le risque infectieux des enfants exposés in utero à l'ustekinumab étaient inexistantes et très limitées pour le vedolizumab.

Objectifs: L'objectif principal de cette thèse était d'évaluer le risque d'infections sérieuses chez les enfants exposés in utero à l'ustekinumab. Comme objectif secondaire, nous avons évalué le risque d'infections sérieuses chez les enfants exposés in utero au vedolizumab.

Méthode: Le risque d'infections sérieuses a été estimé dans une étude de cohorte rétrospective utilisant des données administratives américaines. Nous avons identifié des naissances vivantes chez les femmes ayant un diagnostic de psoriasis, d'arthrite psoriasique et/ou de maladies inflammatoires intestinales. Ces grossesses ont été classées comme étant exposées à l'ustekinumab, le vedolizumab, aux TNFi, d'autres agents biologiques, aux ARMM traditionnels ou non-exposées à un médicament d'intérêt. L'issue primaire était la survenue d'une infection sérieuse au cours de la première année de vie. Le risque d'infections sérieuses a été calculé en utilisant une régression logistique uni-variée et multi-variée avec des équations d'estimation généralisées, en se servant du groupe non-exposé à un médicament d'intérêt comme comparateur. L'objectif secondaire a été atteint en limitant l'inclusion dans la cohorte aux femmes avec maladies inflammatoires intestinales, ces maladies étant les seules indications clinique du vedolizumab.

Résultats: Une analyse de la littérature structurée sur l'utilisation de l'ustekinumab pendant la grossesse a indiqué qu'il n'y a aucune étude qui montre un risque excessif d'événements indésirables en lien avec la grossesse. Pour l'étude de cohorte rétrospective, nous avons identifié 16,130 enfants nés de 14,712 mères avec des maladies inflammatoires chroniques. Au total, il y avait 52 enfants exposés a l'ustekinumab et 43 au vedolizumab. Les analyses multi-variées ont montré un rapport de cotes (RC) pour le risque d'infections sérieuses de 1.57 [intervalle de confiance à 95% (95% IC) 0.37, 6.58] dans le groupe ustekinumab comparativement au groupe non exposé. Dans le groupe d'enfants nés de mères avec maladies inflammatoires intestinales (objectif secondaire), le groupe exposé au vedolizumab avait un RC de 0.87 (95% CI 0.13, 6.15).

Discussion: En plus d'une revue de la littérature, nous avons réalisé deux analyses de cohorte rétrospective d'enfants exposés in utero à l'ustekinumab et au vedolizumab, respectivement. Nous n'avons pas démontré de risque élevé chez les enfants exposés in utero à ces médicaments, bien que nos intervalles de confiance soient larges. En conclusion, il sera nécessaire d'effectuer davantage de recherche avant que des déclarations plus définitives puissent être faites sur la sécurité de l'utilisation de l'ustekinumab et du vedolizumab durant la grossesse.

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Contributions of Authors

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I was responsible for performing the literature review, establishing the study protocol and creating variable definitions, performing the statistical analyses, and writing all manuscripts, as well as writing this thesis.

Évelyne Vinet, MD PhD

Dr. Vinet was my thesis supervisor. She conceived of the thesis topic, acquired the data and contributed substantially to all aspects of the thesis including study design, interpreting the data, writing manuscripts and presentations. Dr. Vinet also provided expert knowledge on the treatment of rheumatic disease in pregnancy. Dr. Vinet critically revised this thesis and the manuscripts it contains for important intellectual content.

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Dr. Bernatsky was my thesis supervisor. She provided insight and assistance on study design, acquiring the data, and interpreting results. Dr. Bernatsky critically revised this thesis and the manuscripts it contains for important intellectual content.

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Dr. Afif was a co-author on the manuscripts. He critically revised all the manuscripts and provided expert knowledge of IBD and its treatments.

List of Acronyms

5- ASA – 5-aminosalicylate

AAD – American Academy of Dermatology

ACR – American College of Rheumatology

AGA – American Gastroenterology Association

AZA – azathioprine

BSA – body surface area

CD – Crohn's disease

CDAI – Crohn's disease activity index

CI – confidence interval

CPT – current procedural terminology

CsA – Cyclosporin

DMARD – disease modifying anti-rheumatic drug

EULAR – European League Against Rheumatism

GA – gestational age

GEE – generalized estimating equations

HR – hazard ratio

IBD – inflammatory bowel diseases

IgG – immunoglobulin G

MP – mercaptopurine

MTX – methotrexate

NDC – national drug code

NPF – National Psoriasis Foundation

OR – odds ratio

PASI – psoriasis area severity index

PH – proportional hazards

PsA – psoriatic arthritis

PsO – psoriasis

RA – rheumatoid arthritis

RCT – randomized control trial

SGA – small for gestational age

SLE – systemic lupus erythematosus

TB – tuberculosis

TNFi – tumour necrosis factor inhibitor

UC – ulcerative colitis

US – United States

1. Introduction

Chronic inflammatory diseases are a major cause of morbidity and have a particularly high prevalence among women of reproductive age. Many of these diseases are associated with adverse pregnancy outcomes and, as such, finding ways of safely controlling the symptoms of these diseases during pregnancy is of significant interest. Biologics have played a major role in the treatment of chronic inflammatory diseases for several decades now, though their safety in pregnancy is not entirely understood, especially among newer biologics. Ustekinumab is one such newer biologic. It was first approved in 2009, and is currently indicated for psoriasis (PsO), psoriatic arthritis (PsA), and inflammatory bowel diseases (IBD). Ustekinumab safety in pregnancy has not been extensively studied, with hardly any work dedicated to the risk of serious infections in exposed offspring, a biological possibility given that ustekinumab (and most biologics) are actively transported across the placenta and infection is a known risk among users.

The main objective of this thesis is to assess the risk of serious infections in offspring exposed in utero to ustekinumab. The thesis begins with background information on the relevant chronic inflammatory diseases (PsO, PsA, IBD) and the drugs used to treat them, establishing the necessary context for the rest of the thesis. I then devote the entirety of chapter 3, which includes the first manuscript of this thesis, to a structured review of the literature on ustekinumab safety, particularly during pregnancy.

The remainder of the thesis (chapters 4 to 8) is dedicated to a retrospective cohort study whose primary aim was to answer the main objective of this thesis (i.e., to evaluate the risk of serious infection in offspring exposed in utero to ustekinumab). chapter 4 describes the methods used to conduct this retrospective cohort study of children born to mothers with chronic inflammatory diseases. The next two chapters (5 and 6) present manuscripts #2 and #3 which describe this study and its results. Manuscript #2 addresses the serious infection risk of ustekinumab, while manuscript #3 examines the serious infection risk associated with in utero exposure to vedolizumab, another novel biologic, among the subgroup of IBD offspring. Chapter 7 provides a discussion of the important original findings of this thesis, as well as its strengths and limitations. Finally, chapter 8 presents potential avenues for future research related to biologic drug safety in pregnancy and conclusions.

2. Background

2.1. Chronic inflammatory diseases & pregnancy

2.1.1 Psoriasis and psoriatic arthritis

PsO is a common inflammatory skin disorder which typically manifests as sharply demarcated chronic erythematous plaques covered by silvery white scales (though there are several less common variants with different clinical presentations) (1). Psoriasis is believed to affect 2-4% of the population globally, but rates vary substantially, with increasing prevalence found among Caucasians (2) and with increasing latitude (1,2). Age at disease onset tends to be bimodally distributed, with the majority of patients first experiencing symptoms during their late teens and early twenties, and another peak occurring in the 7th decade (3). The exact causes of PsO are unknown, though strong evidence suggests both genetic and environmental factors (3). PsO has a considerable impact on the quality of life and psycho-social function of affected patients (4–6) and is associated with an increased risk of cardiovascular disease and depression (7). In addition, at least 5% (but perhaps as high as 20%) of PsO patients experience extra-cutaneous articular manifestations, known as psoriatic arthritis (PsA).

PsA is a form of inflammatory arthritis typically involving negative serological tests for rheumatoid arthritis and an association with psoriasis. PsA has different clinical presentations, the most common of which (accounting for some 70% of cases) is oligo-articular asymmetrical arthritis, affecting different joints on different sides of the body (8). PsA can affect any joint in the body, but the hands and feet are most commonly involved. Symmetrical polyarthritis (affecting the same joints areas on each side of the body) accounts for approximately 15% of cases. Manifestations affecting mainly the distal interphalangeal joints, the toes, or the spine account for the remaining 5% of cases (8). PsA diagnosis comes on average 10 years after PsO diagnosis, usually between age 30 and 55, though pre-existing PsO is not necessarily required for PsA diagnosis, nor do all PsA patients have psoriatic skin lesions. PsA is considered a severe form of arthritis, with deformities and joint damage occurring in a large percentage of patients, leading to bone erosion in 47% of patients in the first 2 years, despite systemic drug use in one study (9).

With PsO onset occurring in the late-teens and early twenties (and PsA occurring in some on approximately 10 years later), there is a high prevalence of disease among women prior to or during their reproductive years. It is well established that the complex hormonal and immune system changes that the body undergoes during pregnancy can affect underlying chronic inflammatory conditions (10). It is estimated that approximately 50% of women with PsO and/or PsA experience clinical remission or substantial improvement in symptoms during pregnancy, typically with the disease rebounding in severity after delivery (11–13). The remaining 50% of women experiencing no change or a worsening of disease symptoms (13).

While pregnancy can alter maternal disease activity, some chronic inflammatory diseases, including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), are associated with an increased risk of adverse outcomes, particularly spontaneous abortion and preterm birth (11–14). Thus, there has been considerable interest in determining if similar effects are seen among patients with PsO and PsA, especially among those with severe disease, though at this time the evidence is not as strong as it is for other inflammatory conditions. Individual studies have found that there are weak, though statistically significant, associations between PsO (with or without PsA) and spontaneous abortion (14,15), small for gestational age (SGA) (12,16), and preterm birth (15). However, a systematic review from Bobotsis et al. (13) in 2016 determined that there was no strong evidence of an increased risk for adverse pregnancy outcomes among mothers who did not take systemic drugs for PsO and/or PsA. There has only been one large retrospective cohort study (n = 1,463) by Yang et al. (12) studying pregnancy outcomes among women with PsO and showing a potentially increased risk of low birth weight among mothers with PsO. All participants in this study, however, had no systemic drug therapy within 2 years of giving birth, a likely source of selection bias leading to a potential under-representation of mothers with severe PsO (who are more likely to have adverse pregnancy outcomes). Overall, there is a lack of conclusive research into the true burden of PsO and PsA on pregnancy outcomes independent of drug exposure, though the limited evidence that exists points to an increased risk similar to other chronic inflammatory conditions.

2.1.2 Inflammatory bowel diseases

IBD encompass a number of idiopathic chronic inflammatory diseases of the gastrointestinal tract and are most commonly subdivided into Crohn's Disease (CD) and ulcerative colitis (UC). UC is characterized by inflammation from the rectum to, and typically including the entirety of, the colon. On the other hand, CD is characterized by inflammation of the entire intestinal tract, from anus to mouth, and often involves the formation of fissures, fistulas, and abscesses, which are not found in UC (17–20). Some 5-15% of IBD patients have indeterminate colitis, where neither subtype of IBD can be reliably distinguished (17,18). IBD are less prevalent than PsO, affecting approximately 0.1% of the population in North America and Europe (21,22). As with PsO and PsA, Caucasians are more likely than people of other races and ethnicities to experience IBD (19,21). Age at first diagnosis is on average around 30 years, with younger age at diagnosis typically associated with more severe disease (23–26).

As in PsO, IBD have high prevalence among women of reproductive age, with an estimated 25% of female patients diagnosed before their first pregnancy (27). Unlike in PsO, there appears to be little association between pregnancy and disease activity, with the risk of a flare among pregnant women with IBD being equivalent to that of non-pregnant patients over the same follow-up period (25,28,29). Yet, there has been a rising interest related to the potential effect of IBD on fetal outcomes. In 2007, Cornish et al. (30) published a meta-analysis examining the relationship between IBD and several adverse pregnancy outcomes. As compared to pregnant women without IBD, IBD was associated with increased risks of preterm birth, low birth weight and cesarean section. These results have been replicated in more recent studies (31,32). Although IBD is often grouped with SLE and RA as inflammatory conditions that increase the risk of spontaneous abortion, multiple population-based cohort studies have suggested that this may not be the case (33–35), reporting similar spontaneous abortion rates among women with IBD as in the general population.

2.2. Therapies for chronic inflammatory diseases

2.2.1 Psoriasis and Psoriatic Arthritis

Medical treatment of PsO varies substantially based on the severity of plaques, the surface area of the body with plaque involvement and the location of the plaques (36,37). In mild

cases, often defined as less than 5% body surface area (BSA) involvement (38), treatment usually consists of topical steroids and/or light therapy (11,36,37). In those with moderate (5-10%) or severe (more than 10% of BSA) disease, treatment is typically systemic, sometimes in conjunction with topical and light therapies. Systemic treatment is also often administered to patients with <5% BSA but for whom the disease is present in a particularly distressing location, such as the face or genitals (36). Systemic treatments for PsO are varied and include the oral retinoid acitretin, cyclosporin (CsA) (sometimes spelled ciclosporin), methotrexate (MTX), and biologic medications (37). For the purposes of this thesis, biologics refer to highly-specific proteins (usually monoclonal antibodies) that target a specific pathway of the immune system and are typically derived from living cells, whereas non-biologic disease modifying anti-rheumatic drugs (DMARDs), which are also called traditional DMARDs, refer to small molecules that typically have broader effects. Compared to biologics, traditional DMARDs are typically more accessible (both logistically as biologics require subcutaneous or intravenous infusions and economically as biologics are much more expensive).

As PsA can lead to severe joint damage and disability, systemic therapies are typically warranted for disease control (9). Traditional DMARDs, including MTX, leflunomide and biologics of several classes (i.e., tumour necrosis factor inhibitors (TNFi), ustekinumab, secukinumab) form the cornerstone of PsA treatment (9,39).

2.2.2 Inflammatory bowel diseases

In IBD, the goals of treatment are typically to achieve remission in patients with active disease and to maintain remission once it has been attained. Therapy for IBD is heterogeneous and dependent on disease subtype (CD versus UC), disease severity, and potential co-morbidities. Common initial therapies include systemic corticosteroids, usually budesonide and prednisone, 5-aminosalicylates (5-ASA), and biologics (17,40,41). Although not frequently used as first-line treatments, other immunomodulating drugs are also used in IBD including MTX, CsA, tacrolimus, and thiopurines (azathioprine (AZA), mercaptopurine (MP)), especially among cases that have proven resistant to typical first-line therapies (17,40).

2.3. DMARD safety in pregnancy

2.3.1 Non-biologic DMARDs

Non-biologic DMARDs play a major role in the systemic treatment of PsO, PsA and IBD. On top of the general safety concerns specific to a given drug, there are a host of other concerns which must be discussed when considering a pregnant population. Firstly, acitretin and MTX are teratogenic, and thus their use prior to or during pregnancy is problematic. Acitretin has been shown to be highly teratogenic in animal studies and human reports of offspring exposed in utero have described, among many others, serious cardiac, thymic, and nervous system birth defects (11,42,43). Acitretin is an especially problematic drug with respect to pregnancy due to its long half-life of up to 150 weeks (11,42). Acitretin itself has a half-life of only 33-96 hours, but it has the potential to re-estrify to etretinate, which has a half-life of up to 150 weeks. As such, a woman would need to stop taking acitretin 3 years before she intended to become pregnant to ensure the drug and its by-products had fully left her system. Due to the obvious impracticalities associated with women planning future pregnancies years in advance and the risk of unexpected pregnancies, acitretin is generally avoided in the treatment of women with PsO who are of childbearing potential (11).

