Tumour Necrosis Factor Inhibitors and Serious Infections in Pregnant Women with Chronic Inflammatory Diseases and Their Offspring

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ABSTRACT

Pregnant women with chronic inflammatory diseases, such as rheumatoid arthritis, account for 10% of pregnancies. Almost universally, these women worry whether their medications will adversely affect their pregnancy and/or baby. Their concerns are heightened by a lack of data, due in part to pregnant women being excluded from clinical trials and underrepresented in observational studies. Disease flares during pregnancy are common and may be associated with adverse pregnancy outcomes. Tumour necrosis factor inhibitors (TNFi), which affect the immune system, are increasingly prescribed, but guidelines remain unclear on whether to continue treatment during pregnancy. Similarly, offspring exposed as fetuses to TNFi may experience immunosuppression and might be at an increased risk of infections in their first year of life as a result of TNFi entering their bloodstream *in utero*. Concerns over offspring immunosuppression may also lead to the deferral of childhood live vaccinations. Therefore, there is a critical need for large real-world studies to better assess the risk of serious infections in pregnancies related to TNFi.

The objectives of this manuscript-based thesis are (1) to assess the risk of serious infections during pregnancy and postpartum in women with chronic inflammatory diseases exposed to TNFi compared with unexposed women, (2) to evaluate the risk of serious infections during their first year of life in children born to women with chronic inflammatory diseases who used TNFi during pregnancy compared with children born to unexposed women with chronic inflammatory diseases, (3) to assess if the risk of serious infections in TNFi-exposed offspring is differential according to TNFi subtypes, and (4) to examine the risk of diarrhea-associated events in children exposed *in utero* to TNFi who receive the rotavirus vaccine (a live vaccine) in their first 6 months of life, compared with those who are not vaccinated by 6 months.

To address these objectives, a cohort of mothers and offspring was created using data from MarketScan, a large United States private health insurance claims database. Manuscript #1 is a comprehensive narrative review of TNFi and serious infections in reproductive-aged women and their offspring. Manuscript #2 focuses on maternal serious infections during pregnancy and postpartum. Manuscript #3 is a descriptive analysis of the use and discontinuation of TNFi during pregnancy and was a secondary objective that is complementary to objective 1. Manuscript #4 assesses the risk of serious infections in the offspring associated with maternal TNFi use, further stratified by TNFi placental transfer ability and timing during pregnancy. Manuscript #5 evaluates

the risk of diarrhea-associated healthcare use in offspring exposed *in utero* to TNFi who received the rotavirus vaccine before 6 months of age compared to those unvaccinated by that age. Together, these manuscripts fill important knowledge gaps surrounding the safety of TNFi during pregnancy for both mother and baby, with the ultimate goal of generating evidence for best practice guidelines.

RÉSUMÉ

Les femmes enceintes atteintes de maladies inflammatoires chroniques, comme la polyarthrite rhumatoïde, représentent 10% des grossesses. Presque toutes ces femmes s'inquiètent que leurs médicaments aient des effets néfastes qui nuisent à leur grossesse et/ou enfant. Ces inquiétudes sont renforcées par le manque de données, dû en partie au fait que les femmes enceintes sont exclues des essais cliniques et sous-représentées dans les études observationnelles. Les exacerbations de la maladie pendant la grossesse sont courantes et peuvent être associées à des issues défavorables de la grossesse. Les inhibiteurs du facteur de nécrose tumorale (TNFi), qui affectent le système immunitaire, sont de plus en plus prescrits, mais les directives restent floues quant à la poursuite du traitement pendant la grossesse. De même, les enfants exposés aux TNFi en tant que fœtus peuvent potentiellement devenir immunosupprimés et pourraient faire face à un risque accru d'infections au cours de leur première année de vie en raison de la présence de TNFi dans leur circulation sanguine *in utero*. Les inquiétudes concernant l'immunosuppression de la progéniture peuvent également conduire à reporter les vaccins vivants atténués chez ces enfants. Par conséquent, il est essentiel de réaliser des études à grande échelle en conditions réelles pour mieux évaluer le risque d'infections sévères reliées aux TNFi pendant les grossesses.

Les objectifs de cette thèse par manuscrits sont (1) d'évaluer le risque d'infections sévères pendant la période gestationnelle et le post-partum chez les femmes atteintes de maladies inflammatoires chroniques exposées au TNFi par rapport aux femmes non exposées, (2) d'évaluer le risque d'infections sévères au cours de la première année de vie chez les enfants nés de femmes atteintes de maladies inflammatoires chroniques qui ont utilisé des TNFi pendant la grossesse par rapport aux enfants nés de femmes non exposées atteintes de maladies inflammatoires chroniques, (3) d'évaluer si le risque d'infections sévères chez la progéniture exposée aux TNFi est différentiel selon les sous-types de TNFi, et (4) d'examiner le risque d'événements associés à la diarrhée chez les enfants exposés *in utero* au TNFi qui reçoivent le vaccin contre le rotavirus au cours des 6 premiers mois de vie, par rapport à ceux qui sont non exposés.

Pour répondre à ces objectifs, une cohorte constituées de mères et de leur progéniture a été créée à l'aide des données de MarketScan, une grande base de données de demandes d'indemnisation d'assurance santé privée aux États-Unis. Le manuscrit #1 est une revue narrative complète du TNFi et des infections graves chez les femmes en âge de procréer et leur progéniture. Le manuscrit #2 porte sur les infections maternelles sévères pendant la gestation et la période post-

partum. Le manuscrit #3 est une analyse descriptive de l'utilisation et de l'arrêt des TNFi pendant la grossesse et constitue un objectif secondaire complémentaire de l'objectif 1. Le manuscrit #4 examine le risque d'infections sévères chez les enfants exposés *in utero* aux TNFi, en fonction de la capacité de transfert placentaire des TNFi et du moment de l'exposition pendant la grossesse. Le manuscrit #5 évalue le risque d'événements de santé associés à la diarrhée chez la progéniture exposée *in utero* aux TNFi en fonction de l'administration ou non du vaccin contre le rotavirus avant l'âge de 6 mois. Ensemble, ces manuscrits comblent d'importantes lacunes dans les connaissances concernant l'innocuité des TNFi pendant la grossesse pour la mère et le bébé, avec pour objectif ultime de générer des données probantes pour l'élaboration de directives cliniques.

PREFACE

This thesis uses the terms ‘woman’ or ‘mother’ throughout. This includes all people who are pregnant or have given birth.

This thesis has been prepared according to the guidelines for a manuscript-based thesis and includes the following 5 manuscripts:

Flatman LK, Malhamé I, Colmegna I, Bérard A, Bernatsky S, Vinet É. Tumour necrosis factor inhibitors and serious infections in reproductive-age women and their offspring: a narrative review. Scand J Rheumatol. 2024;*53*(5), 295–306.

Flatman LK, Beauchamp ME, St-Pierre Y, Malhamé I, Bérard A, Bernatsky S, Vinet É. Tumour Necrosis Factor Inhibitors and Risk of Serious Infections in Pregnant Women with Autoimmune Diseases. *Under review with ACR Open Rheumatology (12 March 2025).*

Flatman LK, Bernatsky S, Bérard A, Vinet É. Patterns of Use and Discontinuation for Tumour Necrosis Factor Inhibitors in Pregnant Women: Insights from a Real-World Sample. *Under review with the Journal of Rheumatology (14 January 2025).*

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Flatman LK, Beauchamp ME, St-Pierre Y, Malhamé I, Bérard A, Bernatsky S, Vinet É. Diarrhea Events in Offspring Exposed to TNF Inhibitors & Rotavirus Vaccine. *To be submitted to Annals of Rheumatic Diseases.*

Details of co-authors’ contributions to each manuscript are outlined on **pages xv-xvi.**

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This thesis is written in memory of my Gramma, who taught me the cinnamon bread recipe, was one of my biggest supporters and best friend, and passed away during my degree – this PhD, or how she remembered it, "Professional Hair Dresser," is for you. Love you much.

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CONTRIBUTION TO ORIGINAL KNOWLEDGE

The contents of this thesis constitute an original contribution to the field of rheumatology, pharmacoepidemiology, and perinatal epidemiology, providing novel insights into (1) the relationship between gestational use of tumour necrosis factor inhibitors (TNFi) and the risk of serious infections in mothers and their offspring, and (2) the risks associated with rotavirus vaccine administration within 6 months after birth in offspring exposed to TNFi *in utero*.

Manuscript #1 represents the most comprehensive review to date on the issue of serious infections in pregnant women and their offspring exposed to TNFi. It offers a detailed review of the literature, including prospective and retrospective cohort studies, registry data, meta-analyses, and systematic reviews. Furthermore, it both updates the currently available literature reviews on the topic of TNFi and pregnancy with respect to serious infections and examines the question from a broader perspective, including many previously overlooked references. Additionally, it provides a summary of new guidelines on vaccination in exposed offspring. Finally, this review is the first to address serious infections in women exposed to TNFi during both pregnancy and postpartum.

Manuscript #2 is the largest real-world analysis to date on the association between the use of TNFi and serious infections during pregnancy and postpartum. Leveraging data from over 62,000 women with chronic inflammatory diseases and over 70,000 pregnancies, our findings provide crucial information on the safety of TNFi use in this population. Our research addresses a critical gap in understanding the impact of TNFi usage on infection risk during these vulnerable periods for women. While previous studies have explored this association, our study improves upon earlier research by utilizing a time-varying exposure definition, capturing both pregnancy and postpartum, and providing robust hazard ratio estimates. This comprehensive analysis contributes to clinical decision-making by offering reassurance for maintaining TNFi treatment in pregnancy and postpartum when necessary for disease control.

Manuscript #3 is the most comprehensive descriptive analysis to date on the prescribing patterns of TNFi and concomitant medication use (i.e., corticosteroids and non-biologic immunomodulators) during pregnancy. It provides a detailed description of real-world prescribing

patterns, showing increased confidence in the safety of TNFi during pregnancy and an increase in the proportion of pregnancies exposed to TNFi between 2011 and 2021. Our findings have significant implications for clinical practice and patient counselling, offering valuable insights into the safety and evolving use of TNFi in pregnancy. Furthermore, our results provide evidence on the increasing uptake of best practice guidelines recommending the continuation of TNFi throughout pregnancy.

Manuscript #4 provides novel insights into the relationship between TNFi exposure during pregnancy and the risk of serious infections in offspring during their first year of life. It is the first large-scale study to comprehensively evaluate the differential impact of TNFi exposure across trimesters, with a specific focus on the effects of TNFi with high versus low placental transfer. By analyzing data from a cohort of offspring born to mothers with chronic inflammatory diseases, this research offers new evidence on how third-trimester exposure, particularly to TNFi with high placental transfer, may increase the risk of serious infections compared to exposure limited to the first or second trimesters.

Manuscript #5 makes several important contributions to the understanding of rotavirus vaccination safety in infants exposed to TNFi *in utero*. It is the largest study to date to examine the association between rotavirus vaccination and diarrhea-associated healthcare visits in this population, providing robust evidence on the absence of increased risk following vaccination. The findings are particularly notable given the focus on TNFi-exposed infants in the third trimester and those exposed to high placental transfer TNFi, addressing a critical gap in the literature. Our study reinforces recent updates to rheumatology guidelines, which conditionally recommend rotavirus vaccination during the first 6 months of life in TNFi-exposed offspring, based on very limited prior studies. The findings offer reassurance regarding the safety of the vaccine in this population and provide new data which will help strengthen future recommendations, informing clinical practice, and parental decision-making.

CONTRIBUTION OF AUTHORS

Dr. Évelyne Vinet developed the original research questions for this thesis. The contributions of co-authors to the manuscripts included in this thesis are as follows:

Manuscript #1.

Flatman LK, Malhamé I, Colmegna I, Bérard A, Bernatsky S, Vinet É. Tumour necrosis factor inhibitors and serious infections in reproductive-age women and their offspring: a narrative review. Scand J Rheumatol. 2024;*53*(5), 295–306.

The idea behind this review originated from both Dr. Vinet and myself. I performed a review of the literature and drafted the first version of the manuscript. Drs. Vinet, Malhamé, Colmegna, Bérard, and Bernatsky provided important suggestions for revision. All authors were involved in revising the article for important intellectual content.

Manuscript #2.

Flatman LK, Beauchamp ME, St-Pierre Y, Malhamé I, Basso O, Bérard A, Bernatsky S, Vinet É. Tumour Necrosis Factor Inhibitors and Risk of Serious Infections in Pregnant Women with Chronic Inflammatory Diseases. *Under review with ACR Open Rheumatology (12 March 2025).*

The original idea behind this paper originated from Dr. Vinet. I created the cohort creation protocol, and Y St-Pierre built the cohort. I performed the data analysis with input from ME Beauchamp. I further drafted the first versions of the manuscript. Dr. Vinet reviewed the first versions of the manuscript before all authors provided important suggestions for revision on subsequent versions. All authors were involved in revising the article for important intellectual content.

Manuscript #3.

Flatman LK, Bernatsky S, Bérard A, Vinet É. Patterns of Use and Discontinuation for Tumour Necrosis Factor Inhibitors in Pregnant Women: Insights from a Real-World Sample. *Under review with the Journal of Rheumatology (14 January 2025).*

The idea behind this paper originated from both Dr. Vinet and myself. I performed the descriptive data analysis and drafted the first versions of the manuscript. Drs. Vinet, Bernatsky,

and Bérard provided important suggestions for revision. All authors were involved in revising the article for important intellectual content.

Manuscript #4.

Flatman LK, Bernatsky S, St-Pierre Y, Beauchamp ME, Malhamé I, Bérard A, Vinet É. Serious Infections in Offspring Exposed to Tumour Necrosis Factor Inhibitors During Pregnancy: Comparison of Timing During Pregnancy and Placental Transfer. *To be submitted to Annals of Rheumatic Diseases.*

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Manuscript #5.

Flatman LK, Beauchamp ME, St-Pierre Y, Malhamé I, Bérard A, Bernatsky S, Vinet É. Diarrhea Events in Offspring Exposed to TNF Inhibitors & Rotavirus Vaccine. *To be submitted to Annals of Rheumatic Diseases.*

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LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ADA	Adalimumab
AGA	American Gastroenterological Association
AIC	Akaike information criterion
AS	Ankylosing Spondylitis
BCG	Bacillus Calmette–Guérin
bDMARD	Biologic DMARDs
BIC	Bayesian information criterion
BMI	Body mass index
CD	Crohn's disease
csDMARDs	Conventional DMARDs
CI	Confidence interval
CIHR	Canadian Institutes of Health Research
CPT	Current Procedural Terminology
CRA	Canadian Rheumatology Association
CZP	Certolizumab pegol
DAG	Directed acyclic graph
DMARDs	Disease-modifying antirheumatic drugs
ETN	Etanercept
EULAR	European Alliance of Associations for Rheumatology
Fc	Fragment crystallizable region
FDA	Food and Drug Administration
GLM	Golimumab
HR	Hazard ratio
IBD	Inflammatory bowel disease
ICD	International Classification of Diseases
IFX	Infliximab
IgG	Immunoglobulin G
IRR	Incidence rate ratio
JAK	Janus kinase

LRT	Likelihood ratio test
MMR	Measles, mumps, rubella
NDC	National Drug Codes
OR	Odds ratio
PROM	Premature rupture of membranes
PS	Propensity score
PsA	Psoriatic arthritis
PsO	Psoriasis
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
RR	Relative risk
RV1	Monovalent rotavirus vaccine (Rotarix)
RV5	Pentavalent rotavirus vaccine (RotaTeq)
SES	Socioeconomic status
Th1	T-lymphocyte helper 1
Th2	T-lymphocyte helper 2
TNF	Tumour necrosis factor
TNF-α	Tumour necrosis factor-alpha
TNFi	Tumour necrosis factor inhibitor
TNFR	TNF receptor
TNFR1	TNF receptor type 1
TNFR2	TNF receptor type 2
UC	Ulcerative colitis
US	United States

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CHAPTER 1 - INTRODUCTION

"Will my medication harm my pregnancy? What about my baby?" Questions from mothers with chronic inflammatory diseases

Mothers almost universally worry that medication may harm their pregnancy and their babies.[1] This concern is greatest among women with chronic inflammatory diseases, who are often prescribed immunomodulators like tumour necrosis factor inhibitors (TNFi) to manage their symptoms and limit flares.[2,3] TNFi target the immune system and are prescribed to roughly 20% of pregnant women suffering from chronic inflammatory diseases, such as rheumatoid arthritis (RA) (Table 1.1.1).[4]

Table 1.1.1 US Food and Drug Administration (FDA) approved TNFi medications

Name	Brand name	Date of FDA approval	Dosage form (injection type)	FDA approved indications
infliximab	Remicade[5]	August 1998	Intravenous	CD, RA, AS, PsA, UC, PsO
etanercept	Enbrel[6]	November 1998	Subcutaneous	RA, PsA, AS, PsO
adalimumab	Humira[7]	December 2002	Subcutaneous	RA, PsA, AS, CD, PsO, UC
certolizumab pegol	Cimzia[8]	April 2008	Subcutaneous	CD, RA, PsA, AS, PsO
golimumab	Simponi[9]	April 2009	Subcutaneous	RA, PsA, AS, UC
golimumab	Simponi Aria[10]	July 2013	Intravenous	RA, PsA, AS

Abbreviations: AS, ankylosing spondylitis; CD, Crohn's disease; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; UC, Ulcerative Colitis.

The benefit of TNFi drugs is their ability to control RA and other chronic inflammatory diseases that occur in reproductive years, including Crohn's disease, ankylosing spondylitis (AS), and psoriatic arthritis (PsA). However, these drugs may be associated with infections in people who take TNFi.[4] The first manuscript in this thesis provides a literature review on the relevant research surrounding TNFi and serious infections and the third manuscript provides a descriptive analysis of TNFi patterns in pregnant women. Data on risks in pregnant women has been understudied due to the exclusion of pregnant patients from clinical trials and since pregnant women are underrepresented in observational studies. Thus, the first objective of this thesis was to ***assess the risk of serious infections during pregnancy and postpartum in women with chronic inflammatory diseases exposed to TNFi compared with unexposed women***. Specifically, I wanted to answer the question of whether women with chronic inflammatory diseases who use

TNFi during pregnancy have an increased risk of infections i) during pregnancy and ii) within 90 days of delivery, compared to those not using TNFi.

Offspring exposed early *in utero* to TNFi may also experience immunosuppression and subsequent serious infections in their first year of life.[11-14] This is a result of TNFi entering the fetal bloodstream at different concentrations. Based on the concentration of TNFi entering the fetal blood, these drugs can be stratified as "high" or "low" subtypes.[2,15-20] Data on serious infections in offspring separated by TNFi subtypes do not exist. A better understanding of the potential risks of each subtype is critical for delivering safe care to newborns. The lack of available research leads to the second objective of this thesis, which was to ***evaluate the risk of serious infections during the first year of life in children born to women who used TNFi during pregnancy compared with children born to unexposed women with chronic inflammatory diseases***. This answers the question, "Do children born to women with chronic inflammatory diseases who are exposed *in utero* to TNFi have an increased risk of serious infections in their first year of life compared to those unexposed?" I also wanted to ***assess if the risk of serious infections in TNFi-exposed offspring differs according to TNFi subtypes*** (i.e. high vs low placental transfer). Here, I answer the question, "Does infection risk among TNFi-exposed neonates differ depending on the TNFi subtype?"

As TNFi can be detected in infants for as long as 6 months, adverse effects may occur into early life. Issues thus arise with routine childhood immunizations, particularly the live vaccine for rotavirus, which uses weakened viruses to create lasting immune responses.[14] This key vaccination is meant to prevent rotaviral gastroenteritis, a common serious illness in newborns. In newborns with suppressed immune systems, as may occur with *in utero* TNFi exposure, live vaccines could potentially initiate a systemic spread of the weakened viral vaccine vector, leading to infection, as seen in a 2010 case report of a child exposed *in utero* to TNFi who died after experiencing an infection after a live vaccine (Bacillus Calmette-Guérin, BCG, vaccine).[14,21] This report caused Canadian, European, and American rheumatology guidelines to recommend withholding rotavirus vaccine in offspring exposed i*n utero* to any TNFi until 6 months of age instead of routine immunization starting at 2 months.[2,3,22] Unfortunately, this alternative approach also presents risks, as rotavirus is a common, severe form of gastroenteritis in unvaccinated infants. Therefore, there is the possibility that the risk of delaying the vaccine is greater than the risk of vaccine complications. However, there is no data on rotavirus disease after vaccination or the impact of

postponing vaccines in TNFi-exposed offspring. Thus, it is imperative to provide quality data to inform current guidelines to minimize these infectious disease complications. This leads to the final objective of the thesis, which was to ***examine the risk of diarrhea-associated events in children exposed in utero to TNFi who receive the rotavirus vaccine in their first 6 months of life, compared with those who are not vaccinated by 6 months.*** This answers the question, "Do children exposed *in utero* to TNFi who receive their rotavirus vaccine at the routine schedule before 6 months of age have a higher risk of diarrhea-associated healthcare events than TNFi-exposed offspring who receive their delayed rotavirus vaccine after 6 months of age?"

CHAPTER 2 - LITERATURE REVIEW

2.1 Preamble to Manuscript #1

In manuscript #1, I discuss evidence surrounding the use of TNFi and the risk of serious infections, and I provide a comprehensive review of the literature on this subject in reproductive-age women and their offspring. This manuscript, entitled "Tumour necrosis factor inhibitors and serious infections in reproductive-age women and their offspring: a narrative review", was published in the Scandinavian Journal of Rheumatology (2024; 53(5), 295–306). A reprint of this article is included in Appendix B. Additional evidence on this topic is presented below.