MTX is also a known teratogen and has been associated with numerous congenital malformations including cardiac, skeletal, and central nervous system birth defects (44). Although some authors suggest that low dose (<10 mg/week) exposure to MTX during the first trimester may be safe, reports of malformations developing at doses less than 10 mg/week were published as early as 1990, indicating that any exposure should likely be avoided (45). Unlike acitretin, MTX does not carry teratogenic risks for years after exposure. As such, it is typically recommended that it be discontinued only 3 months prior to conception and is generally considered to be safe for general use among women of childbearing age, provided effective contraceptive methods are used (11,46,47).

CsA is generally considered safe in pregnancy, with the European League Against Rheumatism (EULAR) indicating that there is no evidence of increased risks of congenital malformations or spontaneous abortion and recommending CsA as a potential DMARD for use in pregnant patients and among those who are breastfeeding (46). There have been some signals

indicating that there is an increased risk of prematurity and low birth weight among offspring exposed to CsA (48), though these studies involved women using CsA post-transplant to prevent organ rejection. This patient population typically use much higher doses of CsA than would be used among women with IBD or PsO, limiting the generalizability of these results to this patient population. Thus, there should be limited concern for the safety in pregnancy of CsA at the dosage used for the treatment of PsO and IBD (11,46).

For decades, corticosteroids have been used during pregnancy to control many diseases, including IBD. Yet the risks associated with corticosteroid exposure in utero remain incompletely understood, as its use in active disease likely renders most results confounded by indication. Prior observational studies have reported possible associations with adverse outcomes including low birth weight and preterm birth (28) and an increased risk of cleft lip, though a more recent systematic review suggests there may be no such association (48). Regardless of the extent to which a causal relationship exists between corticosteroid exposure and adverse pregnancy outcomes, both the EULAR (46) and the IBD in Pregnancy Consensus Group (49) have determined that the benefits of corticosteroid treatment during pregnancy clearly outweigh any potential risk. They therefore both recommend that, when indicated, corticosteroids should be used among pregnant women with IBD, though both groups acknowledge that the level of the evidence supporting this recommendation is weak.

Regarding safety of 5-ASA, a 2008 meta-analysis found that 5-ASA was not associated with greater risk of congenital abnormalities, stillbirth, preterm delivery, or spontaneous abortion (50). As such 5-ASA therapy has been recommended to be continued during pregnancy in women who have IBD, with one caveat. Phthalates, which have been associated with developmental problems in both humans and animals, are used in some 5-ASA formulations. Consequently, the IBD in Pregnancy Consensus Group recommends that phthalate-free 5-ASA formulations should be used among pregnant women or those contemplating pregnancy (47).

Both tacrolimus and thiopurines are also considered safe in pregnancy, with cohort studies finding mixed results, though generally indicating no harm (51), and their use is generally recommended during pregnancy (46,47,52). As was discussed previously, it is important to consider the inherent confounding by indication when interpreting pregnancy outcome results in women exposed to DMARDs. For instance, as mentioned in section 2.1.2, IBD themselves are

associated with several adverse pregnancy outcomes independent of drug use. Those exposed to DMARDs during pregnancy are sicker and more likely to experience adverse events than those not exposed to DMARDs, irrespective of the drug effect.

2.3.2 Biologic DMARDs

2.3.2.A Tumour necrosis factor inhibitors in pregnancy

Tumour necrosis factor inhibitors (TNFi), the largest class of biologics, have been extensively studied in pregnancy. However, there is not sufficient evidence for definitive safety statements to be made about all of them specifically. Previous studies have shown that infliximab, adalimumab and etanercept are not associated with an increased risk of congenital malformations in exposed offspring (53,54), leading guidelines, including those of the EULAR and the Canadian Association of Gastroenterology, to not recommend avoiding their use during pregnancy (46,47). Similarly, current evidence suggests no increased risk of malformations in offspring exposed to golimumab, though the evidence is currently too weak to recommend its use in pregnancy (46).

During pregnancy, there is active trans-placental transport of maternal circulating immunoglobulins G (IgG) through their fragmented crystallizable (Fc) portion. Most TNFi (i.e., adalimumab, infliximab, golimumab) are monoclonal IgG harbouring a Fc region, while etanercept and certolizumab are respectively a fusion protein with a Fc portion and a pegylated Fab fragment without a Fc component. The Fc portion is crucial for allowing active transport of antibodies across the placenta from mother to fetus to provide immunity to the offspring. This has the unfortunate consequence of also actively transporting most biologic drugs across the placenta during the 2nd and 3rd trimesters. As such, the majority of TNFi are actively transported across the placenta, with some reaching higher blood levels in the fetus than in the mother. Infliximab and adalimumab have the highest trans-placental transfer (reaching cord blood levels of 160% and 150% of maternal blood levels respectively), while etanercept and certolizumab display the lowest passage (cord blood levels of 4-7% and <0.25% of maternal blood levels respectively) (55).

As fetuses could be exposed to therapeutic (and potentially supra-therapeutic) TNFi doses, there are concerns that TNFi could cause immunosuppression in the offspring. Until

recently, there had been only very limited data [i.e. small sample size (n=80) or retrospective data collection using maternal report of outcome and covariates] on the risk of serious infections in children born to mothers with IBD and exposed in utero to TNFi, showing no increased infection risk (56,57). In 2018, Vinet et al. published the first study assessing the risk of serious infections among offspring of women with RA exposed to TNFi in utero compared with that of unexposed offspring (58). Using data from the IBM MarketScan databases, the study included 2,989 offspring, of which 380 (12.7%) were exposed to TNFi during pregnancy. The cumulative incidence of serious infections (within the first year of life) was similar among offspring of women with RA with no in utero TNFi exposure (2.0%, 95% CI 1.5, 2.8) to offspring of women without RA (1.9%, 95% CI 1.9, 2.2). In contrast, the cumulative incidence of serious infections in RA offspring with TNFi exposure was 3.2% (95% CI 2.0, 6.8). After adjusting for potential confounders, there was a trend towards an excess risk of serious infections among offspring of women with RA exposed to TNFi versus offspring of women with RA unexposed to TNFi (OR 1.4, 95% CI 0.7, 2.8), although CIs were wide and included the null value. There was also a trends towards a potential 3-fold increase in the risk of serious infections with IFX (which has the highest placental transfer among TNFi) vs other TNFi (OR 3.0, 95% CI 0.7, 11.8) (58).

Due to the potential immunosuppressive action of these drugs on the immune system of the exposed offspring, most best practice guidelines recommend discontinuation of infliximab and adalimumab before 20 weeks gestation and etanercept before 31/32 weeks gestation (46,47). As there is much less placental transfer of certolizumab compared to the other TNFi, guidelines have cautiously suggested that certolizumab can safely be used throughout pregnancy and breastfeeding (46,47). However, no or very limited data exist on the infectious risk conferred by other monoclonal biologic drugs (such as ustekinumab and vedolizumab) in exposed offspring.

2.3.2.B Vedolizumab in pregnancy

Compared to TNFi, there has been less research into the safety of vedolizumab in human pregnancy. Animal studies using both pregnant rabbits and monkeys exposed to supra-therapeutic vedolizumab doses demonstrated no developmental toxicity in the exposed fetus (59). Two recent reviews of vedolizumab safety in human pregnancy identified 7 studies and 141 pregnancies (60) and 5 studies and 284 pregnancies (61), respectively. Both reviews and most individual studies concluded that, though numbers remain small, there have yet to be any signals

indicating that vedolizumab increases the risk of adverse pregnancy outcomes (i.e., fetal loss, preterm birth, congenital anomalies).

As discussed in section 2.3.2, antibodies with an Fc portion, among them vedolizumab, are actively transported across the placenta. Unlike most TNFi and ustekinumab (as will be discussed in chapter 3), offspring exposed to vedolizumab in utero do not routinely have higher systemic drug levels than those of their mothers, with mean maternal:infant ratios of 0.53 (range: 0.00 - 1.7) across 27 pregnancies (53,62). The impact of these lower concentrations in offspring have not been explicitly studied, but any potential concerns of immunosuppression in offspring exposed to TNFi or ustekinumab may therefore theoretically be dampened with vedolizumab. To date, 3 studies (with sample sizes ranging from 41 to 73 pregnancies) have examined the risk of infection among offspring exposed to vedolizumab (though in all studies infection was not the primary outcome assessed) and have found no increased risk of infection as compared to pregnancies exposed to other drug classes (53,63,64). Though acknowledging the weak level of evidence, the American Gastroenterological Association (AGA) IBD Parenthood Project Working Group suggested in their best practice guidelines that vedolizumab therapy (which has a half-life of approximately 25 days) could be maintained until 6-10 weeks before expected delivery (49).

3. Literature review

In chapter 2 I provided an introduction to the chronic inflammatory diseases relevant to this thesis, the different therapies used in their management, including both traditional and biologic DMARDs, and the safety of these drugs in pregnancy. In chapter 3 I provide a summary of the efficacy of ustekinumab for the treatment of chronic inflammatory diseases and a comprehensive literature review regarding its safety in pregnancy. The latter is the focus of manuscript #1.

3.1. Ustekinumab efficacy in chronic inflammatory diseases

Ustekinumab is a fully human IgG1 monoclonal antibody that inhibits IL-12 and IL- 23, which help activate certain T-cells. Both IL-12 and IL-23 are major cytokines in the pathogenesis of several chronic inflammatory diseases, including PsO, PsA, and IBD (65,66). Ustekinumab was originally tested for use in PsO, with initial phase II and III placebo-controlled randomized controlled trials (RCTs) finding ustekinumab to be efficacious in treating moderate-to-severe PsO (67,68,68). Following these trials, ustekinumab was approved in the United States (US) for the treatment of adults with moderate-to-severe PsO in September of 2009. A 2010 trial was the first to compare ustekinumab to an active comparator (etanercept), finding a significantly greater improvement (67.5% with 45 mg ustekinumab; 73.8% with 90 mg ustekinumab; 56.8% with etanercept) in the number of patients experiencing at least a 75% improvement in Psoriasis Area and Severity Index (PASI) among those randomized to ustekinumab versus those randomized to high-dose etanercept (69). These original PsO trials were conducted in largely Caucasian populations, with phase III trials subsequently showing similar results in Asian populations (70,71). Phase III trials of ustekinumab for use in adults with active PsA demonstrated improved disease activity in the ustekinumab group, leading to ustekinumab approval in the US for PsA in 2013 (72,73).

Ustekinumab use for the treatment of IBD began with testing in patients with CD. Phase II and III trials showed that ustekinumab could be used both for induction and maintenance therapy with improvement in rates of remission as compared to placebo (74–77) with effects maintained in most patients for the entire 92-week follow up in one trial (78). Following these

studies, ustekinumab was approved in the US in September 2016 for adults with moderate-to-severe CD, though it is known to have been used off-label for CD well before this approval (79). A phase III trial published in 2019 demonstrated efficacy of ustekinumab for the treatment of UC, leading to its approval for this indication in the US in October 2019 (80).

Based on these RCTs and subsequent observational studies, treatment guidelines recommend ustekinumab as either a primary or secondary biologic for the treatment of both PsO, PsA and IBD. Current IBD guidelines recommend ustekinumab use mainly as a second-line biologic among patients with moderate to severe UC or CD, though ustekinumab monotherapy in biologic-naïve patients with CD may be considered (20,81,82). In PsO and/or PsA, ustekinumab use can be considered as either either a primary or secondary biologic, including its use as the first systemic (not just biologic) treatment (83,84).

3.1.1 Ustekinumab Safety

As with all drugs, understanding ustekinumab's safety profile was a key part of the original phase III trials. Adverse event frequencies were relatively consistent across trials, including upper respiratory tract infections (~7%), nasopharyngitis (~10%), arthralgias (~2.5%) and headaches (~5.5%) (68,70–72,80,85,86). The most common serious adverse events were serious infections (typically defined as requiring or prolonging hospitalization), which occurred rarely (<1%). Infections of any type and severity were the most common adverse event, affecting approximately 30% of participants. These trials, however, were meant to demonstrate efficacy and did not have follow-up past (typically) 72 weeks.

When longer-term safety data from the original PsO trials was published, it was shown that 75% of participants exposed to ustekinumab experienced infections of any kind, with 1.3% and 3.6% of these infections considered serious[i] in the 45 mg and 90 mg dosing groups respectively (88). Long-term safety data showed that the number of infections was similar between the placebo and ustekinumab groups in the PsO population, but with numerically increased infection rates in the higher (90 mg) ustekinumab dosing group as compared to the lower (45 mg) dosing group, though this difference was not statistically significant (87).

i Serious infection was defined as infection requiring or prolonging hospitalization, and/or causing death or significant disability (87)

There is less available evidence about long-term safety of ustekinumab for the treatment of CD, as its approval for this indication is more recent. Doses used in CD tend to be higher than those used in PsO and/or PsA and consequently the fears of adverse effects are greater. This said, currently published long-term safety data show similar results to those seen in the PsO and PsA trials (78). An analysis of all the phase II/III trials for ustekinumab across all indications (PsO, PsA, and CD) published in 2019 showed that the risk of all infections and serious infections was similar between the placebo and ustekinumab groups for each indication (89). Its use for CD was associated with more infections than when used for PsO/PsA, though this difference was likely due to disease morbidity rather than ustekinumab itself. It should be noted that no trial was powered to detect rare, though potentially serious, adverse events, which may only be recognized once tens of thousands of person-years of exposure have been accrued and analyzed (such as pregnancy-related adverse events).

Administrative databases offer large sample sizes of exposed subjects, providing the possibility to assess drug safety and drug survival time (which can be seen as an indirect measure of drug tolerability and safety). In a study using a Danish registry, drug survival time among patients taking ustekinumab was shown to be longer than that for infliximab, adalimumab, and etanercept, all TNFi frequently used for treating chronic inflammatory diseases (90). A higher proportion of patients remained on ustekinumab compared to any of the TNFi at end of follow-up (100 months), suggesting a similar (if not more favourable) safety profile. The results of the trials discussed above, and the first observational studies of ustekinumab use, suggest that ustekinumab is a safe and efficacious alternative to TNFi in patients with chronic inflammatory diseases who are either TNFi-naïve or have failed previous TNFi treatment.

3.2. Preamble to manuscript #1

In the first manuscript of this thesis, I conducted a comprehensive literature review to assess the available evidence regarding ustekinumab safety during pregnancy in terms of both maternal and fetal outcomes. This manuscript, titled "Ustekinumab safety in pregnancy: a comprehensive review", has been submitted to Arthritis Care & Research. Following manuscript #1 I provide a more detailed discussion of the literature review and its potential limitations.

Ustekinumab safety in pregnancy: a comprehensive review

Short title: Ustekinumab & pregnancy

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3.3. Introduction

Chronic inflammatory conditions, including inflammatory bowel diseases (IBD), psoriasis (PsO), and psoriatic arthritis (PsA), are prevalent chronic diseases among women of reproductive age. Patients with active disease during pregnancy, especially with IBD, are at increased the risk of adverse birth outcomes (1,2). For this reason, physicians are focused on approaches to control disease activity prior to and during pregnancy. Biologic therapies, such as tumour necrosis factor inhibitors (TNFi) and interleukin (IL)-12/23 inhibitors have increasingly been used as first and second-line systemic therapies for many inflammatory conditions, such as IBD, PsO, and PsA. Traditional disease modifying anti-rheumatic drugs (DMARDs) and TNFi drugs have been relatively well studied during pregnancy. Most traditional DMARDs (e.g. sulfasalazine, azathioprine, 6-mercaptopurine, cyclosporine, tacrolimus) are believed to be safe during pregnancy, with the exception of methotrexate and mycophenolate mofetil, both well-known teratogens (3). TNFi are also believed to be safe during pregnancy and do not appear to increase the risk of adverse pregnancy outcomes, including spontaneous abortions, congenital malformations, and serious infections in exposed offspring, though the quality of the evidence varies across the different TNFi subtypes (3,4).