2.1.1 Tumour necrosis factor-alpha

TNF-alpha is produced by multiple cells, such as macrophages, T and B lymphocytes, neutrophils, endothelial cells, and natural killer cells.[23] TNF-alpha is initially produced as a type II transmembrane protein, which is cleaved to form an active soluble form.[23] Once produced, TNF-alpha can bind to two cell-surface receptors, TNF receptor type 1 (TNFR1; CD120a; p55/60) and TNF receptor type 2 (TNFR2; CD120b; p75/80).[24] These two receptors bind membrane-bound TNF-alpha, soluble TNF-alpha, and a secreted homotrimeric molecule lymphotoxin-alpha.[24] TNFR1 is located on most human cells and contains a death-domain motif, while TNFR2 is primarily situated on immune system and endothelial cells.[24] Due to a lack of structural homology, the two TNF receptors activate different signalling pathways when bound by TNF-alpha.[23] TNFR1 can induce apoptosis by activating the death domain, while both receptors can promote inflammation, host defence, cell survival and proliferation by activating gene transcription.[23]

TNF-alpha and TNFR signalling pathway plays a role in the defence against infections and is required for the activation of phagocytosis, leukocyte recruitment, production of regulatory cytokines, T-cell mediated response, and the formulation of granuloma.[25] TNF- or TNFR1-deficient mice had an increased susceptibility to intracellular pathogens and reduced inflammatory responses to bacterial endotoxins.[23,24] This highlights the relevance of TNF-alpha in establishing proper inflammatory responses and conferring immunity. TNFi inhibit TNF-alpha and people with chronic inflammatory diseases are often prescribed TNFi to manage their symptoms and limit flares to reduce inflammation and joint destruction (Figure 2.1.1).

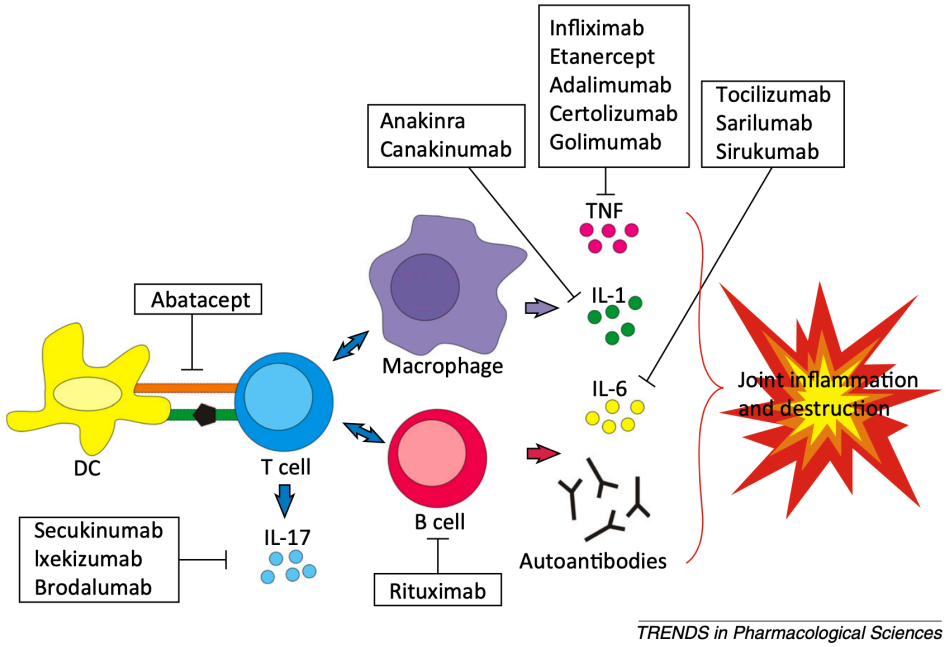

Figure 2.1.1 Overview of biological treatments targeting proinflammatory cells and cytokines
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2.1.2 Tumour necrosis factor inhibitor (TNFi) exposure and serious infections

In addition to the two meta-analyses highlighted in the manuscript, multiple other studies investigated the association between TNFi and serious infections in adults taking TNFi, including a 2016 meta-analysis of 71 randomized controlled trials (RCTs) with a combined total of 22,760 RA, PsA, and AS patients who examined the risk of infections (any or serious requiring hospitalization) for adults using TNFi.[26] Thirty-seven of the included RCTs had any infection as an outcome measure. These 37 studies included 12,796 adults and found that exposure to TNFi was associated with at least one infection during the study period (odds ratio, OR, 1.20; 95% confidence interval, CI, 1.10, 1.30).[26] Similar results were found when the authors looked at 58 RCTs involving 20,796 patients who had serious infections, defined as infections requiring antimicrobial therapy and/or hospitalization, as an outcome (OR 1.41, 95% CI 1.16, 1.73).[26] Most of these studies' exposure groups were TNFi in combination with a traditional disease-modifying antirheumatic drugs (DMARD), such as methotrexate. Furthermore, they directly compared studies with different exposure groups and also different lengths of follow-up (range 1-36 months).

Observational studies that specifically focused on infections requiring hospitalization reported an increased risk associated with TNFi. Curtis et al. performed a retrospective cohort study of US patients with RA from a large US healthcare organization, comparing 2,393 persons

using TNFi (etanercept, infliximab, or adalimumab) with 2,933 persons using methotrexate.[27] This study reported a 2-fold higher risk of hospitalization with a bacterial infection among patients on TNFi treatment (hazard ratio, HR, 1.9; 95% CI 1.3, 2.8).[27] The most common bacterial infections were pneumonia and cellulitis.[27] A prospective clinical cohort study including German RA patients registered in a biologic registry also found that RA patients treated with biologics had a higher risk of infections requiring hospitalization. This risk was concentrated in patients on TNFi. The risk of serious infections in users of etanercept (n=512) was over 2 times the risk in the control group (conventional DMARDs, csDMARDs; n=601) (adjusted relative risk, RR, 2.16; 95% CI 0.9, 5.4), and in those using infliximab (n=346), the risk was 2.1 times the risk in the control group (RR 2.13; 95% CI 0.8, 5.5).[28] Respiratory tract infections were more common in TNFi users (infliximab or etanercept) than controls.

An administrative database study by Bernatsky et al. looking at TNFi (infliximab or etanercept) exposed RA subjects in Quebec (n=261) and infections requiring hospitalization found an incidence rate ratio (IRR) of 1.93 compared to controls; however, their confidence interval was wide and included the null value (95% CI 0.70, 5.34).[29] This is likely due to the small sample size, given these drugs had only been available in Canada for one year at the time the study was performed. Using the British biologics registry, Dixon et al. found no statistically significant difference in incidence rate of serious infections (defined as those that led to hospitalization or death or required intravenous antibiotic treatment) in a TNFi (etanercept, infliximab, or adalimumab) treated RA cohort (n=7,664) compared with RA patients taking traditional (non-biologic) DMARDs (n=1,354). In this study, the confidence interval was wide and included the null (IRR 1.03; 95% CI 0.68, 1.57).[16] The most common site of infection was the lower respiratory tract. A larger study by Galloway et al. using the British biologics registry found that RA users of TNFi (etanercept, infliximab, or adalimumab; n=11,881) had a non-statistically significant increased rate of serious skin and soft tissue infections (defined as those that led to hospitalization or death or that required intravenous antibiotic treatment) compared to traditional DMARD users (n=3,673; HR 1.3; 95% CI 0.8, 2.2).[30] A Brazilian clinical registry study including RA and spondyloarthritis (AS, PsA) patients found that serious infections were more common among TNFi (infliximab, adalimumab, golimumab, etanercept, certolizumab) users (n=1,698) than among controls (csDMARDs; n=572) (IRR 2.96; 95% CI 2.01, 4.36).[31]

All of these studies suggest that there may be an increased risk of infection associated with TNFi use in non-pregnant patients with chronic inflammatory diseases. I was particularly interested in whether this risk may be further elevated during pregnancy. The summary of our findings is described in the following manuscript.

2.2 Manuscript #1: Tumour Necrosis Factor Inhibitors and Serious Infections in Reproductive-Age Women and Their Offspring: A Narrative Review

2.2.1 Title Page

Tumour Necrosis Factor Inhibitors and Serious Infections in Reproductive-Age Women and Their Offspring: A Narrative Review

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Category: Review

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2.2.2 Abstract

Tumour necrosis factor inhibitors (TNFi) are commonly used to treat patients with chronic inflammatory diseases and function by inhibiting the pro-inflammatory cytokine tumour necrosis factor alpha. Although beneficial in reducing disease activity, they are associated with an increased risk of serious infections. Data on the risk of serious infections associated with TNFi use during the reproductive years, particularly in pregnancy, are limited. For pregnant women, there is an additional risk of immunosuppression in the offspring due to TNFi's active trans-placental passage ability, which increases in the second and third trimesters. Several studies explored the risk of serious infections with TNFi exposure in non-pregnant and pregnant patients and offspring exposed in utero, indicating an increased risk in non-pregnant patients and a potentially increased risk in pregnant patients. The studies on TNFi-exposed offspring showed conflicting results between in utero TNFi exposure and serious infections during the offspring's first year. Further research is needed to understand differential risks based on TNFi subtypes. Guidelines conditionally recommend the rotavirus vaccine before 6 months of age for offspring exposed to TNFi in utero, but more data are needed to support these recommendations due to limited evidence. This narrative review provides an overview of the risk in non-pregnant patients and summarizes evidence on how pregnancy can increase vulnerability to certain infections and how TNFi might influence this susceptibility. This review focuses on the evidence regarding the risk of serious infections in pregnant patients exposed to TNFi and the risk of infections in their offspring.

2.2.3 Introduction

Tumour necrosis factor inhibitors (TNFi) are powerful immunomodulating drugs widely used in chronic inflammatory diseases, including during pregnancy (1). While TNFi have been associated with increased infections in non-pregnant patients, data on pregnant women are lacking. Given that pregnant women are already at a higher risk of infections in pregnancy and postpartum due to several immune system changes, this narrative review primarily aims to explore the association between TNFi use during pregnancy and the risk of severe infections for both pregnant patients and their offspring. This review also provides an overview of the risk in non-pregnant patients and briefly summarizes evidence on how pregnancy can increase vulnerability to certain infections and how TNFi might influence this susceptibility. Relevant manuscripts were identified for this narrative review by searching through PubMed for original articles (including clinical trials, observational studies, and meta-analyses) combining search terms related to serious infections, TNFi use in pregnant and non-pregnant subjects, as well as exposed offspring. The reference lists of identified papers were also searched for additional articles. From this selection, the most relevant studies were summarized to describe the current literature and identify knowledge gaps pertaining to serious infections and TNFi use during the reproductive years.

2.2.4 Tumour necrosis factor-alpha and the immune system

TNF-alpha, a pro-inflammatory cytokine, is produced by multiple cells and through several critical cell functions (e.g., cell survival, differentiation, proliferation, and apoptosis) is involved in immunity and inflammation (2). TNF-alpha and TNF receptor (TNFR) signalling pathway plays a role in the defence against infections (3). In response to bacteria, specifically the lipopolysaccharide on the bacteria's cell surface and other bacterial products, large amounts of cytokines and soluble TNF-alpha are released by macrophages to initiate inflammation activating phagocytosis, leukocyte recruitment, and eradicating the bacteria (4). A similar mechanism protects against parasites (3). TNF-alpha also has antiviral activity that can induce resistance in uninfected cells or selectively kill virus-infected cells directly or by producing interferons (3).