Ustekinumab was first approved in the United States for use in adults with moderate/severe PsO in 2009. It has since been approved for use in IBD (Crohn's disease (CD) in 2016, ulcerative colitis (UC) in 2019). Ustekinumab, an IL-12/23 inhibitor, is currently the only approved drug of its class (briakinumab, another IL-12/23 inhibitor was withdrawn from the market in 2011 following concerns of increased major adverse cardiac events in adults) (5). Ustekinumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody. IgG1 are

actively transported across the placenta during the second and third trimesters via their Fc portion. There is extensive cross-placental transfer of ustekinumab during the second and third trimesters of pregnancy, exposing offspring to potentially high levels of ustekinumab in utero. It is because of this that studying the impact of ustekinumab and other similarly structured drugs exposure on pregnancy outcomes is of particular importance. Consequently, we aimed to critically review the available data on ustekinumab safety in offspring exposed during pregnancy, to provide an overview of what is known and current gaps in knowledge.

3.4. Methods

3.4.1 Search strategy

We searched the MEDLINE database via PUBMED from inception to January 28th, 2021. The search term were: (“Ustekinumab”) AND (“Pregnancy” OR “pregnant”). The titles and abstracts of each article were read to assess relevance; both animal and human studies of any research design, as well as clinical guidelines were considered relevant. Only articles in English were considered. The search produced 66 results with no duplicates. Of the 66 articles, 37 were deemed relevant and were read in full. In addition, we searched the grey literature and reviewed the references of papers which met inclusion criteria. This yielded 7 relevant manuscripts and abstracts which were included for full review. A flow chart detailing inclusion process can be seen in Figure 3.1.

3.5. Ustekinumab in pregnancy

3.5.1 Animal studies

Only one animal study was identified. This study of 60 monkeys investigated the risks of UST during pregnancy and lactation using cynomolgus macaques, a species in which UST was shown to have similar IL-12/23 activity as it does in humans (6). Investigators evaluated the effect of both intravenous and subcutaneous UST at doses more than 45 times larger than would ever be used in humans. Following all pregnancies from conception until delivery, and the newborn monkeys up to 6 months after birth, the investigators noted that there were no apparent embryotoxic nor teratogenic effects of UST on the offspring (6).

This study also assessed maternal blood ustekinumab concentrations throughout pregnancy and in their offspring several times in early life. The investigators found that serum concentration levels in the monkeys varied markedly depending on dosing groups, although concentrations were very high across the different groups. On gestational day 100, when cesarean section was performed, the pregnant female and the fetus both still had high serum concentrations of ustekinumab, with the fetal-maternal concentration ratio ranging from 0.39 ±0 .14 µg/mLin the 22.5 mg/kg dosing group to 0.43 ±0.13 µg/mL in 45 mg/kg group. These results showed that maternal levels were twice as high as fetal levels at the time of birth, though the offspring did have high levels of ustekinumab. In this study there was no indication that ustekinumab exposure in utero impacted mortality, growth, or sexual and immunological development.

3.5.2 Human case reports, series and observational studies

A handful of studies have attempted to quantify ustekinumab placental transfer during pregnancy by measuring its cord blood concentration at the time of delivery (4,7,8). The paucity of information is likely due to very few pregnancies in which ustekinumab was intentionally continued throughout pregnancy. Since ustekinumab has a half-life of approximately 3 weeks, measurable concentrations of UST at birth would be unlikely if its use was stopped immediately prior to, or during, the first trimester. However, maternal and offspring drug clearance of biologic drugs such as TNFi has been shown to be substantially different, with infants having longer elimination times. Existing studies show that cord blood levels are often higher in offspring than in the mother, as opposed to animal studies, which showed the opposite. Rowan et al. (8) followed one woman who took ustekinumab throughout gestation (final dose: 33 weeks, delivery: 37 weeks) and found ustekinumab levels in cord blood that were almost twice maternal blood levels at birth (4.3 µg/mL versus 8.0 µg/mL). In another study, Klenske et al. (7), also prospectively followed one woman throughout her pregnancy (last ustekinumab dose: 30 weeks, delivery: 38 weeks) and found ustekinumab blood levels of 0.3 µg/mL in mother and 4.1 µg/mL in offspring, a greater than 10x increase.

In the PIANO study (4), investigators measured UST blood levels in 7 infants at birth and at 3 and 6 months of age. The median cord or infant to maternal concentration ratio was 1.4 (ranging from 0.7 to 13.7). These results suggest that fetuses exposed to UST throughout pregnancy may be born with higher ustekinumab blood concentrations than their mothers. Little is currently known about the potential adverse effects of post-birth ustekinumab exposure in neonates.

There have been 14 case reports and 2 case series for a total of 32 reported pregnancies exposed to ustekinumab. Table 3.1 lists these case reports and case series along with their exposure periods, indications for maternal use of ustekinumab, and pregnancy outcomes. A total of 26 of the 32 reported pregnancies (81%) involved exposure during the first trimester only. Overall, there were 28 (88%) uneventful live births and 4 (13%) spontaneous abortions. In all cases of spontaneous abortions, mothers had additional risk factors for fetal loss aside from maternal disease (including smoking, >20 cigarettes/day and prior fetal loss). Importantly, the 10 pregnancies in the case series by Watson et al. (9) represent only 7 different women. In addition, both spontaneous abortions occurred in the same year to the same woman; she would go on to have a subsequent pregnancy that resulted in lived birth, although it was complicated by gestational diabetes, hypertension, inrauterine growth restriction and oligohydramnios. Both pregnancies reported in Mugheddu et al. (10) were also from the same woman. Most authors did not discuss outcomes among children after birth; 4 studies reported normal development in 4 children, with follow-up ranging from 12-25 months (11–14). As is standard in case series/reports, there was no control group in any of these studies and reporting bias likely affected which exposed pregnancies generated case series/reports.

In addition to these case series/reports, there have been 2 retrospective and prospective cohort studies of women exposed to ustekinumab and 3 registries of exposed pregnancies which are described in Table 3.2. Cather et al. (15) presents the results of 29 pregnancies reported among participants of the phase II and III PsO trials for ustekinumab. Scherl et al. (16) presents the outcomes of the 26 patients who became pregnant during the CD phase II/III trials. Both of these have only been published as scientific meeting abstracts and have not been published or peer-reviewed. Geldhof et al. (17) describes a registry of pregnant women exposed to

ustekinumab during or immediately prior to pregnancy that were reported to the pharmaceutical company producing ustekinumab. This study was only published as a meeting abstract. This study included 478 exposed pregnancies and suggested that rates of spontaneous abortions (18.4%) and congenital anomalies (3.8%) were similar to general population rates. Of the 478 maternal exposures, 58 were exposed to ustekinumab throughout gestation. It should be noted that the origin of these 478 cases was not disclosed. The cases included in this study likely included those reported by Cather et al. (15) and Scherl et al. (16), as pregnancies during phase II/III trials would surely have been know to the company. As well, drug registries established by pharmaceutical companies are subject to reporting bias and a lack of a reference group. There is typically under-reporting of cases, meaning the true denominator of exposed pregnancies is unknown. Also, as complicated pregnancies are more likely to be reported than those that are uncomplicated, data from passive surveillance may exaggerate potential harmful effects.

Wils et al (18) published in 2021 the results of a French, multi-centre, retrospective cohort study of 29 pregnancies in 27 women exposed to ustekinumab while pregnant. The earlier studies((15,16)) had a relatively high proportion of elective abortions, which may be explained by ustekinumab's novelty and the uncertainty associated with its use in pregnancy. By 2021, when the French study was published, sufficient evidence had emerged to indicate that ustekinumab was likely not a severe teratogen, potentially leading less women to opt for elective termination. This paper reported that maternal complications had occurred in 2 patients (1 gestational diabetes, 1 threat of preterm birth) and 5 (19%) neonatal complications including 3 preterm deliveries, 2 low birth weights, and 1 congenital birth defect (a cardiac malformation) (18). The temporality of exposure varied within this study population, with 7 patients stopping ustekinumab within two months of conception, 13 discontinuing use within the first trimester

(with IBD relapse in 4 patients) and 9 maintaining ustekinumab use throughout pregnancy (with relapse in 3) (18). This level of granular details regarding either offspring outcomes or exposure period was not provided in prior studies by Cather (15) or Scherl et al. (16).

The PIANO study (4), was a prospective cohort of pregnant women with IBD. The study, the first prospective study in this area, recruited 1712 patients exposed to different traditional DMARDs and biologic drugs, with most pregnancy outcomes being collected via maternal report. A total of 18 pregnancies were exposed to ustekinumab; exposed pregnancies resulted in 17 live births, with the outcome of the final pregnancy not reported.

Across the 21 studies included in this review, only the PIANO study (4) and that by Wils et al. (18) followed the offspring past birth to evaluate their risk of serious infections. Of the 43 live-born offspring exposed in utero to ustekinumab, none developed a serious infection within the first year of life. It should be noted that within PIANO, serious infections were defined by self-report as “febrile illnesses requiring hospitalization and antibiotics, or sepsis”, and thus it is unknown if any serious infections due to viral or non-bacterial pathogens occurred (4).

Across all the case reports, case series, registries, and cohort studies, there were no signals suggesting that ustekinumab increases the risk of adverse pregnancy outcomes. These findings are similar to what is known regarding TNFi, which display similar placental transfer. There is substantially more evidence, however, regarding TNFi safety in pregnancy (~5000 exposed pregnancies), allowing for stronger conclusions to be drawn regarding their safety in pregnancy. The potential risks of having high blood levels of UST in offspring after birth, however, have not been adequately studied and remain poorly understood.

3.6. Guidelines

Several clinical practice guidelines have addressed the safety of UST in pregnancy. These guidelines are meant to guide clinical practice by summarizing the state of the evidence regarding the safety of different pharmacological therapies for IBD and/or PsO. We will focus on the guidelines published on behalf of official professional organizations representing the three medical specialties that care for these patients, the American College of Rheumtaology (ACR) (19), the European League Against Rheumatism (EULAR) (3), the American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) (20), and the American Gastroenterological Association (AGA) (21). Most of these guidelines use established methods for evaluating evidence, including the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology (22) (EULAR, ACR) and the Oxford Centre for Evidence-based Medicine – Levels of evidence (23) (EULAR).

The EULAR (3) 2016 guidelines for antirheumatic drug use before, during, and after pregnancy stated that there was limited evidence available regarding the safety of ustekinumab in pregnancy and it should thus be replaced prior to conception by other medication, clarifying that ustekinumab should only be used when “no other pregnancy-compatible drug can effectively control maternal disease”. EULAR rated this recommendation as GRADE level 2, meaning the true effect may be markedly different than the published effect estimates, and a level 4 on the Oxford scale, indicating the studies used to make the decision were limited in nature, including case-series and/or poor quality cohort or case-control studies.

In 2019, the AAD-NPF guidelines (20) on biologic therapy in PsO were published. Although the guideline writers used a validated grading system to evaluate most of their

recommendations (24), their recommendations regarding the use of biologic therapy during pregnancy and lactation were only judged based on expert consensus. This guideline states that the safety of ustekinumab in pregnancy is uncertain, and make no statement as to how patients should be counseled or managed regarding this issue.

In the same year, the AGA's IBD Parenthood Project Working Group published their guidelines, which were based on an expert analysis of the available data (21). These guidelines advocate planning the final dose of ustekinumab 6-10 weeks prior to delivery if using standard 12-week ustekinumab dosing or 4-5 weeks prior to delivery if using 4-week dosing, and resuming both postpartum. These are the first guidelines to advocate that ustekinumab be continued during the 1st and 2nd trimesters of pregnancy. The authors provide no description of how they weighed the available evidence or the strength of their recommendation.

The ACR's 2020 guidelines on managing reproductive health in rheumatic disease advocate continuing ustekinumab therapy while trying to conceive, but stopping once pregnancy has been confirmed (19). However, the authors acknowledge the need to carefully weigh the risks and benefits should disease not be controlled with other pregnancy-compatible medications. This evidence was judged as being conditional, reflecting that the limited available data led to some uncertainty in their recommendation.

In summary, only the AGA guidelines (21) recommend continued use of ustekinumab through the first and second trimesters of pregnancy. Other than the EULAR recommendations, which came out earlier than the others, the same evidence was available to all professional organizations when making their recommendations, although each agency used their own criteria for determining how they used this available evidence. Of note, lack of disease control across

ustekinumab indications has varied effects on pregnancy. Active IBD is well known to increase the risk of several adverse pregnancy outcomes (i.e., preterm birth, spontaneous abortion) (1) more than active PsO or PsA, potentially explaining the AGA's willingness to recommend continued ustekinumab use through the earlier stages of pregnancy as compared to the recommendations from rheumatologists or dermatologists.

3.7. Conclusions

The current state of the evidence regarding the safety of ustekinumab in pregnancy is both limited and slowly evolving. Studies conducted to date have not identified an excess risk of adverse pregnancy outcomes, but the total number of exposed pregnancies in these studies remains small and they are limited by their lack of reference group and potential for reporting bias. There are also certain long-term outcomes, such as serious infections in exposed offspring, which require further investigation before more definitive conclusions can be made regarding the potential risks of in utero ustekinumab exposure. This paucity of data regarding ustekinumab safety in pregnancy represents an important knowledge gap as women with chronic inflammatory conditions need to be appropriately counseled when contemplating pregnancy or during pregnancy itself. Administrative databases have not yet been employed to study pregnancies exposed to ustekinumab. With their large sample sizes and long follow-up durations, high generalizability, and the ability to link outcomes in mother and offspring, they represent an important way to assess ustekinumab safety in pregnancy going forward.