2.2.5 Role of TNF-alpha in chronic inflammatory diseases

TNF-alpha is also pathogenic in chronic inflammatory diseases. In diseases such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), psoriasis (PsO), psoriatic arthritis

(PsA), and ankylosing spondylitis (AS), there are excessive amounts of TNF-alpha and disease activity correlates with high TNF-alpha serum levels (5). These immune-mediated inflammatory diseases are prevalent in the United States (US) and Europe at 5-7% (6) and are treated with non-steroidal anti-inflammatory drugs, glucocorticoids, and disease-modifying anti-rheumatic drugs (DMARDs) comprised of conventional DMARDs (csDMARDs; e.g. hydroxychloroquine, methotrexate, sulfasalazine), biologic DMARDs (bDMARDs; e.g. TNFi, interleukin-6 receptor inhibitors, anti-integrin agents, interleukin 12/23 antagonists), and targeted synthetic DMARDs (e.g. Janus kinase (JAK) inhibitors) (7, 8). Biologic DMARDs are most commonly prescribed to patients with active disease who failed csDMARDs.

Five TNFi were approved for use in the US starting in 1998 with infliximab (9). Since then, etanercept (10), adalimumab (11), certolizumab (12), and golimumab (13, 14) have been approved. TNFi biosimilars were also approved in 2013 as cost-effective alternatives with similar properties and mechanisms of action as originators (15, 16). TNFi are administered via subcutaneous injection or intravenous infusion. Most TNFi are monoclonal immunoglobulins G (IgG) with a fragment crystallizable (Fc) region (adalimumab, infliximab, golimumab), while etanercept is a fusion protein comprising a TNF receptor and the IgG Fc region, and certolizumab is a pegylated Fab fragment of an anti-TNF monoclonal antibody without an Fc region (15, 17).

The mechanisms of action for the five TNFi differ slightly (18). Adalimumab and infliximab prevent the interaction of TNF-alpha with the two cell-surface TNF receptors by binding to soluble TNF-alpha and possibly membrane-bound TNF-alpha to reduce macrophage and T-cell function. Golimumab has a high affinity for both forms of TNF-alpha and inhibits it from binding to its receptors stopping TNF-initiated signalling cascades. Etanercept blocks TNF-alpha activity and lymphotoxin-alpha, and certolizumab neutralizes both forms of TNF-alpha.

2.2.6 TNFi exposure may lead to serious infections

TNFi use in chronic inflammatory diseases may result in serious infections (Table 2.2.1). Highlighting two meta-analyses, one published in 2021 which included 18 observational studies and RCTs with 37,693 patients with RA, PsA, and AS showed that TNFi use is associated with an increased risk of serious infections (odds ratio, OR, 1.72; 95% confidence interval, CI, 1.56, 1.90) (19). However, this meta-analysis combined studies with different TNFi exposures (e.g. adalimumab only vs infliximab or etanercept; TNFi + DMARDs), different follow-up periods

(between 70 days to 2 years), and only looked at TNFi use in the context of RA, PsA, and AS. Most studies were neither specifically designed nor powered to evaluate serious infections associated with TNFi. Finally, another meta-analysis of 44 RCTs in patients with IBD found that when they focused on the fourteen low risk of bias studies, the use of biologics (TNFi, natalizumab, vedolizumab) significantly reduced the risk of serious infections compared to placebo groups (OR 0.56; 95% CI 0.35-0.90) (20). Vedolizumab is an anti-integrin monoclonal antibody with a local effect on the gut and not a systemic immunosuppressant, thus potentially having a lower risk of serious infections than TNFi (21). As a result of the pooling of studies concerning TNFi and vedolizumab, the measure of effect for biologics and serious infections may be diluted. The majority of these studies suggest that there may be an increased risk of infection associated with TNFi use in non-pregnant patients with chronic inflammatory diseases. This risk may be further elevated during pregnancy.

2.2.7 Infections during pregnancy

Pregnant women are disproportionally affected by infections due to an increase in susceptibility and/or severity associated with specific organisms, such as the bacteria Listeria, the parasite Plasmodium falciparum (malaria), and certain viruses, including influenza, hepatitis E, herpes simplex, and SARS-CoV-2 (29, 30). These observed increases in susceptibility and/or severity may be due to the shift in T-lymphocyte helper (Th) subsets from Th1 to Th2 immunity during pregnancy (29). Th2 cells suppress the cytotoxic T-lymphocyte response, decreasing cell-mediated immunity, which could explain part of the increased severity of certain infections in pregnancy (29). A study in the general population found that 3% of pregnant women are hospitalized for an infection during pregnancy (31). During the postpartum period, 6%-20% of women experienced an infection, with the variability in risk explained by the type of delivery (i.e. vaginal vs caesarean delivery) (32-36). The most common postpartum infections were mastitis, urinary tract infections, endometritis, and surgical site infections (32-34).

In patients with chronic inflammatory diseases, disease activity varies over time, often with periods of remission or low disease activity. However, disease flares are frequent (37). Specifically, flares during pregnancy are not uncommon and may be associated with adverse pregnancy outcomes. A study by Gerardi et al. found that the risk of flares during pregnancy in women with RA was associated with discontinuing bDMARDs early in pregnancy (OR 2.86; 95%

CI 1.11, 8.32) (38). They found links between pregnancy flares and preterm delivery (OR 4.63; 95% CI 1.03, 20.83) (38). Based on the available literature, guidelines have recommended continuing TNFi during pregnancy (1, 39-41). Studies have shown no increased risk of pregnancy complications, such as miscarriages, fetal deaths, congenital malformations, low birth weight, and/or preterm births (40-42). As a result, they are prescribed in up to 20% of pregnant women with chronic inflammatory diseases, representing a 3-fold increase over the past ten years (43).

2.2.8 Risk of serious infections associated with TNFi use in pregnancy

Pregnant women are commonly excluded from clinical trials (44). They are often underrepresented in observational studies due to possible challenges surrounding the recruitment and retention of pregnant women. The largest studies on serious infections in pregnant women with chronic inflammatory diseases are observational and population-based (Table 2.2.2). An observational cohort study using US administrative data identified 776 women with RA, AS, PsA, or IBD receiving TNFi during pregnancy (45). Pregnant TNFi users in combination with steroids or non-biologics had a higher risk of serious infections requiring hospitalization (such as bacterial or opportunistic infections) versus pregnant women on non-biologics, but the 95% CI was wide (hazard ratio, HR, 1.36; 95% CI 0.47, 3.93) (45). A similar study using a French national health system database focusing on 1457 pregnant women with IBD found that exposure to TNFi (infliximab, adalimumab, golimumab, or certolizumab) during pregnancy was associated with in-hospital infections (OR 1.25; 95% CI 1.04, 1.50), and when looking at third-trimester exposure (>24 weeks), the association was similar (OR 1.31; 95% CI 1.09, 1.59) (46). These two studies restricted the analyses to only the gestational period, excluding postpartum infections resulting from hospitalization for childbirth. They also classified TNFi as a fixed exposure, potentially introducing immortal-time bias as the unexposed time when the patient is not taking the medication may be misclassified as exposed (47). Therefore, if a serious infection occurs when the woman is not currently taking TNFi but was previously during the study period, the outcome will be misclassified as an exposed outcome and associated with the exposure instead of being classified as unexposed (48). Similarly, a multi-centre cohort study in Europe looking at gestational infections in women with IBD found that the proportion of infections in patients taking TNFi during gestation (n=388) was higher than in those not on TNFi (n=453) (4.1% vs. 0.9%; p=0.002), but did not look at the postpartum period (49).

More evidence among pregnant women taking TNFi is needed regarding the risk of serious infections during pregnancy and postpartum. Analyzing infectious events related to hospitalization for delivery is important. Women with chronic inflammatory diseases have a 2-fold higher rate of caesarean delivery (approximately 40% of affected women), and infection complicates up to 10% of caesarean deliveries among healthy women (36, 50). However, most studies only look at infections occurring during gestation. A Canadian population-based cohort study of 6,218 women with autoimmune diseases focused on the postpartum period could not find an association between biologics (TNFi, abatacept, alefacept, anakinra, belimumab, natalizumab, rituximab, tocilizumab, and ustekinumab; n=90) and an increased risk of serious maternal postpartum infections (OR 0.79; 95% CI 0.24, 2.54) (51). However, the exposure and outcome were rare, resulting in potentially unstable estimates. Ultimately, assessing infection risk in women exposed to TNFi throughout pregnancy and postpartum will improve our understanding of these medications and inform guidelines to optimize pregnancy management for patients and their offspring.

2.2.9 Placental transport of TNFi during pregnancy

During pregnancy, there is the trans-placental passage of maternal circulating IgG proteins. During the first trimester, the transfer occurs mainly via simple diffusion across the placenta, while active transfer begins around gestational week 16 and increases throughout pregnancy, mediated by neonatal Fc receptors (52). Between 17-20 weeks, the fetal to maternal level of IgG is 10% of the maternal concentration, while at term, it is 130% of maternal levels (53). All TNFi contain an Fc region except certolizumab; therefore, most TNFi are actively transported across the placenta via the fetal Fc receptors, enter the fetus' bloodstream, and may reach higher blood levels in the fetus than in the mother due to active placental transfer and the biological half-life being longer in newborns than in adults (54). Infliximab, adalimumab, and golimumab have the highest trans-placental transfer (reaching cord blood levels of, respectively, 160%, 150%, and 121% of maternal blood levels), while etanercept and certolizumab display the lowest passage (cord blood levels of, respectively, 4% and <0.25% of maternal blood levels) (15, 17, 55-58). As fetuses can be exposed to therapeutic (and potentially supra-therapeutic) TNFi doses, TNFi could theoretically cause immunosuppression in the offspring (59).

Furthermore, due to differences in placental transfer ability as a result of the differing TNFi structures, evaluating the potential risks of each subtype is critical for delivering appropriate care

to mother and child. Similarly, due to the fear of excessive immunosuppression in the offspring, many experts recommend cessation of TNFi (primarily infliximab, adalimumab, and golimumab) during late pregnancy (late second or early third trimester) (1, 39, 41). Specifically, the American College of Rheumatology (ACR) conditionally recommends (with low evidence) continuing infliximab, etanercept, adalimumab, and golimumab prior to and during pregnancy (41). The European Alliance of Associations for Rheumatology (EULAR) suggests the continuation of infliximab and adalimumab up to gestational week 20 and up to gestational week 30-32 for etanercept unless these drugs are indicated, in which case they can be used throughout pregnancy (1). Due to limited evidence, EULAR recommends considering alternative medications instead of continuing golimumab throughout pregnancy (1). The American Gastroenterological Association (AGA) suggests continuing scheduled dosing throughout all three trimesters for adalimumab, golimumab, and infliximab, but if possible, recommends planning the final dose according to the drug half-life to minimize placental transfer near the time of delivery (39). As a result of certolizumab's low placental transfer ability, all three guidelines (ACR, EULAR, AGA) strongly recommend continuing certolizumab prior to and throughout pregnancy (1, 39, 41).