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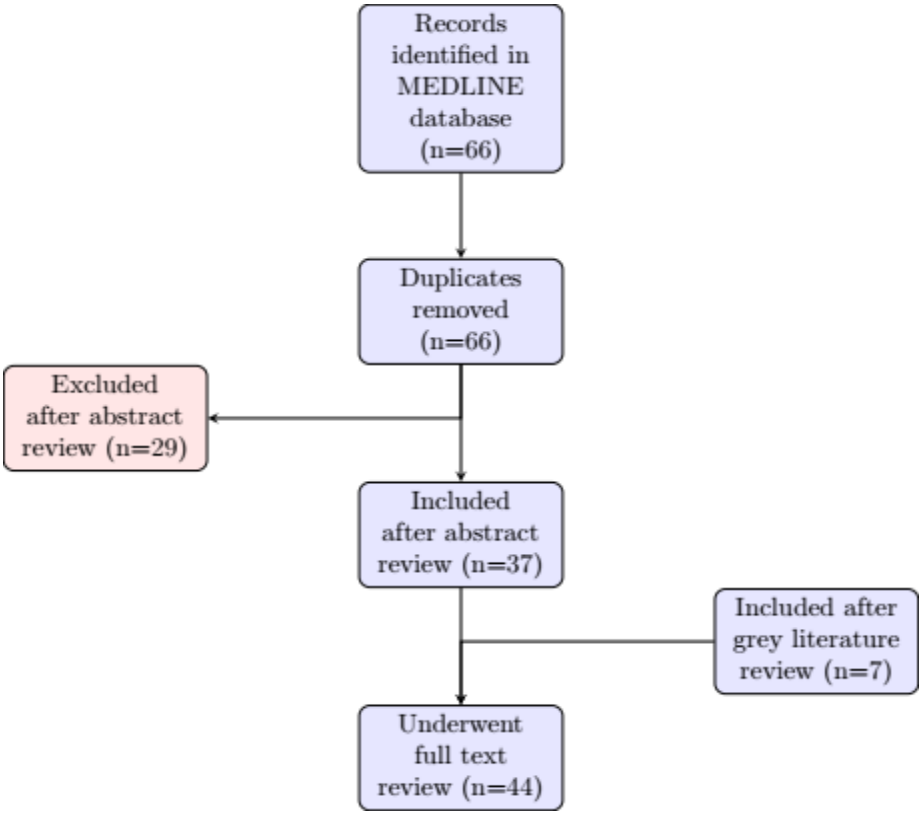

Figure 3.1 Flow chart outlining steps for article inclusion

Table 3.1: Characteristics of pregnancies exposed to ustekinumab (n=32) reported in the 16 included case series/reports

Author	Indication	Age of mother (years)	Exposure period (trimester)	Outcome
Fotiadou et al. (25)	PsO	35	1st	Spontaneous abortion at 12 weeks
Andrulonis & Ferris (26)	PsO and PsA	22	1st	Uncomplicated live birth
Sheeran & Nicolopoulos (27)	PsO	21, 34	1st	Uncomplicated live births
Rocha et al. (11)	PsO	25	1st	Uncomplicated live birth
Alsenaid & Prinz (12)	PsO	24	2nd	Uncomplicated live birth
Galli-Novak et al. (13)	CD and PsO	28	3rd	Uncomplicated live birth
Lund & Thomsen (28)	PsO	25, 29, 33	1st	Uncomplicated live births
Cortes et al. (14)	CD	37	Throughout pregnancy	Uncomplicated live birth
Echeverria-Garcia et al. (29)	PsO	35	2nd	Uncomplicated live birth
Venturin et al. (30)	CD	32	1st	Spontaneous abortion at 8 weeks
Rowan et al. (8)	CD	35	Throughout pregnancy	Uncomplicated live birth
Galluzzo et al. (31)	PsO	32, 32, 34, 37	1st	Uncomplicated live births
Megna et al. (32)	PsO	28	1st	Uncomplicated live birth
Klenske et al. (7)	CD	24	Throughout pregnancy	Uncomplicated live birth
Mugheddu et al. (10)	PsO	40, 41	1st	Uncomplicated live birth

Watson et al. (9)	PsO	20, 34, 19, 19, 38, 38, 38, 39, 22, 39	All 1st except #5, 2nd	2 spontaneous abortions, rest live births

Table 3.2: Characteristics of the pregnant women exposed to ustekinumab (n=580) and reported in 3 registries and 2 cohort studies

	Cather et al. (15)	Scherl et al.(14)	Geldhof et al. (17) [1]	Wils et al.(16)	Mahadevan et al. (4)
Indication	PsO	CD	PsO/PsA/CD	CD	CD/UC
Number of pregnancies	29	26	478	29	18
Pregnancies with known outcomes	26	24	All	All	17
Outcomes no. (%)					
Live births	14 (53)	15 (63)	341 (71)	26 (90)	17 (100)
Spontaneous abortion	5 (19)	4 (17)	88 (18)	2 (7)	-
Elective abortion	7 (27)	5 (21)	-	1 (3)	-
Congenital malformation	0 (0)	0 (0)	14 (4)	1 (3)	-

PsO: Psoriasis; PsA: Psoriatic arthritis; CD: Crohn's disease; UC: Ulcerative colitis

[1] Note: Geldhof et al. (17) may double count cases that were also presented elsewhere

3.9. Discussion of the literature review

With manuscript #1, I highlight the important knowledge gap related to ustekinumab safety in pregnancy. Available data, although limited, suggest that ustekinumab poses no clear excess risk of adverse maternal or fetal outcomes when used during the gestational period. However, most clinical guidelines are still apprehensive to recommend its use during pregnancy (46,84). Of particular note to this thesis, there is hardly any evidence regarding the risk of serious infections in offspring exposed in utero to ustekinumab. The two identified studies addressing this issue were limited by their small sample sizes (n=18-29), which did not allow the detection of any serious infection events in exposed offspring (53,63).

This review has several limitations which must be acknowledged. Firstly, though conducted using a structured search, this review is not a rigorous systematic review. Only one database was searched (Medline via PubMed), which is the search database most relevant for this review, but allows for us to have missed relevant articles indexed exclusively in other databases. In addition, the grey literature was searched, looking at preprint databases and past rheumatology, gastroenterology, and dermatology abstract repositories. The grey literature, though providing several relevant articles, have not undergone peer-review and may contain preliminary results unsupported by formal analysis.I also reviewed the references of papers which met inclusion criteria looking for relevant literature. I searched the title and abstract for all hits and included every relevant article identified from the search for discussion in the paper. However, only one reviewer (i.e. Jonah Gorodensky) conducted all stages of the review including performing the query and reviewing abstracts. For increased validity, in a systematic literature review, a second reviewer should ideally conduct independently the literature search and review. As well, a librarian was not included in the literature search; doing so would have increased the robustness of our search. Finally, I did not assess the quality of included studies using a standardized scale (e.g. Newcastle-Ottawa quality assessment scale) as required for a systematic literature review.

As well, there are dozens of best practice guidelines which include statements regarding ustekinumab use in pregnancy, usually at most a brief paragraph and often times just a sentence in an appendix. All these guidelines make very similar recommendations (i.e., replace prior to conception due to limited available data on which to determine safety), with only the AGA

guidelines suggesting that ustekinumab be continued through the second trimester (49). As a mean of consolidating these various guidelines, in manuscript #1, I only discussed the clinical guidelines from the major American and European professional organizations representing dermatologists, rheumatologists, and gastroenterologists, the three medical specialties that most frequently care for patients with chronic inflammatory diseases for which ustekinumab is used.

Overall, this literature review highlights the importance of my thesis work, identifying an important knowledge gap. There is currently very little evidence regarding serious infection risk in offspring exposed to ustekinumab. Furthermore, the manuscript highlights that, until now, there have been no published studies serious infections in offspring exposed in utero to ustekinumab using administrative data.

4. Cohort study methods

In this chapter, I provide a more detailed description of the methods used to conduct the retrospective cohort study. As was shown previously, there is a paucity of data regarding the safety of ustekinumab use in pregnancy, particularly with respect to infection risk among exposed offspring. This cohort was assembled to answer the thesis' primary objective of quantifying the risk of serious infection in offspring exposed to ustekinumab in utero (manuscript #2). Similar methods were used to address the secondary objectives of this thesis, which was to evaluate the risk of serious infections in children exposed in utero to vedolizumab (manuscript #3). Methods are also described, albeit in less detail, in manuscripts #2 and #3, which are presented in chapter 5 and 6 respectively. I hope to use the current chapter to provide additional insight and rationale into the methods used in both manuscripts. This study was approved by the McGill University Faculty of Medicine Institutional Review Board, study number A11-M107-14A.

4.1. Data source

The data source for this thesis was the IBM MarketScan commercial database. MarketScan commercial database (hereinafter referred to simply as MarketScan) is a large American convenience sample of people who receive health insurance through their work and their dependents. The database includes more than 230 million unique individuals, with approximately 40 million unique individuals included in any given year who are followed longitudinally for as long as they retain eligible insurance (91). Of note, a single patient can be followed even if they switch between eligible insurance companies, so follow-up lasts as long as any eligible insurance is retained. The database contains information on, among other things, hospitalizations, outpatient visits, and outpatient drug claims. Each individual has a unique, de-identified code which allows for the longitudinal follow-up across insurance companies, and, most relevant to this thesis, the ability to link mothers with their offspring. Due to its large size, MarketScan is well suited to address questions regarding rare diseases, exposures or outcomes. There has been extensive use of MarketScan to answer questions related to pregnancy (i.e, (28,92–94)), rheumatic diseases (i.e, (95,96)), or both (i.e, (58)), as well as drug safety in general, making this database well-suited for this thesis.

Within the database, diagnoses and procedures were coded using the International Classification of Disease (ICD)-9th Revision until December 31st, 2015, and the ICD-10th Revision from January 1st, 2016 until present, as well as Current Procedural Terminology (CPT) and Diagnosis Related Groups (DRG) codes. Drugs are coded using National Drug Codes (NDC). These NDC can be obtained from from the American Food and Drug Administration's website.[ii] In the process of conducting this thesis I wrote an R package to automatically collect these NDC codes and corresponding drug information from the FDA's website. The package and its documentation is available on my GitHub and can be freely used.[iii]

4.2. Creating the study cohort

4.2.1 Identifying offspring born to women with chronic inflammatory diseases

For this thesis the study period was January 1st, 2011 to December 31st, 2018. As was discussed in section 4.1, these dates imply a change from ICD-9 to ICD-10 midway through the study period. We began by identifying all pregnancies that resulted in a live birth based on a ICD-9/10 code for vaginal or cesarean delivery (58,93,94). Multiple pregnancies, ectopic or molar pregnancies, those ending in spontaneous or induced abortions, and stillbirths were identified using relevant ICD-9/10, CPT or DRG codes and excluded (94). A complete list of relevant inclusion and exclusion codes can be found in the supplemental to manuscript 1 (section 5.10, Table 5.5). For a pregnancy to be included in the cohort, there had to be at least one year of continuous enrollment in MarketScan prior to date of delivery, allowing us to assess drug exposure during the entire gestational period.

From the cohort of pregnancies that resulted in live births, we identified women diagnosed with any of the chronic inflammatory diseases of interest (PsO, PsA, and IBD). Diagnosis of PsA and/or PsO was made the basis of ≥1 inpatient claim or ≥2 outpatient claims before delivery (ICD-9: *696.1X*, *696* ICD-10: *L40.0, L40.1, L40.2, L40.3, L40.4, L40.8, L40.9, M09.0, L40.5, M07.X*). This algorithm has been validated using Canadian administrative data, where it was shown to have sensitivity of 52% and specificity of 99% for PsO and 51% and 100% respectively for PsA, with clinician diagnosis based on chart review acting as the reference

ii https://open.fda.gov/
iii https://github.com/jonahgorodensky/oFDAinfo

standard (97). These sensitivities are relatively low and imply that we may fail to identify some patients with PsO/PsA while the very high specificities suggest that the patients we do capture are very likely have the disease. Though it could be problematic that we are missing women with PsO/PsA, our exposure of interest is not the disease per-se but rather the drug exposure. PsO in particular can vary widely, from a mild to a severe and debilitating disease. Those with more severe disease are more likely to: 1) be included in our study due to their having more interaction with the healthcare system regarding their disease and, 2) be exposed to the drugs of interest. Given that our primary objective was to assess the effect of a specific drug exposure on serious infection risk in offspring (and not the effect of the disease itself), I do not believe that the low sensitivity of the PsO/PsA case definition invalidate our findings.

The algorithm to identify IBD cases was similar to the one used to identify PsA/PsO: ≥1 inpatient or ≥2 outpatient claims for IBD before delivery (combining UC and CD, ICD-9: *555.xx, 556.xx ;* ICD-10: *K50.xx, K51.x*). This has been validated, with any hospitalization shown to have sensitivity of 82.2% and specificity of 96.1% in the UK General Practice Research Database, and ≥2 outpatient codes shown to have sensitivity of 86.5% and specificity of 91.6% in Kaiser Permanente administrative physician claims data, using medical charts as reference in both (98). As was discussed in section 2.1.2, IBD is not a single disorder, but rather encompasses several diseases, most notably CD and UC. It is well established, however, that accurately differentiating between UC and CD in administrative data is very difficult. Also, there is no data suggesting that ustekinumab use or pregnancy outcomes would differ between UC and CD. Thus, I did not sub-categorize patients based on which type of IBD they had. Granted, ustekinumab was approved for each disease at different times, with FDA approval for UC occurring after the end of the study period. However, it is known that ustekinumab was widely used off-label in UC over the same time period (99,100). Thus, it is likely that some of the IBD pregnancies exposed to ustekinumab identified in our study occurred in mothers with UC, not just CD.

In addition to identifying live-born pregnancies occurring in mothers with PsO/PsA/IBD, we randomly selected pregnancies of women without any of the chronic inflammatory diseases of interest to act as a healthy reference group, though they could have had other serious diseases which were not considered as part of this study. This allowed for an understanding of baseline

serious infection risk and covariate distribution in the general MarketScan population, which is not representative of the American population in general (this will be discussed further in section 7.2). These unaffected pregnancies were matched to pregnancies with a disease of interest based on maternal age, year of delivery and geographic location of residence. Geographic location was identified at the state level (if state was known) or at the more general region (ie. north-east, south-west) if state was unknown (91).

To create the final study cohort of offspring we identified the children born alive to the women described above, deterministically linking mothers with their infants using family identifiers and delivery dates. This method is widely used with MarketScan data (58,93,94), having been shown to accurately link 70% of live births (94), and is similar to the algorithms used in other databases (101). Once entered into the cohort, offspring were followed from birth (the date of cohort entry) until 12 months of age, first serious infection, end of insurance eligibility, death, or end of study period (December 2018), whichever came first. One woman could contribute more than one pregnancy to the cohort. A flow chart of describing cohort creation is provided as part of manuscript #2 (Figure 5.1).

4.2.2 In utero exposures in offspring

In utero drug exposures were defined as at least one filled prescription or infusion procedure code during the pregnancy period for the drugs of interest. The pregnancy period was defined based on estimated gestational age, which will be discussed further in section 4.3.1. The exposure of interest varied between manuscripts #2 (ustekinumab) and #3 (vedolizumab), with minor differences in exposure group definitions.

In manuscript #2 (chapter 5), the main exposure of interest was ustekinumab, defined as exposure during the pregnancy period. The TNFi group was defined as pregnancies unexposed to ustekinumab but exposed to adalimumab, infliximab, certolizumab, etanercept, or golimumab. The other biologic group was defined as pregnancies unexposed to ustekinumab or TNFi but exposed to a non-TNFi biologic (vedolizumab, secukinumab, guselkumab, ixekizumab, brodalumab, natalizumab). Pregnancies unexposed to any biologic but exposed to a systemic traditional DMARD (apremilast, MP, mesalamine, MTX, sulfasalazine, 5-ASA, CsA, tacromilus, leflunomide) constituted the fourth exposure group. Exposure groups were mutually exclusive, meaning a given offspring could only be a part of one group.

In manuscript #3 (chapter 6), the exposure of interest was vedolizumab, defined by any offspring exposed during the pregnancy period. The TNFi group was defined as pregnancies unexposed to vedolizumab but exposed to adalimumab, infliximab, or certolizumab. The other biologic group was defined as pregnancies unexposed to vedolizumab or TNFi but exposed to a non-TNFi biologic (ustekinumab, secukinumab, guselkumab, ixekizumab, brodalumab, natalizumab). Pregnancies unexposed to any biologic but exposed to a traditional DMARD (MP, mesalamine, 5-ASA) constituted the last exposure group.

The main comparator group was offspring born to women with a chronic inflammatory disease (PsO, PsA and/or IBD) but unexposed to any relevant drug during the gestational period. This group was used as the primary reference group, rather than healthy controls, in an attempt to reduce potential confounding by indication, ensuring that the resulting effect estimates were from the drug and not confounded by underlying the disease. As was discussed in section 2.2.2, chronic inflammatory diseases are often linked with increased risk of adverse birth outcomes, thus when assessing risks associated with drug exposure it is imperative to compare populations with equivalent disease status. There are obvious potential problems with residual confounding by disease activity that complicate the comparability of the groups exposed versus unexposed to certain drugs and these issues will be discussed in sections 4.3.1 and 7.2.