2.2.10 Risk of serious infections in TNFi-exposed offspring

In offspring exposed in utero to known immunosuppressants (e.g. TNFi), the risk of serious infections may differ from unexposed children. In the general population, the risk of infections requiring hospitalization during the first year of life is around 2% (60, 61). The studies below demonstrate conflicting evidence regarding the association between TNFi-exposed offspring and the risk of serious infections (Table 2.2.3).

Exposure to biologic drugs, not restricted to TNFi. Three studies and one meta-analysis evaluated the association between biologic exposure in offspring and the risk of serious infections; however, these studies did not focus solely on TNFi as they also included anti-integrins and anti-interleukin 12/23 (51, 62-64). A meta-analysis of 10 studies that included infants exposed in utero to biologics used to treat IBD, including TNFi, showed no significant increase in infection-related hospitalization risk during exposed children's first year of life compared to unexposed children (OR 1.33; 95% CI 0.95, 1.86) (62). The meta-analysis included a study on vedolizumab that found the risk of serious infections to be 0.37 (95% CI 0.09, 1.48) (65). A cohort study (64) also combined TNFi with other biologics, including vedolizumab, possibly affecting the observed

effect of biologics and serious infections. The PIANO (Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes) prospective observational study in the US found no increased risk of infection requiring hospitalization in exposed offspring (n=848) compared to unexposed offspring (n=423) when assessing the use of biologics (TNFi, anti-integrin, and anti–interleukin-12/23) (OR 0.92; 95% CI 0.70, 1.20) (64). However, it's worth noting that 5% (n=41) of the biologic-exposed offspring were exposed to vedolizumab, which could have influenced the results. Another study by Tsao et al. in a cohort of Canadian offspring born to mothers with RA, IBD, PsO, PsA, AS, juvenile idiopathic arthritis, and systemic autoimmune rheumatic diseases showed no association between in utero biologics exposure and serious infections requiring hospitalization (OR 0.56; 95% 0.17, 1.81) (51). Chambers et al. investigated pregnant women with RA and their offspring in the US and Canada but found no association between biologic (unspecified) exposed or unexposed offspring (RR 0.71; 95% CI 0.30, 1.71) regarding the risk of serious infection (63). This lack of association remained even after analyzing only offspring exposed after gestational week 24 (n=155; RR 1.00; 95% CI 0.40, 2.48) and after gestational week 32 (n=143; RR 0.90; 95% CI 0.34, 2.39) (63).

Exposure to TNFi, combining high and low placental transfer subtypes. A meta-analysis, including 39 studies on pregnancy and neonatal outcomes in women with IBD, RA, and PsO, found a small increased risk of infections in newborns in the TNFi-exposed group compared to diseased controls (OR 1.12; 95% CI 1.00, 1.27) when looking at 7 includes studies which focused on the risk of infections in offspring born to mothers with IBD and RA (66). The range of TNFi-exposed offspring among these 7 studies was 15 to 1,457 (total=2,507). However, this analysis had some limitations, such as not including certain studies, combining different exposure definitions and TNFi subtypes, only including offspring born to mothers with IBD and RA, and comparing outcomes that looked at any infection or infection leading to hospitalization. Future analyses are needed to explore the risk of serious infections in all chronic inflammatory disease groups according to specific TNFi subtypes.

A population-based cohort study involving 1,027 children born to mothers with RA, PsO, PsA, AS, and IBD in Denmark, Finland, and Sweden found an increased risk of infant hospital admissions for infection in their first year associated with TNFi use (incidence rate ratio, IRR, 1.43; 95% CI 1.23, 1.67) compared to the general population (67). Specifically, the use of adalimumab (IRR 1.35; 95% CI 1.00, 1.83), etanercept (IRR 1.37; 95% CI 1.05, 1.78), and

certolizumab (IRR 1.50; 95% CI 1.13, 1.98) were associated with first-year hospitalization for infection.

Another study using Danish health registries revealed an elevated risk of any infections in children born to mothers treated with TNFi in Denmark (n=493) compared to unexposed children, including children born to healthy women (n=728,055) (HR 1.44; 95% CI 1.19, 1.74) (68). This elevated risk was observed for urological/gynecological, respiratory, and other infections (68). Alternatively, an administrative database study did not find an increased risk of hospitalization for infection within the first 12 months of life in American offspring born to mothers with RA exposed to TNFi during pregnancy (n=380) compared to unexposed RA offspring (n=2,476) (OR 1.4; 95% CI 0.7, 2.8) (69). However, this study might have been underpowered due to its smaller sample size. Regarding offspring born to mothers with IBD exposed to TNFi, except etanercept, in utero, two studies did not find associations with an increased risk of infection during their first year of life compared to TNFi-unexposed children born to mothers with IBD (46, 70).

In specific studies focusing on exposure to infliximab, adalimumab, or certolizumab, a multi-centre European study of children born to IBD mothers did not find an association between TNFi and infections that required hospital admissions in the first year of life (HR 1.2; 95% CI 0.8, 1.8) (49). Similarly, another study from France and Belgium on IBD offspring found a non-significant difference in the proportions of neonatal infection between the TNFi-exposed group and the control group (p=0.73) (71).

Exposure to high placental transfer TNFi. In utero exposure to high placental transfer TNFi (infliximab or adalimumab) was assessed in several studies. De Lima et al. studied TNFi-exposed children born to IBD mothers (n=55) in the Netherlands and compared them with unexposed non-IBD offspring (n=459) but found no statistically significant difference in infections requiring hospitalization (p=0.49) (72). Kanis et al. also examined 1000 IBD offspring from the Netherlands and found an adjusted IRR of 1.66 (95% CI 0.91, 3.04) for TNFi-exposed offspring compared to unexposed offspring in terms of hospital admission due to infection (73). Finally, a Czech Republic multi-centre study found no association between TNFi-exposed IBD offspring and infection leading to antibiotic treatment and/or hospitalization compared with the general population (OR 0.86; 95% 0.32, 2.32) (74). Chambers et al. investigated adalimumab exposure in offspring born to mothers with RA and Crohn's Disease in a pregnancy registry in the US and Canada, finding no significant differences in the risk of serious infections when compared to both diseased

unexposed children (RR 0.97; 95% CI 0.34, 2.77) and a healthy group (RR 1.77; 95% CI 0.62, 5.05) (75).

Due to the diverse study designs, including the type of TNFi and whether other biologics were included, the comparison groups, and maternal chronic inflammatory disease diagnoses, direct comparison across studies is challenging. This leads to conflicting results, with some studies demonstrating a slight increase in the risk of serious infections while others could not establish a risk. Additionally, the studies may be underpowered to detect a clinically meaningful difference between exposed and unexposed groups. Finally, some studies analyzed the risk of serious infections according to individual TNFi; however, no known study, besides those from our group, separated TNFi according to placental transfer ability and compared the risk of infection across subtypes. Therefore, it is crucial to assess the TNFi subtypes separately, as their different trans-placental passage abilities may impact the infection risk during the child's first year of life.

2.2.11 In utero exposure to TNFi can delay rotavirus vaccine in offspring

TNFi can be detected in infants for up to 6 months (54). Thus, adverse events may occur, including those linked with routine childhood immunizations. Live vaccines such as rotavirus, Bacillus Calmette-Guérin (BCG), and measles, mumps, and rubella (MMR) use weakened viruses to create lasting immune responses (59). In patients with suppressed immune systems, like those exposed in utero to TNFi, live vaccines could lead to the systemic spread of the microorganism or virus with infection. This was described in a case report of a child exposed in utero to TNFi who developed a fatal infection at 4.5 months old after receiving the BCG vaccine at 3 months (59). Previous rheumatology guidelines recommended withholding rotavirus vaccine in offspring exposed in utero to any TNFi until 6 months of age instead of routine immunization starting at 2 months (1, 39, 41).

Most severe rotavirus disease, which can be fatal, occurs primarily among unvaccinated children aged 3-12 months old (76). In North America, the rotavirus vaccine is the only live vaccine administered before 6 months of age as part of the routine immunization schedule. Two oral live attenuated vaccines (with similar efficacy and safety) are available for the prevention of rotavirus disease, the pentavalent (RV5) and the monovalent (RV1) rotavirus vaccines. RV5 is administered at 2, 4, and 6 months of age, while RV1 is administered at 2 and 6 months (77, 78). Rotavirus vaccines effectively prevent rotavirus disease, reducing diarrhea-related events by >90%

(77, 78). Delaying vaccine administration until 6 months of age may be associated with a greater risk of diarrhea-associated morbidity. However, there are limited data on rotavirus disease after vaccination or the impact of postponing vaccines in TNFi-exposed offspring. The new 2022 ACR vaccination guidelines conditionally recommend administering the rotavirus vaccine within the first 6 months of life but are based on three observational studies with a combined 58 TNFi-exposed offspring (79). The small sample size of these studies highlights the need for larger ones. Thus, it is urgent to provide quality data to confirm the recommendations made by the 2022 guidelines to minimize complications and confusion.

2.2.12 Conclusion

Several studies investigated the risk of serious infections associated with TNFi exposure (either directly for pregnant or non-pregnant patients or in utero for offspring). Non-pregnant patients have an increased risk of infections associated with the use of TNFi. In pregnant patients, there is limited data during the gestational period and no data postpartum; however, available data suggest a potential increased risk. Concerning offspring exposed to TNFi in utero, multiple studies show small relative increases in risk with a small absolute difference. Knowing if the risk is differential according to TNFi subtypes and the potential risk of adverse maternal and fetal outcomes associated with switching TNFi subtypes before pregnancy would be very informative. Moreover, new guidelines conditionally recommend administering the rotavirus vaccine before 6 months of age in offspring exposed to TNFi in utero. This conditional recommendation is based on limited evidence, highlighting the need for more data to support these guidelines.

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2.2.13 References

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2.2.14 Tables

Table 2.2.1 Characteristics of systematic reviews and meta-analyses (n=3 studies) and observational studies (n= 6 studies) included in this review on serious infection outcomes in non-pregnant patients taking tumour necrosis factor inhibitors

Author	Design	Disease	Exposure	Comparison	Outcome	Size of the exposed population	Size of the unexposed population	Results
Bonovas et al., 2016 (20)	Systematic Review and meta-analysis (44 RCTs)	IBD	biologics (ADA, CTZ, GOL, IFX, natalizumab, vedolizumab)	Placebo	Infections associated with hospital admission	8627	5405	OR 0.56; 95% CI 0.35-0.90
Li et al., 2021 (19)	Meta-analysis of 18 observational studies and RCTs	RA, PsA, AS	ADA, CTZ, ETN, GOL, IFX	Without TNFi (controlled or placebo)	Infections requiring antimicrobial treatment and/or hospitalization	26,431	11,262	OR 1.72; 95% CI 1.56, 1.90
Minozzi et al., 2016 (22)	Systematic review and meta-analysis of 58 RCTs	RA, PsA, AS	ADA, CTZ, ETN, GOL, IFX	Placebo or no treatment, or multi-interventional therapies	Infections that require antimicrobial therapy and/or hospitalization	13,430	7,366	OR 1.41, 95% CI 1.16, 1.73
Bernatsky et al., 2007 (23)	Nested case-control; administrative database	RA	IFX, ETN	Controls who have not yet experienced the outcome	Infections requiring hospitalization	261		IRR 1.93; 95% 0.70, 5.34
Cecconi et al., 2020 (24)	Prospective cohort; Brazilian registry study	RA, AS, PsA	IFX, ADA, GOL, ETN, CTZ	csDMARDs	A serious adverse event was defined as a condition that causes death or is life-threatening, implies inpatient hospitalization or prolongation of an existing one, and involves persistent or significant disability or a congenital abnormality	1,698	572	IRR 2.96; 95% CI 2.01, 4.36
Curtis et al., 2007 (25)	Retrospective cohort; large United States healthcare organization	RA	ETN, IFX, ADA	Methotrexate	Hospitalization with a bacterial infection	2,393	2,933	HR 1.9; 95% CI 1.3, 2.8

Author	Design	Disease	Exposure	Comparison	Outcome	Size of the exposed population	Size of the unexposed population	Results
Dixon et al., 2006 (26)	Prospective cohort; British biologics registry	RA	ETN, IFX, ADA	Traditional DMARDs	Infections that led to hospitalization or death or required intravenous antibiotic treatment	7,664	1,354	IRR 1.03; 95% CI 0.68, 1.57
Galloway et al., 2012 (27)	Prospective cohort; British rheumatology biologics registry	RA	ETN, IFX, ADA	Traditional DMARDs	Serious skin and soft tissue infections defined as resulting in hospitalization, requiring intravenous antibiotics or causing death	11,881	3,673	HR 1.3; 95% CI 0.8, 2.2
Listing et al., 2005 (28)	Prospective cohort; biologics registry	RA	ETN, IFX	csDMARDs	Serious adverse event: a condition that causes death or is life-threatening, implies inpatient hospitalization or prolongation of an existing one and involves persistent or significant disability or a congenital abnormality	ETN: 512 IFX: 346	601	ETN: RR 2.16; 95% CI 0.9, 5.4 IFX: RR 2.13; 95% CI 0.8, 5.5

ADA, Adalimumab; AS, ankylosing spondylitis; CI, confidence interval; csDMARDs, conventional synthetic DMARDs; CTZ, Certolizumab pegol; DMARDs, disease-modifying anti-rheumatic drugs; ETN, Etanercept; GOL, Golimumab; HR, hazard ratio; IFX, Infliximab; IRR, incidence rate ratio; OR, odds ratio; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RCT, randomized controlled trial; RR, risk ratio.

Table 2.2.2 Characteristics of studies included in this review (n=4 studies) on serious infection outcomes in women taking tumour necrosis factor inhibitors during pregnancy

Author	Design	Disease	Exposure	Comparison	Outcome	Size of the exposed population	Size of the unexposed population	Results
Chaparro et al., 2018 (49)	Retrospective cohort	IBD	IFX, ADA, CTZ	Unexposed	Infection during pregnancy	388	453	4.1% (TNFi) vs. 0.9% (unexposed); p=0.002
Desai et al., 2017 (45)	Retrospective cohort	RA, AS, PsA, IBD	ADA, CTZ, ETN, GOL, IFX	Non-biologics	Composite of bacterial infection or opportunistic infection identified using discharge diagnosis codes from hospital admission records	776	816	HR 1.36; 95% CI 0.47, 3.93
Luu et al., 2018 (46)	Retrospective cohort	IBD	IFX, ADA, GOL, CTZ	Unexposed	Infections requiring hospitalization	1457	9818	OR 1.25; 95% CI 1.04, 1.50 3rd trimester: OR 1.31; 95% CI 1.09, 1.59
Tsao et al., 2019 (51)	Retrospective cohort	RA, IBD, PsO, PsA, AS, juvenile idiopathic arthritis, and systemic autoimmune rheumatic diseases	Abatacept, ADA, alefacept, anakinra, belimumab, CTZ, ETN, GOL, IFX, natalizumab, rituximab, tocilizumab, ustekinumab	Disease-matched women with no biologics	Serious infections requiring hospitalization during the postpartum period	90	6128	OR 0.79; 95% CI 0.24, 2.54

ADA, Adalimumab; AS, ankylosing spondylitis; CI, confidence interval; CTZ, Certolizumab pegol; ETN, Etanercept; GOL, Golimumab; HR, hazard ratio; IBD, inflammatory bowel disease; IFX, Infliximab; OR, odds ratio; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis.

Table 2.2.3 Characteristics of studies included in this review (n=16 studies) on serious infection outcomes in offspring exposed in utero to tumour necrosis factor inhibitors

Author	Design	Maternal disease	In utero exposure	Comparison	Outcome	Size of the exposed population	Size of the unexposed population	Results
Barenburg et al., 2021 (66)	Systematic Review and Meta-Analysis (7 studies)	IBD, RA, PsO	IFX, ADA, GOL, CTZ, ETN	Children born to diseased controls	Infections in newborns	2507	13,059	OR 1.12; 95% CI 1.00, 1.27
Bröms et al., 2020 (67)	Retrospective Cohort	RA, PsO, PsA, AS, IBD	ETN, IFX, ADA, CTZ, GOL	Children of the general population	Hospital admissions for infection in the first year	1027	1,617,886	Any: IRR 1.43; 95% CI 1.23, 1.67 ADA: IRR 1.35; 95% CI 1.00, 1.83 ETN: IRR 1.37; 95% CI 1.05, 1.78), CTZ: IRR 1.50; 95% CI 1.13, 1.98
Chambers et al., 2017 (63)	Prospective Cohort	RA	biologics (not specified)	Children born to diseased unexposed or healthy cohort (no RA) mothers	Infections requiring hospitalizatio n or those from a specific checklist (up to one year of age)	252	463 (diseased), 469 (healthy control)	Diseased unexposed: RR 0.71; 95% CI 0.30, 1.71 Healthy controls: RR 1.09; 95% CI 0.43, 2.72
Chambers et al., 2019 (75)	Prospective Cohort	RA, CD	ADA	Children born to diseased unexposed or healthy cohort (no CID) mothers	Infections requiring hospitalizatio n or those from a specific checklist (up to one year of age)	229	111 (diseased), 203 (healthy control)	Diseased unexposed: RR 0.97; 95% CI 0.34, 2.77 Healthy control: RR 1.77; 95% CI 0.62, 5.05
Chaparro et al., 2018 (49)	Retrospective cohort	IBD	IFX, ADA, CTZ	Unexposed	An infection that led the child to be admitted to the hospital at any time during follow-up	388	453	HR 1.2; 95% CI 0.8, 1.8

Author	Design	Maternal disease	In utero exposure	Comparison	Outcome	Size of the exposed population	Size of the unexposed population	Results
De Lima et al., 2016 (72)	Prospective Cohort	IBD	IFX, ADA	Children born to non-IBD mothers not treated with TNFi	Infections requiring hospitalization during 1st year of life	55	459	p=0.49
Duricova et al., 2019 (74)	Prospective Cohort	IBD	IFX, ADA	Unexposed children of non-IBD mothers (general population offspring)	Infection leading to antibiotic treatment and/or hospitalization	72	69	OR 0.86; 95% 0.32, 2.32
Gubatan et al., 2021 (62)	Systematic Review and Meta-Analysis	IBD	IFX, ADA, GOL, CTZ, natalizumab, vedolizumab, ustekinumab	Infants not exposed to biologics	Infection-related hospitalization	1965	6584	OR 1.33; 95% CI 0.95, 1.86
Kanis et al., 2021 (73)	Retrospective Cohort	IBD	IFX, ADA	Unexposed children	Admission to hospital because of infection during first 5 years of life	163	564	IRR 1.66; 95% CI 0.91, 3.04
Luu et al., 2018 (46)	Retrospective Cohort	IBD	IFX, ADA, GOL, CTZ	Unexposed offspring	Infections requiring hospitalization	797	4836	OR 0.85; 95% CI 0.64, 1.13
Mahadevan et al., 2021 (64)	Prospective Cohort	IBD	IFX, ADA, CTZ, GOL, vedolizumab, natalizumab, ustekinumab	Children born to women with IBD who did not take thiopurines or biologics	Infection requiring hospitalization	848	423	OR 0.92; 95% CI 0.70, 1.20
Meyer et al., 2022 (70)	Retrospective Cohort	IBD	IFX, ADA, GOL, CTZ	Unexposed offspring	Infection requiring hospitalization as the primary diagnosis during the	3399	18,954	HR 1.10; 95% CI 0.95, 1.27

Author	Design	Maternal disease	In utero exposure	Comparison	Outcome	Size of the exposed population	Size of the unexposed population	Results
					first 5 years of life			
Nørgård et al., 2020 (68)	Retrospective Cohort	IBD, rheumatologic diseases, PsO, connective tissue disease, liver disease	IFX, ADA, ETN, GOL, CTZ	Unexposed children	Infections that were diagnosed in a hospital in children ≤1 year of age	493	728,055	HR 1.44; 95% CI 1.19, 1.74
Seirafi et al., 2014 (71)	Case-control	IBD	IFX, ADA, CTZ	Unexposed offspring born to IBD mothers	Neonatal infection	133	99	p=0.73
Tsao et al., 2019 (51)	Retrospective Cohort	RA, IBD, PsO, PsA, AS, juvenile idiopathic arthritis and systemic autoimmune rheumatic diseases	abatacept, ADA, alefacept, anakinra, belimumab, CTZ, ETN, GOL, IFX, natalizumab, rituximab, tocilizumab, ustekinumab	Offspring born to disease-matched women with no biologics	Serious infections requiring hospitalization anytime during the first year of life	100	8507	OR 0.56; 95% 0.17, 1.81
Vinet et al., 2018 (69)	Retrospective Cohort	RA	ADA, CTZ, ETN, GOL, IFX	Randomly selected control children born live and exposed to RA mothers	Hospitalization with infection as the primary reason for admission within the first year of life	380	2,476	OR 1.4; 95% CI 0.7, 2.8

ADA, Adalimumab; AS, ankylosing spondylitis; CD, Crohn's Disease; CI, confidence interval; CID, chronic inflammatory disease; CTZ, Certolizumab pegol; ETN, Etanercept; GOL, Golimumab; HR, hazard ratio; IBD, inflammatory bowel disease; IFX, Infliximab; IRR, incidence rate ratio; OR, odds ratio; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; RR, risk ratio; TNFi, tumour necrosis factor inhibitor.