4.2.3 Outcome

The outcome of interest was serious infections. This was defined as any single inpatient ICD-9/10 code for an infection of any type within the first year of life. Infection codes were derived from validated studies, including Henriksen et al., which found discharge diagnoses for infection to have sensitivity of 79.9% (95% CI 78.1%, 81.3%) and specificity of 83.9% (95% CI 82.6%, 85.1%) (102). This study was conducted across a range of infection subtypes (i.e., bacterial, viral) in a Danish database, although this was in an adult rather than an infant population (102). Two cohort studies looking at neonatal infections also provided lists of diagnostic codes for infection, though neither validated their code list (103,104). These studies were used to compile an extensive list of ICD-9/10 codes used to identify serious infection in this thesis. Serious infections were not restricted to a specific class of pathogen or body area and included bacterial, viral, and fungal infections.

Offspring were limited to one outcome (infection) and were censored on the date of first serious infection diagnosis. Observations that did not experience an event were censored at 12 months, end of insurance eligibility, death or end of study period, whichever came first. Certain biologics, especially TNFi, are associated with an increased risk of tuberculosis (TB) and, if it develops, poor outcomes (ie. hospitalization, meningitis, death) from the infection (105). This has led to recommendations for most biologics that testing for latent TB be done before initiation, and that all patients taking biologics be actively monitored for TB. Thus, special attention was given in our cohort to whether there were any diagnoses of TB in any group.

4.3. Statistical Analyses

4.3.1 Covariates

All multivariate models were adjusted for potential confounders. These variables were identified as potential confounders (associated with exposure and outcome) based on subject matter expertise and in keeping with similar studies already published in this area. Potential confounders included the presence of maternal gestational or pre-existing diabetes, maternal age, maternal exposure to systemic corticosteroids at any time from 3 months prior to conception until the end of gestation, maternal concomitant drug exposure (e.g. an offspring in the TNFi group also being exposed in utero to a traditional DMARD), whether or not the delivery was preterm, and disease state (PsO/PsA vs IBD).

Gestational or pre-existing diabetes was included as both are associated with adverse birth outcomes, including extreme birth weights (both high and low), congenital malformations, stillbirth, and neonatal death (106,107). Diabetes is associated with infections and poorer prognoses when infection is present in mothers, with some evidence suggesting diabetes may be associated with neonatal infection (108). Gestational or type I or II diabetes pre-existing before pregnancy was identified as any single physician billing or hospitalization with a relevant ICD-9/10 code corresponding to either disease (ICD-9: 250.xx, 648.0x, 648.8x; ICD-10: E10.xx, E11.xx, O24.xx).

Preterm birth is well known to be both associated with infections in offspring (109–113), potentially due to an underdeveloped immune system (111,113). Due to this relationship, it was

crucial that we identify and control for preterm birth within our cohort. To assess whether a delivery was preterm, established algorithms were used to first approximate gestational age (GA). Preterm birth was considered as a binary variable for our purposes (either preterm or not) though the algorithm used could, in most cases, provide an approximation of GA. Identifying gestational age began by identifying whether a GA ICD code was present in the records of mother or child. All of the codes are presented with their respective GA in Appendix A, table 9.1. An assigned GA of less than 37 weeks or less considered preterm. If none of these codes were present, but one of O60.xx (ICD-10) or 644.0x, 644.1x, 644.2x (ICD-9) (all codes referring simply to preterm labour/delivery) was present the pregnancy was also deemed preterm, though estimating exact GA was not possible. If GA was unknown term pregnancies were assigned 40 weeks gestation and pre-term pregnancies were assigned 37 week gestation. This method of identifying preterm birth is based largely on the work of Marić et al. (93), Margulis et al. (114), and Ailes et al. (92), and has been shown to have high sensitivity (91%) and specificity (98%) at identifying binary preterm birth with reviewing the delivery discharge record acting as reference standard (114).

Exposure to corticosteroids was defined as any single filled prescription for corticosteroids during pregnancy or during the pre-conception period. Topical or inhaled corticosteroids were not considered exposure for this study. In IBD, hospitalized patients are sometimes treated with intravenous corticosteroids, mostly hydrocortisone and methylprednisolone. In MarketScan, drugs dispensed to inpatients are not available, limiting the ability to assess intravenous corticosteroid use (which is generally administered during hospitalizations), to only relevant procedure codes (91). We considered any such code as exposure to intravenous corticosteroids. Concomitant drug use was assessed in the same way as drug exposure in section 4.2.2, wherein exposure to a drug of interest other than a patient's main exposure group (ie. a patient in the ustekinumab group also exposed to MTX) was considered concomitant. Corticosteroid use and concomitant use were included as both have been linked with an increased risk of maternal infection (which is itself linked with neonatal infection) (115,116).

Disease state, defined as which of PsO, PsA and/or IBD a patient had, was also included as a covariate. This was important since each exposure group may have had differential

distribution of disease states based on the indications of the drugs comprising these groups. It has been shown that the different disease processes have differential effects on pregnancy outcomes (see section 2.1), including preterm birth, and are themselves differentially associated with the outcome of interest, serious infections. As disease was associated with both drug exposure and outcome it was an important confounder to adjust for.

4.3.2 Primary statistical analysis

Descriptive statistics were used to characterize the different exposure groups and quantify the crude number of serious infections per group. Continuous variables were described as mean (standard deviation, SD) and binary variables (such as corticosteroid use) were described as absolute numbers and percentages . Crude cumulative incidence proportions for infection were calculated as percentages with 95% CI calculated using Wilson CI estimates for binomial proportions using the BinomCI function of the DescTools R package (117). These CIs are an asymmetric extension of the normal approximation and are known to have good coverage while being less conservative than Clopper-Pearson CI. These intervals are also robust to small sample sizes and low proportion of events, important in the ustekinumab, vedolizumab, and other biologic groups (118).

The primary analysis employed univariable and multivariable logistic regression using generalized estimating equations (GEEs) to calculate ORs for serious infection. Logistic regression typically takes the form

$$Y_i = \beta_0 + \beta_1 X_i \ldots \beta_n X_n + \epsilon_i$$

where *i* represent individuals. These models rely on the assumption that errors (ε_i) are independent of one another. As this study allows for multiple offspring from one mother to be included, this assumption does not hold. It is known that pregnancy outcomes are more similar within a single mother than they are across several mothers, which violates the assumption that errors be independent. There are several ways of accounting for this clustering, including random-effects models, Bayesian hierarchical methods, and GEEs (119). For this thesis we chose the latter for several reasons, including their robustness and ease of interpretation.

GEE are semi-parametric models, with the general equation

$$E[Y_{ij} \vee X_i] = \beta_0 + \beta_1 X_{ij} \ldots \beta_n X_{ij}$$

where i represents a cluster and j represents an index within that cluster. Within the context of this thesis, i represents a mother who may have more than one included pregnancy and j represents an individual pregnancy. GEE requires pre-specifying the correlation structure within a cluster. I chose to model the correlation structure as being exchangeable, meaning any two pregnancies born to the same mother could be considered equally correlated. This said, GEE are robust to misclassified correlation, so effect and variance estimates would be correct regardless of the true correlation structure, useful as understanding the true correlation between infection risk in offspring born to the same mother is difficult (120).

GEEs are also preferred over random-effects models when the number of clusters is large and the size of clusters is small, as is the case when looking at pregnancies in administrative data. The number of included pregnancies to a given women is very small relative to the number of total included pregnancies, meaning a very high number of small clusters (max cluster size in our cohort was 4). If these data were modeled using random-effects models, it would likely lead to high standard errors (121).

GEE are also optimal for this analysis because of their interpretation. Unlike random-effects models, whose coefficients can be interpreted at the individual (woman) level, GEE coefficients are interpreted at the population-average level. For the purposes of this thesis, these different interpretations can be understood as the difference between understanding the results as the effects of drug exposure on an individual's risk of serious infection relative to the reference group versus the average increased risk across an exposure group (i.e. the risk in the group exposed to ustekinumab) relative to the reference. Our interest in understanding the risk among offspring exposed in utero to ustekinumab make the population-average interpretation of GEEs most suitable to our analysis.

4.3.3 Sensitivity Analyses

In addition to the primary analysis described above, I performed three secondary analyses, varying the duration of follow-up time, the exposure assessment window, and statistical methods to better understand the robustness of our results.

4.3.3.A Restricting follow-up time to first 3 months

I conducted an analysis wherein follow-up for observing infection was censored at 3 months (90 days) after birth. By definition this analysis reduces the number of infections within the sample, as any child who develops an infection between 3 and 12 months of age is considered as not having an infection. At the same time, the first three months are when the blood levels of drugs in the exposed infants will be highest and therefore biologically most likely to cause immunosuppression. Restricting to the first 3 months helps focus on events that are most likely to be due to drug-related immunosuppression. As well, infections in newborns are more dangerous than those in older infants, making understanding infection risk within the first three months all the more important. This analysis is particularly relevant because current guidelines suggest not giving neonates exposed in utero to biologics during the third trimester live vaccines within the first 6 months of life (49), although it is not clear if this delaying of vaccination in these neonates is warranted. Since there is a differential infection risk between vaccinated and unvaccinated neonates, the period before vaccination is most suitable to control for differential vaccination rates between exposure groups.

4.3.3.B Expanding the exposure assessment window to include the pre-conception period

Another sensitivity analysis involved expanding the exposure assessment window from pregnancy only to also include the pre-conception period. The pre-conception period was defined as the 3 months immediately prior to the pregnancy. Conception was approximated using the method discussed in section 4.3.1. Increasing the exposure period increases the number of exposed pregnancies and therefore allowed us to see whether we detected any signals of increased infections knowing that our sample would be larger. As well, the identification of the pregnancy period was not perfect, and as such there is likely misclassification of drug exposure around the beginning of pregnancy. Some pregnancies exposed to a drug during the first trimester may have been misclassified as preterm (and therefore the beginning of the pregnancy period would have been considered pre-pregnancy). Expanding the exposure window allows us to potentially account for this misclassification. This said, as IgG typically do not cross the placenta until 16 weeks gestation, one would expect that fetuses exposed at conception and/or very early in pregnancy would be less at risk of infection caused by immunosuppression from

maternal drugs. We would expect the result of this analysis to be closer to the null should there be a causal relationship of infection associated with in utero drug use.

4.3.3.C Time-to-event analysis

Finally, we performed a sensitivity analysis wherein we used Cox proportional hazard (PH) models with frailties to assess infection risk while accounting for time to infection. This survival analysis technique allows us to quantify whether there is a different risk of infection over time between the groups of offspring, assuming proportional hazards. Frailties are a method of accounting for the clustering that occurs from women having more than one included pregnancy and are analogous to, but mathematically distinct from, the GEEs discussed in section 4.3.2 (122). Conducting these analyses allowed us to confirm that there was no differential infection risk over time between the groups and that infection occurred on average equally over time within each group. Across the three sensitivity analyses we found our results remained consistent with those of the primary analysis. Results of all sensitivity analyses are discussed in chapter 5 and tables with full numeric results included in the supplemental to manuscript #2 (section 5.10).

The next two chapters are manuscripts detailing the results of the cohort study described here. The first (manuscript #2, chapter 5) will provide results for ustekinumab analysis involving the larger cohort of women within chronic inflammatory conditions. The second (manuscript #3, chapter 6) will describe the vedolizumab study conducted in the subset of offspring whose mothers had IBD.

5. Manuscript #2 – Serious infections in children exposed in utero to ustekinumab

5.1. Preamble to manscript #2

This manuscript, titled "*Serious infections in children exposed in utero to ustekinumab"* is formatted for submission to *Annals of Rheumatic Diseases*. Using the methods described in chapter 4, it addresses the first objective of this thesis, which is to investigate the risk of serious infections in offspring exposed in utero to ustekinumab. In doing so, I attempt to address the knowledge gap identified in manuscript #1. Section 5.10 provides the supplemental material to this manuscript, which will be available online upon publication.

I have presented the findings related to this manuscript at the 2021 Canadian Rheumatology Association annual scientific meeting, during a virtual poster tour, with the abstract ranking among the top 5 trainee abstracts.

Title: Serious infections in children exposed in utero to ustekinumab

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Abbreviations:
aOR: adjusted odds ratio
CD: Crohn's disease
CI: confidence interval
CPT: current procedural terminology
DMARD: disease modifying anti-rheumatic drug
HR: hazard ratio
IBD: inflammatory bowel disease
ICD: International classification of disease
IgG: immunoglobulin G
IL: interleukin
OR: odds ratio
PsA: psoriatic arthritis
PsO: psoriasis
TNFi: tumour necrosis factor inhibitor
UC: ulcerative colitis

5.2. ABSTRACT

Background/objectives: To assess the risk of serious infections in offspring exposed in utero to ustekinumab.

Methods: We conducted a retrospective cohort study using the IBM MarketScan database. We included live births (01/2011-12/2018) among women with psoriasis, psoriatic arthritis, and inflammatory bowel disease. Drug exposure was defined as ≥1 filled prescription or infusion during pregnancy. We evaluated serious infections (infections requiring hospitalization) within the first year of life. We used multiple logistic regression with generalized estimating equations to estimate the odds ratio (OR) for serious infection with ustekinumab versus no drug use, adjusting for potential confounders.

Results: We identified 16,130 offspring born to mothers with chronic inflammatory diseases, including 52 exposed to ustekinumab. Risk of serious infection among offspring exposed to ustekinumab exposure was 3.8% [95% confidence interval (CI) 1.0%, 13.0%], slightly higher than among offspring unexposed to any drug of interest (2.6%, 95% CI 2.3%, 2.8%), but confidence intervals overlapped. After adjusting for potential confounders, the odds ratio for serious infections after ustekinumab exposure versus no exposure to any drug was 1.58 (95% CI 0.37, 6.84).

Conclusion: In the largest cohort of exposed pregnancies assembled to date, we were unable to detect a clear excess risk of serious infection in offspring exposed in utero to ustekinumab. More research is needed before definitive statements regarding infection risk in offspring exposed to ustekinumab can be ascertained.

5.3. INTRODUCTION

Chronic inflammatory conditions, including inflammatory bowel diseases (IBD), psoriasis (PsO), and psoriatic arthritis (PsA), have a high burden among women of reproductive age. There has been significant interest in finding safe ways of controlling disease activity during pregnancy without adversely affecting the pregnancy or offspring. Biologic therapies, such as tumour necrosis factor inhibitors (TNFi) and interleukin (IL)-12/23 inhibitors have increasingly been used as first and second line systemic therapies for many inflammatory conditions including PsO, PsA, and IBD.[1,2] Though largely considered safe for the mother and fetus during gestation, these drugs are powerful immunomodulators and as such may cause immunosuppression in the exposed offspring.

Maternal immunoglobulin G (IgG) is actively transported across the placenta (with transport beginning at around 16 weeks of gestation and increasing throughout pregnancy), giving offspring similar immunity against pathogens as their mother for the first few months of life. Many biologic drugs are monoclonal antibodies and are actively transported across the placenta via the same mechanism.[3] This mechanism could lead to immunosuppression in the offspring born to mothers who used therapeutic monoclonal antibodies (i.e. biologic drugs) during pregnancy. There is relatively little research exploring whether children exposed in utero to biologic therapies are at increased risk of infection after birth, but two recent studies have shown that among 2,989 children born to mothers with rheumatoid arthritis (380 exposed to TNFi),[4] and 1712 born to mothers with IBD (846 exposed to TNFi),[5] there was no clear increased risk of serious infection among offspring exposed in utero to TNFi as compared to unexposed offspring.[4]

Ustekinumab is currently the only approved IL-12/23 inhibitor. The FDA approved its use for PsO in 2009, PsA in 2013, Crohn's disease (CD) in 2016 and ulcerative colitis (UC) in 2019. As with TNFi, there is documented evidence in both animals and humans that ustekinumab crosses the placenta and that offspring often have higher cord blood levels than their mothers, with cord levels reaching 113-186% of maternal levels.[5–8] To date, research on ustekinumab safety in pregnancy has been limited to assessing complications such as preterm birth, fetal loss, and birth defects, with the available evidence largely based on case reports and series. The current evidence suggests minimal risk of birth defects in offspring exposed to ustekinumab in utero.[9] Though most guidelines still advocate avoiding its use in pregnancy,[10–12] some authors have recently suggested that the benefits may outweigh the potential risks in certain clinical situations.[13]

To date there have been few studies looking at cohorts of offspring exposed in utero to ustekinumab and none examining the potential for immunosuppression among exposed offspring. In a large retrospective cohort study, we compared the risk of serious infections in offspring exposed to ustekinumab, TNFi, and non-biologic immunosuppressives, versus offspring unexposed during pregnancy among women with PsO, PsA, and/or IBD.