CHAPTER 3 - MANUSCRIPT #2

3.1 Preamble to Manuscript #2

In manuscript #2, I assess the relationship between TNFi and the risk of hospitalized infections in pregnant women during the gestational and postpartum periods. As mentioned in manuscript #1, most past studies, both original research and reviews, primarily focus on one period only (gestational or postpartum). I looked at both periods to encompass the whole pregnancy period. This manuscript, entitled "Tumour Necrosis Factor Inhibitors and Risk of Serious Infections in Pregnant Women with Chronic Inflammatory Diseases", is under review with *ACR Open Rheumatology* (12 March 2025). Conference abstracts based on the contents of this manuscript were presented at the School of Population and Global Health Research and Public Health Day (Montreal, 2024) as an oral presentation and at the European Alliance of Associations for Rheumatology (Vienna, 2024) as a poster presentation. Additional information regarding cohort creation is presented below.

3.1.1 Data source

To address my thesis objectives, I used IBM MarketScan® commercial database[32] with data from January 1, 2011, to December 31, 2021. MarketScan is one of the longest-running and largest prospective databases of US employer-provided private health insurance claims data.[32] It contains de-identified medical and drug claims for >273 million individuals from large companies (employees, spouses, and dependents) and includes data on physician office visits, hospitalizations, and drug prescriptions.[33] Individual patients can be followed even if they switch between eligible insurance companies, given that coverage by an eligible insurance company is retained during follow-up. Medical diagnoses and procedures are recorded using the International Classification of Diseases 9th and/or 10th revisions (ICD-9/10) codes[34] and American Medical Association Current Procedural Terminology (CPT) procedure codes.[35] ICD-9 was used in the US from 1979 until switching to ICD-10 on October 1, 2015.[36] Drugs are coded using National Drug Codes (NDC) from the American Food and Drug Administration (FDA).

MarketScan has been extensively used in many areas of clinical research, including pharmacoepidemiologic studies in chronic inflammatory diseases and studies focusing on TNFi.[37-42] It has also been used to assess drug safety in pregnancy[43-49] and rotavirus vaccine effectiveness.[50-54] As the database is based on employer-provided health insurance, many, if not

most, will be of reproductive age. The database also includes dependents and spouses of the employees covered by the insurance; therefore, mothers and offspring can be linked using family identifiers. Ultimately, MarketScan was chosen for this thesis because of the availability of exposure and outcome variables and other relevant covariates. Furthermore, compared to using Canadian data, it is more cost-efficient and time-efficient to acquire MarketScan data as it affords for a larger population.

3.1.2 Creating the study cohort

A population-based cohort study, with the study period of January 1, 2011 – December 31, 2021, was conducted, which included all women between the ages of 15 and 45 years who have ≥1 hospitalization for a pregnancy outcome after diagnosis of a chronic inflammatory disease (Figure 3.1.1). Pregnant women needed to be continuously enrolled within MarketScan with medical and pharmacy coverage for ≥12 months before their end of pregnancy.

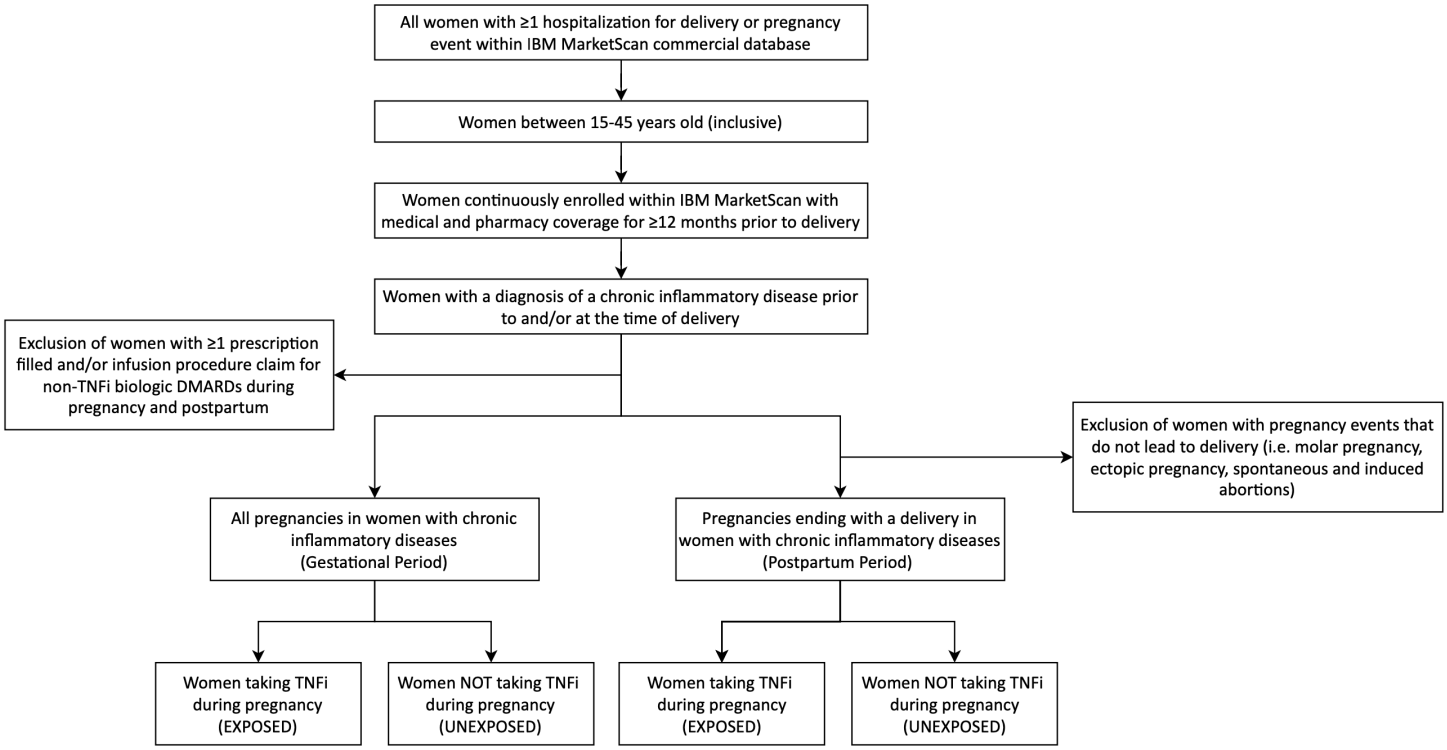

Figure 3.1.1 Patient selection flow diagram

During the 3-months before pregnancy, we looked at the number of specialist visits in the 3 months before pregnancy (based on the specialty recorded under the fee for physician claim, i.e.

STDPROV Internal Medicine (NEC) 204; Dermatology 215; Gastroenterology 275; Rheumatology 300; Pediatric Gastroenterology 438; Pediatric Rheumatology 450), the type of prescription (TNFi exposure during this time), healthcare use (i.e. number of prescription drugs used, hospital admissions (excluding hospital admissions due to transfers), and outpatient visits).

3.1.2.1 Identifying pregnant women

We included two groups of women: 1) all women with ≥1 hospitalization for delivery and 2) all women with ≥1 hospitalization for pregnancy not leading to delivery (i.e. pregnancy event). In the first group, delivery was defined using any inpatient hospital admission record including a pregnancy-related diagnosis or procedure code for vaginal or caesarean delivery identified by the ICD-9 codes 650, 669.7, V27.x, or procedure codes 72.0-72.9, 73.22, 73.59, 73.6, 74.0-74.2, 74.4, 74.99; ICD-10 codes O60.1-3, O68, O69, O70, O80-O83, Z38.01; Diagnosis Related Group codes for vaginal or caesarean delivery, for version 28 – version 35 codes 765, 766, 767, 768, 774, 775; for version 36 - version 39: 783-788, 796-798, 805-807; and CPT codes 59400, 59409, 59410, 59610, 59612, 59614 for vaginal delivery and 59510, 59514, 59515, 59618, 59620, 59622 for caesarean delivery. Deliveries were identified as multiple gestations if one or more of the following codes were present: ICD-9 codes 651.x, V27.2-V27.7, V91.x; ICD-10 codes O30x, O84, Z37.2-Z37.7, Z38.3-Z38.8. We also labelled deliveries with codes indicating a stillbirth (ICD-9 632, 656.4, 768.0, 768.1, 779.9, or procedure code V27.1; ICD-10 O02.1, O36.4, Z37.1, Z37.4, Z37.7).

For the second group, we labelled pregnancies not leading to delivery with codes indicating a molar pregnancy (ICD-9 630; ICD-10 O01, O02.0, O08), spontaneous abortion (ICD-9 632, 634.x; ICD-10 O02.1, O03; or CPT codes 59812, 59820, 59821), legally induced abortion (ICD-9 635.x, or procedure codes 69.01, 69.51, 69.6, 74.91, 75.0, V25.3; ICD-10 O04, O07; Diagnosis Related Group 770, 779 for version 28 and later; or CPT codes 59840, 59841, 59850-59852, 59855, 59857), ectopic pregnancy (ICD-9 633.x; ICD-10 O00, O08; Diagnosis Related Group code 777 for version 28- version 35 (no 777 after v35)), or complication after an abortion, ectopic, or molar pregnancy (ICD-9 639.x). These pregnancies were analyzed for infections during the gestational period. For the postpartum analysis, we excluded pregnancy events that did lead to delivery (i.e. molar pregnancy, ectopic pregnancy, spontaneous and induced abortions). These latter pregnancies rarely result in delivery and would not contribute to postpartum complications per se.[55,56]

3.1.2.2 Identifying women with chronic inflammatory diseases

Pregnant women were only included if they had a diagnosis for a chronic inflammatory disease (i.e. RA, AS, PsA, psoriasis [PsO], or inflammatory bowel disease [IBD]) at any time before delivery or pregnancy event.

The algorithm to identify rheumatoid arthritis cases was based on either 1) ≥1 hospitalization with a relevant diagnostic code for RA (ICD-9 714; ICD-10 M05, M06), or 2) ≥2 physician RA codes (ICD-9 714; ICD-10 M05, M06) with ≥1 by a specialist over 1 year, at any time before the onset of gestation. This algorithm has 80% sensitivity (95% CI 70%, 89%) and 100% specificity (95% CI 100%, 100%).[57]

For ankylosing spondylitis, the algorithm was based on ≥2 physician AS codes (ICD-9 720.0; ICD-10 M45, M08.1). This has a sensitivity of 82% (95% CI 76%, 87%) and a specificity of 100% (95% CI N/A).[58]

The algorithm for psoriasis was based on either 1) ≥1 hospitalization with a relevant diagnostic code for PsO (ICD-9 696.1; ICD-10 L40.0-L40.4, L40.5x, L40.8, L40.9), or ≥2 psoriasis diagnostic codes (ICD-9 696.1; ICD-10 L40.0-L40.4, L40.5x, L40.8, L40.9) ever assigned by any physician, at any time before the onset of gestation. This has been shown to have a sensitivity of 52% and a specificity of 99%.[59]

For psoriatic arthritis, this was based on either 1) ≥1 hospitalization with a relevant diagnostic code for PsA (ICD-9 696.0; ICD-10 M07.0-M07.3, M09.0), or 2) ≥1 psoriasis diagnosis code ever assigned by a physician (ICD-9 696.1; ICD-10 L40.0-L40.4, L40.5x, L40.8, L40.9) AND ≥2 diagnosis codes of spondyloarthritis (ICD-9 721; ICD-10 M47) ever assigned with ≥1 assigned by a rheumatologist or internal medicine specialist, at any time before the onset of gestation. This algorithm has a sensitivity of 51% and a specificity of 100%.[59]

For inflammatory bowel disease (ulcerative colitis and Crohn's disease), this was based on two algorithms, either 1) ≥1 hospitalization with a relevant diagnostic code for IBD (CD: ICD-9 555.x, ICD-10 K50.x; UC: ICD-9 556.x, ICD-10 K51.x) or 2) ≥2 outpatient physician IBD codes IBD (CD: ICD-9 555.x, ICD-10 K50.x; UC: ICD-9 556.x, ICD-10 K51.x), at any time before the onset of gestation. The former has 82.2% sensitivity and 96.1% specificity.[60] The latter has 86.5% sensitivity and 91.6% specificity.[60]

Regarding the type of chronic inflammatory disease, 34% of women in our cohort had more than one disease that could be an indication for a TNFi, and we were not sure of which is the actual indication. Thus women were separated into three groups based on this hierarchical definition: i) those diagnosed with any IBD code, regardless if they also have ICD codes for other conditions of interest, ii) those diagnosed with any RA ICD code but no IBD codes (though they may have AS or PsA/PsO, and iii) those diagnosed with any AS or PsA/PsO code but neither IBD nor RA codes.