5.4. METHODS

5.4.1 Data source and study population

We assembled a cohort of children born to mothers with PsO, PsA, and/or IBD using the IBM MarketScan commercial databases (January 1, 2011 to December 31, 2018). The MarketScan commercial database is a large prospective US database of >230 million people with

employer-provided health insurance containing data on hospitalizations, outpatient visits and drug claims.[14] Diagnoses are recorded within the database using diagnostic codes from the International Classification of Diseases (ICD) 9th edition, and, since January 1, 2016, the ICD 10th edition, with procedures recorded as Current Procedural Terminology (CPT) codes.

We first included all pregnancies resulting in a live birth, based on a single related diagnosis (ICD-9/10) or hospital procedure code for vaginal or cesarean delivery (see supplemental material).[4,15] In doing so we excluded multiple pregnancies, ectopic pregnancies, molar pregnancies, pregnancies ending in spontaneous or induced abortions, and stillbirths. Gestational age was estimated from ICD codes using an established algorithm.[15] Within this subset of women who had live births, we identified mothers with the diseases of interest as having any two outpatients diagnostic codes or any single inpatient code for PsO, PsA, and/or IBD diagnosed before delivery (**ICD 9**: *PsO*: 696.1x; *PsA*: 696; *IBD*: 555.xx, 556.xx; **ICD 10**: *PsO*: L40.0, L40.1, L40.3, L40.4, L40.8, L40.9, M09.0, L40.5; *PsA*: M07, *IBD*: K50.xx, K51).[16,17] These case definitions demonstrated sensitivity and specificity values of 52% and 99% for PsO, 51% and 100% for PsA, and 82% and 96% for IBD, using chart review as reference.[16,17] For each mother with the disease of interest, we identified 10 mothers with neither condition at any time prior to and during pregnancy matched on age, year of delivery, and geographic location to act as a non-diseased control group. To be included in our cohort, women had to be continuously enrolled within the MarketScan database for 12 months prior to delivery. Offspring were deterministically linked to their mothers using family identifiers and delivery dates[15,18] and were followed from birth to an event (defined below) or censoring at the end of follow-up (12 months), end of insurance eligibility, death, or end of study period (December 31, 2018), whichever came first.

5.4.2 Exposure definition

Drug exposures were defined as at least one filled prescription or infusion procedure code during the pregnancy period for a drug of interest. The main exposure of interest was ustekinumab exposure during pregnancy. Other exposure groups included pregnancies unexposed to ustekinumab but exposed to TNFi (ie. etanercept, infliximab, adalimumab, certolizumab, golimumab), those unexposed to ustekinumab and TNFi but exposed to another biologic disease modifying anti-rheumatic drug (DMARD) (i.e. vedolizumab, secukinumab, ixekizumab, natalizumab), those unexposed to any biologic DMARD but exposed to a systemic non-biologic DMARD (i.e. sulfasalazine, mesalamine, cyclosporine, azathioprine, 6-mercaptopurine), and those unexposed to any systemic DMARD therapy. If exposed to more than one type of drug, grouping was assigned to the drug category of greater interest (ustekinumab > TNFi > other biologics, etc), but the use of multiple drugs during pregnancy was included as a covariate.

5.4.3 Outcome

The outcome of interest, serious infections, was defined as any single inpatient ICD-9/10 code for infection of any type within the first year of life (see supplemental material).[19,20] This approach of identifying serious infections has been shown to have a high sensitivity (79.9%) and specificity (83.9%) when using chart review as a reference. Person-time was censored at 12 months, end of insurance eligibility, death, date of admission for the first serious infection, or end of study period, whichever came first.

5.4.4 Covariates

In addition to drug exposures, we included as covariates in all multivariate models: maternal age, maternal gestational or pre-existing diabetes (ICD codes: ICD 9: 250.xx, 648.0x, 648.8x; ICD 10: E10.xx, E11.xx, O24.xx), any exposure to systemic corticosteroids from 3 months prior to conception until the end of gestation, other concomitant drug use (i.e., non-biologic DMARDs), whether or not the delivery was preterm, and disease state (PsO/PsA and/or IBD).

5.4.5 Statistical analyses

5.4.5.A Primary analyses

We calculated descriptive statistics to characterize the different exposure groups and quantify the crude number of infections per groups. Univariate and multivariate analyses using generalized estimating equations (GEE) were used to calculate crude and adjusted odds ratios (aORs) respectively. GEEs were used to account for correlation that might arise from including offspring from mothers with more than one eligible pregnancy during the study period. Analyses were performed using children unexposed to any systemic DMARDs as the reference groups. Multivariate analyses were adjusted for the covariates discussed above.

5.4.5.B Secondary analyses

We conducted three sensitivity analyses to assess the robustness of our results. First, we repeated the primary analysis with follow-up restricted to the first three months of life to verify that infections were not being driven by factors unrelated to in utero exposure (e.g. differential vaccination of offspring). Second, we conducted analyses extending the exposure assessment

window (i.e. the look-back period) to also include the pre-gestational period (3 months prior to gestation). Finally, to ensure that infection occurred on average equally over time within each group, we repeated the analyses using Cox proportional hazards models with frailties, looking at infection rate accounting for follow-up time, though the effect estimates were very similar to those calculated using logistic regression. Results of these sensitivity analyses are provided in the supplemental. All analyses were performed using SAS, version 9.4 and R version 3.6.1.[21]

5.5. RESULTS

We identified 16,130 offspring born to 14,712 mothers with chronic inflammatory disease (**PsA/PsO**: 7,623, **IBD:** 8,319, **PsA/PsO & IBD**: 188) and 160,762 offspring of matched unaffected controls (see Figure 1). The study cohort included 52 offspring exposed to ustekinumab during pregnancy, 1,585 exposed to TNFi, 51 exposed to other biologic drugs, 1,857 exposed to traditional DMARDs and 12,585 unexposed to any systemic DMARDs. Of 51 women exposed to non-TNFi biologic drugs, 36 were exposed to vedolizumab, 8 to secukinumab, 5 to natalizumab, 1 ixekizumab and 1 to both secukinumab and ixekizumab. Of 1,585 women exposed to TNFi during pregnancy, 650 were exposed to infliximab, 610 to adalimumab, 167 to etanercept, 142 to certolizumab pegol and 16 to golimumab. Of the 52 pregnancies in the ustekinumab group, 2 were also exposed to TNFi and only 1 was concomitantly exposed to a traditional DMARD.

Table 1 describes the patient characteristics by exposure group. There was little difference in age among women across exposure groups. Women exposed to ustekinumab and those unexposed to any DMARD were less likely to be exposed to systemic corticosteroids

during pregnancy as opposed to women with inflammatory diseases in other drug exposure groups.

5.5.1 Serious infection risk

Table 2 presents the crude cumulative risk of serious infections in the first year of life. During the first year of life, serious infections occurred in 3.8% (95% confidence interval (CI) 1.0 13.0) of offspring exposed to ustekinumab, 2.6% (95% CI 2.0, 3.6) exposed to TNFi, 3.9% (95% CI 1.1, 13.2) exposed to other non-TNFi biologics, 2.4% (95% CI 1.8, 3.2) exposed to traditional DMARDs and 2.6% (95% CI 2.3, 2.8) unexposed to any relevant drug in utero. The risk of serious infections in the healthy comparator group was 2.0% (95% CI 1.9, 2.1).Table 1: Maternal characteristics of offspring included in study cohort and matched healthy controls (n=176,892)

Within our cohort, we identified 412 infections among offspring whose mothers had PsO, PsA, and or IBD and 3,224 infections among offspring born to healthy controls. Infections were grouped generally by type,[20] which are described in Table 3. Infection types were similar between offspring regardless of maternal disease status. The most frequent types of serious infections were viral or bacterial lower respiratory tract infections, other viral or systemic infections and urinary tract infections, with all other types of infections accounting for less than 5% of overall infections. Of note, we detected no cases of tuberculosis nor other types of mycobacteria infection.

Table 5.1: Maternal characteristics of offspring included in study cohort and matched healthy controls (n=176,892)

	With Disease of Interest					
	Ustekinumab (n = 52)	**TNFi (n = 1,585)**	**Other biologics (n = 51)**	**Traditional DMARDs (n = 1857)**	**No drug exposure (n = 12,585)**	**Healthy control (n = 160,762)**
Age, years (SD)	31.2 (4.6)	32.0 (4.1)	32.1 (3.7)	32.6 (4.1)	32.6 (4.3)	32.5 (4.2)
Preterm birth, n (%)	7 (13)	174 (11)	3 (6)	192 (10)	1,235 (10)	13,876 (9)
Corticosteroid use, n (%)	3 (6)	261 (16)	13 (25)	270 (15)	591(5)	2,664 (2)
Pre-gestational diabetes, n (%)	1 (2)	59 (4)	3 (6)	56 (3)	504 (4)	5,078 (3)
Gestational diabetes, n (%)	5 (10)	211 (13)	5 (10)	230 (12)	1,876 (15)	23,132 (14)

Table 5.2: Crude absolute risk estimates of serious infections in offspring included in the cohort by exposure categories (n=176,892)

Exposure categories	Serious infections, % (95% CI)
Ustekinumab	3.8 (1.1, 13.0)
TNFi	2.7 (2.0, 3.6)
Other biologics	3.9 (1.1, 13.2)
Traditional DMARDs	2.4 (1.8, 3.2)
No drug exposure	2.6 (2.3, 2.8)
Healthy control	2.0 (1.9, 2.1)

5.5.2 Effect estimates of serious infection risk

Results of univariate and multivariate logistic regression using GEEs are presented in Table 4. In multivariate analysis of children exposed to ustekinumab our point estimates were consistent with increased risk, but the CIs were wide and included the null value (aOR 1.58, 95% CI 0.37, 6.84). Effect estimates were similar among offspring exposed to other non-TNFi biologics (aOR 1.26, 95% CI 0.33, 4.74). For those exposed to TNFi (aOR 0.85, 95% CI 0.59, 1.22) or traditional DMARDs (aOR 0.76, 95% CI 0.55, 1.06), there was no clear excess risk.

Of note, children born to healthy control mothers had a lower risk of serious infections compared to children born to mothers with chronic inflammatory diseases, even when unexposed to systemic DMARDs during pregnancy (aOR 0.80, 95% CI 0.71, 0.90).Table 3: Types of serious infections among offspring born to mothers with inflammatory diseases and those born to healthy control mothers (n= 3,636)

5.5.3 Sensitivity analyses

We performed multivariate sensitivity analyses using the same covariates mentioned previously. When restricting follow-up to the first 90 days of life, the effect of ustekinumab on

the risk of serious infections was slightly dampened (OR 1.31, 95% CI 0.18, 9.56; aOR 1.33, 95% CI 0.18, 10.2), though CIs remained wide (supplemental).

Table 5.3: Types of serious infections among offspring born to mothers with inflammatory diseases and those born to healthy control mothers (n= 3,636)

Infection Type	**Healthy control, n = 3,224**	**Inflammatory disease, n = 412**
Lower respiratory tract, n (%)	1759 (55)	229 (56)
Other viral/Systemic, n (%)	499 (15)	67 (16)
Unknown, n (%)	289 (9)	34 (8)
Urinary tract, n (%)	209 (6)	24 (6)
Upper respiratory tract, n (%)	171 (5)	18 (4)
Gastrointestinal, n (%)	132 (4)	21 (5)
Skin, muscles and bones, n (%)	141 (4)	15 (4)
Central nervous system, n (%)	24 (1)	4 (1)

When we extended the exposure assessment window to include the 3 months pre-conception, we identified 19 additional pregnancies which were exposed to ustekinumab during the pre-conception period only, bringing the number of exposed pregnancies to 71. In this sensitivity analysis, the estimated aOR for serious infections was 1.23 (95% CI 0.3, 5.10) when comparing ustekinumab to the reference group of offspring unexposed to any systemic DMARDs (both in the 3 months prior to conception and during pregnancy).

When performing analyses using Cox proportional hazards models, accounting for time to infection, results were similar to the main analysis using logistic regression [unadjusted hazard ratio (HR) 1.6, 95% CI 0.4; 6.5, adjusted HR 1.59, 95% CI 0.4, 6.4].

5.6. DISCUSSION

In the largest cohort of offspring exposed to ustekinumab in utero to date, we were unable to detect a significantly increased risk of serious infection. This is the first study of administrative data to assess ustekinumab safety in pregnancy and provide population-based estimates of the risk of serious infections. We observed a trend towards higher risk of serious infections in offspring exposed to ustekinumab in utero versus those unexposed to any drugs, though CIs were wide and included the null.

Table 5.4: Univariate and multivariate estimates of the odds ratios (OR) for the risk of serious infections comparing different exposure categories among offspring born to mothers with inflammatory diseases (n=16,130)

	Univariate Analysis	**Multivariate Analysis**
Exposure groups	**Odds Ratio (95% CI)**	**Odds Ratio (95% CI)**
No drug exposure	Reference	Reference
Ustekinumab	1.53 (0.37, 6.35)	1.58 (0.37, 6.84)
TNFi	1.04 (0.75, 1.43)	0.85 (0.59, 1.22)
Other biologics	1.55 (0.38, 6.23)	1.26 (0.33, 4.74)
Traditional DMARDs	0.94 (0.69, 1.29)	0.76 (0.55, 1.06)

Note: Adjusted ORs were adjusted for maternal age, maternal diabetes status, preterm status, exposure to corticosteriods, concomitant drug exposure, and disease state

Most studies to date investigating ustekinumab safety in pregnancy have not followed offspring past birth, and as such there has been minimal evidence regarding potential infection risk. Recently, the PIANO study, a prospective cohort study of 1,490 pregnant women with IBD has been published. Among 18 offspring exposed to ustekinumab throughout pregnancy, none experienced a serious infection within the first year of life.[5] Outcomes of exposed offspring in PIANO were measured by maternal report and serious infections were restricted to bacterial infections, making comparing our studies difficult.

This study has many strengths. It is the first to explicitly evaluate the risk of serious infection among live births exposed to ustekinumab in utero, particularly important due to the prevalence of PsO, PsA, and/or IBD among women of reproductive age and the efficacy of ustekinumab at disease control. It is the first study to use a large administrative database to investigate ustekinumab use during pregnancy. The use of a large database allowed us to include a large study population with uncommon diseases and with rare drug exposures. In addition, its data are relatively free from reporting bias seen in the currently available studies investigating ustekinumab exposure in utero. Our sample of 52 offspring exposed to ustekinumab is nearly double the size of the next largest peer-reviewed study[22] and of the case series of women who became pregnant during the original clinical trials (only published as an abstract).[22–24]

As well, due to the availability of maternal medical diagnoses and pharmaceutical claims within administrative databases like MarketScan, we were able to perform multivariate models controlling for important covariates and potential confounders. MarketScan in particular has been used in several other pharmacoepidemiological studies of chronic inflammatory diseases

and is useful as it contains both outpatient drug claims and infusion procedure codes, to give as close to an accurate measurement of drug exposure as possible.[4,25,26]

Our study also has some limitations. Firstly, there may have been residual confounding from disease activity. We adjusted for disease severity using corticosteroid use and/or concomitant drug use as a proxy for disease severity and activity, but these variables are not perfect, though there is no established gold-standard to doing this. Disease activity is likely associated with serious infection through preterm birth, which we did account for, so any residual confounding likely only modestly affects the effect estimates.[27]

Misclassification of cases and outcomes was also possible. As was discussed in the methods, ascertaining cases of PsO/PsA/IBD from administrative data is imperfect. Pregnancies which were misclassified as not having these diseases were likely less severe cases of the diseases and/or early presentations. The sickest patients were likely to be classified correctly and are the same patients likely to be exposed to biologic medications. Though misclassification may affect generalizability, it is unlikely to affect our study validity.

Misclassification on the outcome of interest (serious infections) could exist by either serious infections not being entered as such into the database or misidentifying non-infectious diseases as infections. In these instances, there is no reason to believe the misclassification would be differential between groups and as such any bias would cause the effect estimates to be biased towards the null.

In addition, drug exposure within our study was defined as filled prescription or drug infusion code, as is standard when using administrative data. There is no guarantee that the individuals were all compliant in taking their drugs, and thus our study may overestimate drug

use. This said, most women had out-of-pocket costs when filling their drugs, which is known to be associated with drug adherence and making it more likely that women took the drugs for which they filled a prescription.[26] Finally, estimating the beginning of pregnancy (conception) can be difficult to do within administrative data, though we used established algorithms based on prior literature to do this as effectively as possible.[15,18,28,29]

5.7. CONCLUSION

In the largest study of offspring exposed in utero to ustekinumab, and the first to examine this population using administrative data, we were unable to detect a clear excess risk of serious infection in offspring exposed in-utero to ustekinumab as compared to offspring unexposed to any relevant drug. Further research is needed before definitive statements about the risk of serious infections in offspring exposed in utero to ustekinumab can be made.

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FIGURE CAPTION

Figure 1: Flow chart of cohort inclusion

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Ethics approval: This study was approved by the McGill Faculty of Medicine Institutional review board (number A11-M107-14A)

5.9. Figures

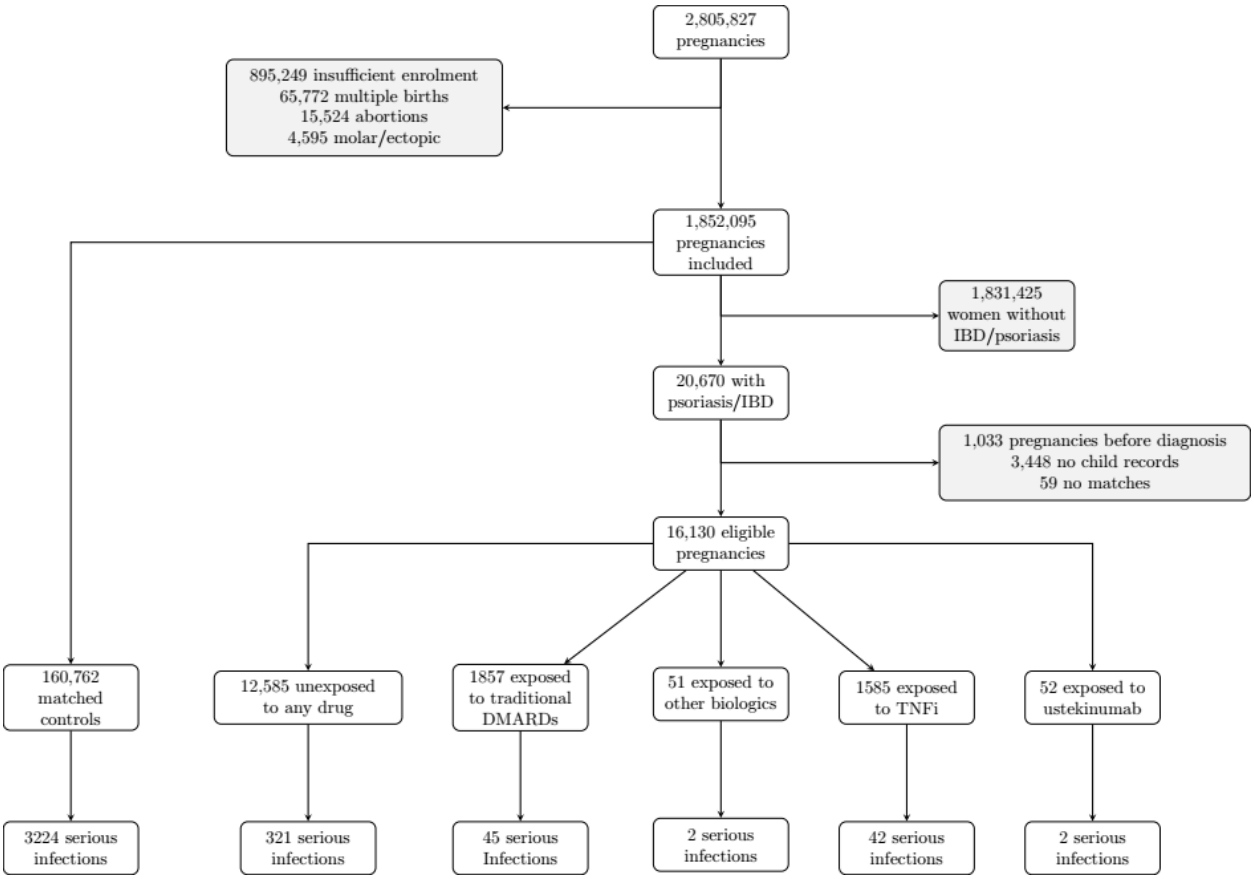

Figure 5.1: Flow chart of cohort inclusion

5.10. Supplemental material to manuscript #2

Table 5.5: ICD 9/10 codes for included and excluded pregnancies

Pregnancy type	ICD-9	ICD-10	CPT	DRG
Included	640-645, 650, 652-679 except 652.40 and 652.41, V27.0, V27.9,72.xx, 73.22,73.59, 73.6,74.0–74.2, 74.4, 74.99	O80-O83, O60.1*X0, O60.1*X1, O42.0 except O42.011, O42.1 except O42.911	59409, 59612, 59514, 59520	744-768
Excluded - stillbirth	646.0, 656.40, 656.41, V27.1		88016	
Excluded - abortion	632, 634-637, 639	O03, O04, O08	59840, 59841, 59850-59852, 59855-59857	770, 779
Excluded – molar and ectopic	630, 633	O00, O01		777
Excluded – multiple birth	651, V27.2-V27.7, V91	O30		

Table 5.6: Adjusted and unadjusted odds ratios (OR) for serious infections comparing the different exposure groups born to women with chronic inflammatory diseases as well as the healthy control group (n = 176,892)

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
No drug exposure	1.0 (Ref)	1.0 (Ref)
Ustekinumab	1.53 (0.37, 6.35)	1.57 (0.37, 6.58)
TNFi	1.04 (0.75, 1.43)	0.96 (0.67, 1.38)
Other biologics	1.55 (0.38, 6.23)	1.41 (0.38, 5.31)
Traditional DMARDs	0.94 (0.69, 1.29)	0.90 (0.66, 1.24)
Healthy control	0.78 (0.70, 0.88)	0.80 (0.71, 0.90)

Note: aORs were adjusted for maternal age, maternal diabetes status, preterm status, exposure to corticosteriods, concomitant drug exposure and disease state

Table 5.7: Adjusted and unadjusted hazard ratios (HR) for serious infections comparing the different exposure groups among offspring born to women with chronic inflammatory diseases to those with no drug exposure (n=16,130)

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
No drug exposure	1.0 (Ref)	1.0 (Ref)
Ustekinumab	1.60 (0.39, 6.49)	1.59 (0.39, 6.42)
TNFi	1.06 (0.77, 1.47)	0.99 (0.69, 1.41)
Other biologics	1.79 (0.44, 7.27)	1.58 (0.38, 6.49)
Traditional DMARDs	0.95 (0.70, 1.30)	0.91 (0.66, 1.25)

Note: aHRs were adjusted for maternal age, maternal diabetes status, preterm status, exposure to corticosteriods, and concomitant drug exposure and disease state

Table 5.8: Adjusted and unadjusted ORs for serious infection comparing the different exposure groups when including drug exposure during pregnancy and during the pre-conception period (3 months prior to pregnancy) (n=16,130)

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
No drug exposure	1.0 (Ref)	1.0 (Ref)
Ustekinumab	1.10 (0.27, 4.51)	1.23 (0.30, 5.10)
TNFi	1.04 (0.76, 1.42)	0.90 (0.63, 1.28)
Other biologics	1.47 (0.37, 5.91)	1.29 (0.34, 4.88)
Traditional DMARDs	1.00 (0.74, 1.34)	0.81 (0.59, 1.11)

aORs were adjusted for maternal age, maternal diabetes status, preterm status, exposure to corticosteriods, and concomitant drug exposure and disease state

Table 5.9: Adjusted and unadjusted ORs calculated comparing the different exposure groups among offspring born to women with chronic inflammatory diseases to those with no drug exposure, only considering infections occurring within the first 90 days after birth (n=16,130)

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
No drug exposure	1.0 (Ref)	1.0 (Ref)
Ustekinumab	1.31 (0.18, 9.55)	1.33 (0.18, 10.2)
TNFi	0.99 (0.64, 1.52)	0.92 (0.57, 1.47)
Other biologics	2.75 (0.68, 11.1)	2.63 (0.73, 9.55)
Traditional DMARDs	0.95 (0.63, 1.44)	0.79 (0.51, 1.22)

aORs were adjusted for maternal age, maternal diabetes status, preterm status, exposure to corticosteriods, and concomitant drug exposure and disease state

6. Manuscript #3 – Serious infections in offspring exposed in utero to vedolizumab

6.1. Preamble to manuscript #3

This manuscript, titled "*Serious infections in offspring exposed in utero to vedolizumab*" is formatted as a 'brief communication' for submission to the *American Journal of Gastroenterology* and presents a second manuscript originating from the retrospective cohort study whose methods are detailed in chapter 4. The abstract pertaining to this manuscript has been accepted for presentation at the 2021 Digestive Disease Week (one of the world's largest gastroenterology scientific meeting), as a poster of distinction (top 10% of accepted abstracts).

Work presented in this manuscript estimates the risk of serious infection in the offspring exposed to vedolizumab and represents a secondary objective of this thesis. Like ustekinumab, vedolizumab is a relatively novel non-TNFi biologic whose safety in pregnancy is poorly understood and is of particular interest as it is used in women with IBD of reproductive age.

Vedolizumab, unlike ustekinumab or many of the TNFi, is not indicated for PsO or PsA but only for IBD. Therefore, using the cohort created with the methods described in chapter 4 and whose results are described in the second manuscript, we further restricted the study population to include only offspring whose mother had IBD. Since this smaller cohort is just a sub-sample of the larger cohort, the same IBD case definition (described in 4.2.1) was used. Other than restricting to IBD and using a different drug (i.e. vedolizumab) as the exposure of interest (as described in 4.2.2), the methods employed in this manuscript are the same as those used in manuscript #2.

Serious infections in offspring exposed in utero to vedolizumab

Short title: Infections and in utero vedolizumab exposure

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6.2. Abstract

Controlling symptoms of inflammatory bowel diseases during pregnancy is important for optimizing both maternal and fetal outcomes. The goal of this study was to assess the risk of serious infections in offspring exposed in utero to vedolizumab. Using the IBM MarketScan database, we created a cohort of children born to mothers with inflammatory bowel diseases and compared the risk of serious infections in those exposed to vedolizumab versus unexposed offspring. We did not detect an increased risk of infections (adjusted odds ratio 0.87; 95% CI 0.13, 6.15) in the vedolizumab group.

6.3. Introduction

Inflammatory bowel disease (IBD) peaks in incidence during reproductive years. Women with IBD are more likely to experience adverse pregnancy outcomes, including preterm birth, compared to women from the general population.(1) As such, finding ways of controlling IBD activity and maintaining remission during pregnancy is of the utmost importance to optimize pregnancy outcomes.

Biologics of several classes are known to be highly efficacious in inducing and maintaining remission in IBD, including tumour necrosis factor inhibitors (TNFi) (i.e., adalimumab, infliximab), interleukin (IL)-12/23 inhibitors (i.e., ustekinumab), and integrin $\alpha_4\beta_7$ inhibitors (i.e., vedolizumab). There has been much interest in assessing their safety in pregnancy. Limited evidence suggests that these drugs do not increase the risk of adverse pregnancy outcomes including preterm birth, spontaneous abortion or stillbirth.(2,3) These drugs, however, are typically immunoglobulins (IgG) which are actively transported across the placenta during the 2^{nd} and 3^{rd} trimesters. Offspring exposed to TNFi or ustekinumab in utero are known to be born with higher blood levels of drug as compared to their mothers, while offspring exposed to vedolizumab are known to have high levels, but lower than those of their mothers.(4,5) TNFi and ustekinumab are known immunosuppressants and there is established risk of infection in exposed adults, raising concerns for potential immunosuppression in offspring exposed in utero. In contrast, vedolizumab, acts locally on the gut and is not associated with increased risk of infection in adults(6), though the risk of infection in exposed offspring has not been ruled out. This issue has been studied with results detecting no signal of increased risk as yet across three studies (164 total pregnancies), though research is limited in scope.(5,7,8)

Using a large population-based cohort of children born to mothers with IBD, we aimed to evaluate the risk of serious infections in offspring exposed in utero to vedolizumab and compare to children exposed in utero to TNFi and other biologics, as well as to unexposed offspring.

6.4. Methods

We assembled a cohort of children born to mothers with IBD using the IBM MarketScan database (January 1, 2011 to December 31, 2018)(9) using the same methodology as described in a prior study from our group.(10) We included pregnancies resulting in a singlet live birth using relevant ICD-9/10 or procedure codes indicating delivery; all pregnancies with outcomes other than live birth were excluded. From this cohort, we identified mothers who had been continuously enrolled in MarketScan for at least 12 months prior to delivery with IBD diagnosed before delivery using previously validated case definitions.(11)

Drug exposure was defined as at least one filled prescription or infusion procedure code for a drug of interest during the pregnancy period. The main exposure of interest was vedolizumab and other exposure groups included exposure to TNFi, other biologics (including ustekinumab), traditional systemic DMARDs or no drug exposure. If there were multiple drug exposures, exposure category was mutually exclusive and assigned hierarchically, with vedolizumab > TNFi > other biologics > traditional DMARDs.

The outcome of interest was serious infection, defined as any single inpatient ICD-9/10 code for infection of any type within the first year of life.(12,13) Offspring were followed from birth until an event or censoring at end of follow-up (12 months of age), death, end of study period, or end of insurance eligibility, whichever occurred first.

Descriptive statistics were used to characterize the different exposure groups and crude infection risks. We used logistic regression using generalized estimating equations (GEEs) to estimate crude and adjusted odds ratios (ORs) for serious infections with the drugs of interest compared to no use, adjusting for maternal age, whether the delivery was preterm, presence of maternal diabetes (either gestational or pre-existing), corticosteroid use, and concomitant use of another drug of interest.

6.5. Results

We identified a total of 8,507 offspring born to 7,633 women with IBD, with descriptive statistics presented in Table 6.1. A total of 43 offspring were exposed to vedolizumab, 1,230 to TNFi, 17 to other biologics (13 of whom were exposed to ustekinumab), 1,822 to traditional DMARDs and 5,395 unexposed to any drug. Of the 43 exposed to vedolizumab, 7 were concomitantly exposed to TNFi and 13 to a traditional DMARD. Maternal age and the prevalence of diabetes were similar across groups (Table 6.1). The vedolizumab groups had lower percentage of preterm birth and higher corticosteroid use than the other exposure groups.

The cumulative incidence of serious infection at 1 year was 2.3% (95% CI 0.4, 12.0) in the vedolizumab group, similar to the rate in the TNFi (2.9%; 95% CI 2.1, 4.0), traditional DMARD (2.5%; 95% CI 1.9, 3.3), and no drug exposure (3.0%; 95% CI 2.6, 3.6) groups. The risk appeared greater in the other biologic group (5.9%; 95% CI 1.0, 27.0.), though confidence intervals were wide and overlapped for all categories. Of note, there were no cases of tuberculosis detected in any group.

Crude and adjusted ORs calculated from logistic regression using GEEs are presented in Table 6.2. Compared to children unexposed to any drug, we observed no clear excess risk of

serious infections in offspring exposed in utero to vedolizumab (adjusted OR (aOR) 0.87; 95% CI 0.13, 6.15), although the CI was wide. For those exposed to non-biologic DMARDs (OR 0.78; 95% CI 0.55, 1.09) or TNFi (aOR 0.95; 95% CI 0.61, 1.40), the effect estimates did not suggest an increased risk. However, there was a potential trend towards an increased risk among children in the other biologic group (aOR 2.05; 95% 0.29, 14.5), though the CI was imprecise.

6.6. Discussion

In this study, among the largest cohort of offspring exposed to vedolizumab in utero ever assembled, we did not detect a substantially increased risk of serious infection within the first 12 months of life, though estimates were imprecise. This aligns with data from the PIANO study(5) a French retrospective cohort study,(7) and the pan-European CONCEIVE study,(8) though the study design and outcome definitions varied across the studies and differed from ours.

Our study has several strengths. We are the first to use large administrative databases to provide population-based estimates of the risk of serious infections in IBD offspring exposed in utero to vedolizumab. Our data source (MarketScan database) include information on medical diagnoses and drugs in both mother and offspring, allowing us to assess exposure, outcome and covariates using established algorithms without the potential for recall bias. MarketScan database with its large size (including more than 230 million individuals) also provides the opportunity for rare outcomes and exposures to be assessed and has been widely used to conduct pharmacoepidemiologic studies in rheumatic diseases.(14–16)

Our study also has some potential limitations. There may have been residual confounding from disease activity. Though we attempted to adjust for this using corticosteroid and/or concomitant drug use as proxy for disease activity, these variables are not perfect. This said,

disease activity is likely associated with serious infection through preterm birth, which we did account for, so any residual confounding likely only modestly affects the effect estimates. In administrative database research, imperfect case ascertainment is always a concern. To circumvent this, we have used previously established case definitions which have shown good validity.(11)

In conclusion, we did not detect a clear excess risk for offspring exposed in utero to, vedolizumab compared to unexposed offspring born to mothers with IBD. Ongoing caution, as well as more research on short and long-term effects, is warranted for vedolizumab and other biologics that are actively transported across the placenta.

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6.8. Tables

Table 6.1: Maternal characteristics of the study population (n=8,507)

	With diseases of interest				
	Vedolizumab (n = 43)	TNFi (n = 1,230)	Other biologics (n = 17)	Non-biologic DMARDs (n = 1,822)	No drug exposure (n = 5,395)
Maternal age (years)	31.6 (4.4)	31.7 (4.0)	32.6 (4.1)	32.6 (4.1)	32.4 (4.3)
Pre-existing diabetes, n (%)	1 (2)	38 (3)	0 (0)	54 (3)	170 (3)
Gestational diabetes, n (%)	3 (7)	143 (12)	0 (0)	224 (12)	767 (14)
Preterm birth , n (%)	2 (5)	133 (11)	2 (12)	191 (10)	569 (11)
Corticosteroid use, n (%)	14 (33)	220 (18)	2 (12)	263 (14)	361 (7)
Concomitant DMARD use, n (%)					
Biologic, n (%)	7 (16)	1 (>1)	-	-	-
Non-biologic, n (%)	13 (30)	240 (19)	2 (13)	-	-

Table 6.2: Crude and adjusted odds ratios for serious infections across different exposure groups (n = 8,507)

Exposure group	Crude ORs (95% CI)	Adjusted ORs (95% CI)
No drug exposure	Ref	Ref
Vedolizumab	0.76 (0.11, 5.52)	0.87 (0.13, 6.15)
TNFi	0.96 (0.66, 1.38)	0.95 (0.61, 1.40)
Other biologic	2.11 (0.31, 14.2)	2.05 (0.29, 14.5)
Traditional DMARDs	0.80 (0.58, 1.12)	0.78 (0.55, 1.09)

7. Discussion

7.1. Discussion of results

As was described in chapter 3, current evidence pertaining to ustekinumab safety in pregnancy is limited. It is believed that ustekinumab likely does not significantly increase the risk of adverse pregnancy outcomes (i.e. preterm birth, spontaneous abortions, congenital malformations), though this evidence is based on only approximately 550 exposed pregnancies reported in the literature, most of which were descriptive and did not have a comparator group. The relationship between ustekinumab and serious infection in exposed offspring is much more unclear and presents an important knowledge gap, having only been investigated in two prior studies. The PIANO study, a prospective cohort of 1,490 completed pregnancies looked at this relationship and found no increased infection risk as compared to pregnancies exposed to thiopurines only, though the study had several limitations, including small number of exposed subjects (only 18 exposed to ustekinumab during pregnancy), use of maternal report for outcome assessment, and outcome restriction to bacterial infections (53). Wils et. al (63) published the outcomes on 29 pregnancies exposed to ustekinumab and identified no serious infections, though also suffering from a small sample size.

The primary objective of my thesis was to address this knowledge gap via retrospective cohort study of the risk of serious infections among offspring exposed in utero to ustekinumab. The data (chapter 5) suggested no clear increased serious infection risk in offspring exposed in utero to ustekinumab versus offspring unexposed to any relevant drugs, though confidence intervals were wide. Our ustekinumab-exposed cohort was the largest assembled to date and represents the first use of administrative databases to study this population. This said, the sample is still relatively small. Our point estimates indicate a possible increased risk of infection among exposed offspring. This is likely caused by the variability inherent with our small sample size, but could be indicative of a true increased risk which this study is under-powered to detect.

This thesis' secondary objective was to examine the risk of serious infection among offspring exposed in utero to vedolizumab. Though the evidence regarding infection risk from in utero vedolizumab exposure is somewhat more established than the evidence for ustekinumab, the number of exposed pregnancies remains small (approximately 150 pregnancies), precluding a

definitive understanding of infection risk. Manuscript #3 thesis mirrored previously published work on vedolizumab, indicating that vedolizumab likely does not increase risk of serious infection in exposed offspring.

Sensitivity analyses demonstrated the robustness of these results. As was discussed in section 4.3.3, three secondary analyses were performed. The first such analysis restricted follow-up time to 3 months after pregnancy. Assuming a causal relationship between immunosuppressive drug exposure and infection risk, one would expect highest risk of infection in the exposed offspring when drug levels are highest. Since exposure to biologics via breast milk does not lead to increased blood concentrations of the drug in the offspring after birth, newborns exposed to ustekinumab/vedolizumab are not exposed to either drug again after birth (123). Their highest risk of infection should therefore theoretically be in the months immediately after birth. Results in ustekinumab exposure showed results similar to that in the 12 months follow up. In the vedolizumab group, the OR in the first three months was 2.04 (95% CI 0.30, 13.8), numerically higher than in 12 month follow-up, though confidence intervals overlapped.

Another sensitivity analysis involved analyzing the data using Cox PH models to estimate hazard ratios (HR). This analysis account for survival time between groups (with failure in this case referring to first infection) and used frailties to account for the clustering that arose from including multiple pregnancies from the same woman. These models found HRs which closely approximated the ORs calculated from logistic regression with GEEs, indicating that time to event was not substantially different across groups and that events occurred within the follow-up period relatively similarly between groups on average. This indicates that our use of logistic regression using GEEs as the main analyses was appropriate.

Although not a primary research interest, this thesis also demonstrated that, in our cohort of patients with PsO, PsA, and/or IBD, TNFi exposure is not clearly associated with serious infections in offspring exposed in utero. As was discussed in section 2.3.2, this finding reiterates what has been shown in other cohorts and adds to the body of evidence suggesting TNFi do not appear to increase the infection risk in exposed offspring (53,58,124), providing more precise estimates. However, specific TNFi, may pose differential infection risk due to their differential trans-placental transfer and is currently an area of active research by my research group.

Finally, this project showed that administrative databases can be used to generate large cohorts of offspring exposed to relatively novel biologics. Such databases have not before been used to evaluate either ustekinumab or vedolizumab in pregnancy. This project innovates by judiciously using the power of pharmacoepidemiology to address drug safety in pregnant women, who are regularly excluded from clinical trials and often underrepresented in observational studies. Our research approach has relevance beyond the specific drugs (i.e. ustekinumab, vedolizumab) and diseases under study (i.e. PsO, PsA, and IBD), as it will be applicable to the study of other biological agents (e.g. rituximab, belimumab), which similarly display active trans-placental transfer and are also used in the treatment of various inflammatory conditions (e.g. vasculitis, systemic lupus erythematosus) that predominantly affect women of reproductive age.

7.2. Strengths and limitations

The study presented in this thesis had several strengths, many of which were discussed within the discussion sections of the manuscripts. Ours was amongst the first studies to actively compare risk of infection among offspring exposed in utero to ustekinumab and vedolizumab against a control population. As of now, most work in the area has been purely descriptive, either due to small samples, lack of a comparator group, or both. Ours was the first study to concretely generate an estimated risk of infection using rigorous statistical methods and the first to control for important covariates that may impact infection risk. Furthermore, we did this using a diseased rather than a healthy comparator for increased robustness. This work can form the basis of future quantitative work in the area and will hopefully lead to more work which seeks to quantify the infection risk in offspring exposed to ustekinumab and vedolizumab. In order to improve the precision of our estimates, repeating these analyses in a year or two could be helpful, as could the use of multiple databases.

This study also has several potential limitations that must be acknowledged. Misclassification may have occurred when defining any of: disease status, drug exposure, outcome, or covariates. As was discussed in 4.2.1, defining PsO and PsA in particular suffer from low sensitivity, which may cause us to misclassify eligible cases. As was discussed, this misclassification would likely have missed milder cases of PsO, who are also unlikely to have the exposures of interest, therefore limiting the effect of this bias on our study. We defined drug

exposure as filled prescription or infusion codes, another potential source of misclassification. Though one can assume patients with an infusion code actually received their drugs, simply filling a prescription is not necessarily indicative of adherence, though we assumed as much in this study. Fortunately, this bias likely did not affect our results significantly, as it has been well established that, due to several factors including the high cost of biologics, patients dispensed biologics overall tend to adhere to them better than patients dispensed oral medications, with high adherence overall (125,126).

Misclassification of preterm birth may have impacted our study in two ways. Firstly, as described in 4.3.1, though sensitivity and specificity were high for binary preterm birth, any imperfect case attainment may have excluded pregnancies exposed during the first trimester, under-counting total pregnancies, though we accounted for this in sensitivity analyses (see table 5.8). Since there is such a strong association between preterm birth and neonatal infection (with certain neonatal infections caused by prematurity) any misclassification of this variable could have impacted our results. Our preterm birth rate (approximately 10% across groups) approximated that of both the general population (127,128) and MarketScan (58), implying that our assessment of preterm birth did not deviate from what one would expect, though individual misclassification may still have impacted results within exposure groups with smaller sample sizes (ie. ustekinumab).

As with all observational studies, this thesis was also susceptible to residual confounding. One potential residual confound was confounding by indication, manifesting as disease severity/state (PsO/PsA and/or IBD) not being balanced between exposure groups. As was discussed above, active IBD is associated with adverse birth outcomes and having active disease of any type makes the patient more likely to be exposed to any drug during pregnancy (a patient in drug free remission has no reason to take drugs during pregnancy). This could have created a situation whereby our “exposed” categories were on average sicker than the comparator (no drug exposure) groups, inflating the infection risk. This can be visualized looking at Tables 5.1 and 6.1, wherein the percentages of pregnancies exposed to corticosteroids (a proxy for disease severity) vary by exposure group. To account for this, we adjusted for concomitant drug use (the assumption being more drug use equals more severe disease), corticosteroid use (corticosteroids are used in short periods in response to disease flares), and disease state. These proxies, though

standard in the field, do not provide particularly granular detail on disease activity the way reviewing medical records from antenatal physician visits might. Though I cannot confidently say that this bias did not substantially impact our results, such a bias would systematically inflate effect estimates. Other residual confounds, such as maternal socio-economic status or maternal smoking were also likely present in the data.

MarketScan is a convenience sample of US insurance companies; unlike the administrative databases seen in Canada or other countries where universal access to publicly funded health care exist, MarketScan is neither made up of the entire American population nor a random sample of it. Rather, the data is acquired from insurance companies and, since American healthcare insurance is most commonly accessed through employment, at least one member of a family must have a job associated with health insurance in order to be included (129). As well, different included insurance plans could reimburse the study drugs of interest, particularly the more costly biologics, at different rates. These limitations do not negate our findings, but potentially limits the ability to generalize out findings to disadvantaged populations in the US. Repeating this study with data from Medicaid, American governmental insurance provided to, among other populations, uninsured pregnant women, could expand generalizability.

Finally, though we used rigorous statistical methods to reduce bias in our effect estimates, our study had limited precision, with wide CI across exposure groups, limiting our ability to make strong inferences. This was due largely to small numbers of exposed pregnancies and low percentage of infections overall, especially within the ustekinumab and vedolizumab groups. As more women become exposed going forward, more precise estimates can be calculated in the coming years. Increased sample size will allow for more sensitivity analyses to be performed, such as modeling risk based on when in pregnancy biologic exposure occurred. Placental transfer begins at approximately 16 weeks gestation and occurs progressively thereafter. Differentiating infection risk between offspring exposed during the first trimester (when the fetus is unlikely to be exposed to maternal antibodies) and second/third trimester exposures would be interesting and could shed additional insight in assessing a causal relationship between drug exposure and infection.

8. Conclusions

Chronic inflammatory diseases have a large burden on women of reproductive age and research seeking to optimize maternal, fetal, and child outcomes is crucial. The objectives of this thesis were to assess the risk of serious infections in offspring exposed in utero to ustekinumab and vedolizumab. Through literature review and a retrospective cohort study, I did not identify a large excess risk of serious infections from either drug, though point estimates suggested a potential trend for increased risk for ustekinumab (with wide confidence intervals including the null values). These results provide important confirmatory evidence regarding the safety of vedolizumab in pregnancy and provide important first steps in understanding the risks associated with in utero ustekinumab exposure.

More research is necessary to fully understand infection risk in exposed offspring, including using other administrative databases. This thesis work provides novel information to help assist in the establishment of clinical guidelines and policies for the care of women with chronic inflammatory conditions, to ultimately improve reproductive outcomes.

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Appendices

A. Appendix to this thesis

Table 9.1: ICD codes for assessing gestational age

ICD-9 code	Assigned gestational age (weeks)
765.21	23
765.22	24
765.23	26
765.24	28
765.25	30
765.26	32
765.27	34
765.28	36
765.29	39
766.21	41
766.22	42

Note: For ICD-10, gestational age can be calculated from Z3A.xx where xx refers to GA in weeks