3.1.2.3 Exclusion criteria

I excluded women exposed to biologic drugs other than TNFi, which are used infrequently during pregnancy, as they are prescribed to <1% of pregnant women with chronic inflammatory diseases.[61] Similarly, simultaneous use of other biologics may be associated with infections and confound the results. It is unclear if the risk associated with them is similar to TNFi exposure. Therefore, I excluded women with ≥1 prescription filled and/or infusion procedure code for non-TNFi biologics (i.e. rituximab, abatacept, tocilizumab, vedolizumab, ustekinumab, secukinumab) during pregnancy (for perinatal fetal/maternal complications) and/or postpartum. Exposure to the aforementioned non-TNFi biologics was identified based on prescriptions using NDC numbers in RED BOOK and J-codes.

3.1.2.4 Onset of gestation

Term deliveries were identified based on maternal or child ICD-9/10 codes present in medical records. If gestational age was unknown and there was no preterm code, the onset of gestation was based subtracting 39 weeks (273 days) from the delivery date. This validated algorithm by Margulis et al. was found to have a sensitivity of 91% (95% CI 91, 91), a specificity of 98% (95% CI 98, 98), and a positive predictive value of 74% (95% CI 74, 75) compared to delivery discharge record.[62]

Preterm deliveries were classified as preterm in the presence of a claim for (1) ICD-9 codes 765 (disorders relating to short gestation and low birth weight) or their ICD-10 approximately equivalent codes P05 (slow fetal growth and fetal malnutrition) and P07 (disorders related to short gestation and low birth weight, not elsewhere classified), or (2) ICD-9 644.0 and 644.2 (in 644, early or threatened labor) or its ICD-10 approximate equivalent O60.1 (in O60, preterm labor) in the first 60 days after delivery.[62] If a preterm code was available, 35 weeks (245 days) were

subtracted from the date of birth to determine the onset of gestation. This method for preterm status by Margulis et al. was found to have a sensitivity of 91% (95% CI 91, 91), a specificity of 98% (95% CI 98, 98), and a positive predictive value of 74% (95% CI 74, 75) compared to delivery discharge record.[62]

Alternatively, if an ICD code for preterm birth included the gestational age range (Table 3.1.1, Table 3.1.2), an algorithm established by Li et al. was used to estimate gestational age. Specifically, for codes that cover a range of weeks, the specified upper limit of gestational age was used. This method for gestational age had a sensitivity of 98.3% (95% CI 98.3, 98.4), specificity of 45.5% (95% CI 44.9, 46.0), and a positive predictive value of 90.9% (95% CI 90.8, 91.0).[63]

Table 3.1.1 Gestational age range ICD-9 codes

Code	Definition	Weeks	Days
765.21	Less than 24 completed weeks of gestation	24	168
765.22	24 completed weeks of gestation	24	168
765.23	25–26 completed weeks of gestation	26	182
765.24	27–28 completed weeks of gestation	28	196
765.0-765.09	Extreme immaturity	28	196
765.25	29–30 completed weeks of gestation	30	210
765.26	31–32 completed weeks of gestation	32	224
765.27	33–34 completed weeks of gestation	34	238
765.28	35–36 completed weeks of gestation	36	252
765.1-765.19	Other preterm infants	35	245
765.2	Preterm with unspecified weeks of gestation	35	245
644.21	Onset of delivery before 37 completed weeks of gestation	35	245

Table 3.1.2 Gestational age range ICD-10 codes

Code	Definition	Weeks	Days
P07.20	Extreme immaturity of newborn (less than 28 completed weeks of gestation) (less than 196 completed days of gestation) (unspecified weeks of gestation)	28	196
P07.21	Less than 23 completed weeks of gestation	23	161
P07.22	23 completed weeks of gestation	23	161
P07.23	24 completed weeks of gestation	24	168
P07.24	25 completed weeks of gestation	25	175
P07.25	26 completed weeks of gestation	26	182
P07.26	27 completed weeks of gestation	27	189
P07.31	28 completed weeks of gestation	28	196
P07.32	29 completed weeks of gestation	29	203
P07.33	30 completed weeks of gestation	30	210
P07.34	31 completed weeks of gestation	31	217
P07.35	32 completed weeks of gestation	32	224
P07.36	33 completed weeks of gestation	33	231
P07.37	34 completed weeks of gestation	34	238
P07.38	35 completed weeks of gestation	35	245
P07.39	36 completed weeks of gestation	36	252

For pregnancies not leading to live births and without a recorded gestational age, the following standard gestational ages were used based on national median gestational age by outcome from an administrative database validation study: stillbirth, 28 weeks[64]; ectopic pregnancies, 8 weeks[64]; spontaneous abortions, 8 weeks[64]; legally induced abortions, 10 weeks[64]; molar pregnancies, 12 weeks[65]. The onset of gestation was determined by subtracting the above weeks from the date of pregnancy outcome code. These algorithms have been commonly used in perinatal research.[66,67]

3.1.2.5 Covariates

I evaluated patient characteristics (e.g., age and geographic location) and comorbidities (e.g., hypertension, pre-gestational diabetes, asthma, chronic kidney disease) measured at baseline

(onset of gestation; fixed) based on ≥1 physician billing and/or hospitalization with relevant, validated diagnostic codes (Appendix A). I also looked at gestational diabetes and further included preterm delivery. The following MarketScan demographic variables were extracted for each woman: age of patient (date of birth; AGE), enrolled family identification (EFAMID), enrollee identification (ENROLID), Metropolitan Statistical Area (MSA), State of employee (STATE), Geographic Location Employee (EGEOLOC), Geographic Region of employee residence (REGION). Maternal age was included as studies have shown that women who were ≥35 years old had a greater odds of labour and delivery complications, including preterm birth and hypertension and that age is a risk factor for serious infections.[68,69] Potential confounders are identified below in the directed acyclic graph (DAG) (Figure 3.1.2).

Maternal hypertension was classified based on either 1) at least one maternal hospitalization with a relevant diagnostic code, or 2) 2 physician billing within 2 years using the same standardized codes (ICD-9 codes 401.x, 402.x-405.x, 642.0, 642.1, 642.2; or ICD-10 codes I10.x-I13.x, I15.x, O131-O133, O169). This was based on a validation study with a sensitivity of 75% (95% CI 71%, 78%) and specificity 94% (95% CI 93%, 95%).[70] A study looking on TNFi and hypertension found that RA patients taking TNFi had a higher risk of developing hypertension.[71]

Pre-gestational diabetes was classified based on ≥1 maternal hospitalization or physician billing with relevant diagnosis codes (ICD-9 codes 250-250.93, 648.00-648.04; or ICD-10 codes O24.0x-24.3x, O24.5-O24.7x, E10-E14). This was based on a validation study with a sensitivity of 85.9% (95% CI 78.8%, 93%) and specificity of 99.8% (95% CI 99.6%, 99.9%).[72] Gestational diabetes was classified based on ≥1 maternal hospitalization or physician billing with relevant diagnosis codes (ICD-9 code 648.8; or ICD-10 codes O24.4x, O24.8x, O24.9x). This was based on a validation study with a sensitivity of 94.7% (95% CI 91.5%, 97.9%) and specificity of 99.1% (95% CI 98.8%, 99.4%).[72] Both pre-gestational (pre-existing) and gestational diabetes have been shown to be associated with adverse fetal and maternal outcomes, including preterm birth, congenital abnormalities and malformations, large for gestational age birthweight, stillbirth, and neonatal death.[73,74] Diabetes is also associated with an increased risk of neonatal infection and poorer prognoses in mothers.[75]

Maternal asthma was classified based on either 1) ≥1 maternal hospitalization with a relevant diagnosis code (ICD-9 code 493-493.92; ICD-10 code J45), or 2) ≥2 outpatient visits at

least 30 days apart with the same relevant diagnosis codes. This was based on a validation study with a positive predictive value of 95% (95% CI 91%, 99%).[76] A study demonstrated that asthma is a risk factor for serious infection in RA patients treated with biologics.[77]

Maternal chronic kidney disease was classified based on ≥1 maternal hospitalization or physician billing with relevant diagnosis codes (ICD-9 code 585, 403, 404; or ICD-10 code N18, I12, I13). This was based on a validation study with a sensitivity of 95.5% (95% CI 91.4%, 97.9%) and a specificity of 90.7% (95% CI 88.5%, 92.1%).[78] In patients with chronic kidney disease, hospitalization with infection is common.[79]

Premature rupture of membranes (PROM) was classified based on ≥1 maternal hospitalization or physician billing with ICD-9 codes 658.1, 658.2; or ICD-10 codes O42, 042.9. PROM increases the risk of both maternal and neonatal infections.[80,81] In mothers, this may have chorioamnionitis or endometritis.[80] In neonates, rupture of membranes may cause bacteria to enter the uterine cavity.[80,82] Prolonged labor was classified based on one maternal hospitalization or physician billing with ICD-9 codes 662.01, 662.11; or ICD-10 codes O63.0, O63.1, O63.9. Prolonged induction/labor is associated with an increase in maternal infections.[83,84] Furthermore, in infants born to mothers with infections, neonatal morbidity increased with maternal infectious complications.[83]

Pre-gestational drug exposure (≥1 prescription filled in the 3 months before the onset of gestation) and gestational drug exposure (≥1 prescription filled during the gestational period) was evaluated for the following drugs:: systemic corticosteroids (methylprednisolone, prednisolone, prednisone, budesonide), non-biologic DMARDs (sulfasalazine, chloroquine, hydroxychloroquine, leflunomide, methotrexate, azathioprine, 6-mercaptopurine, mesalamine, tacrolimus, cyclosporine, apremilast, tofacitinib, baricitinib). Exposure to the aforementioned medications were identified based on prescriptions with their corresponding NDC number. Corticosteroid use and concomitant non-biologic DMARD use[85] were included, as both have been linked with an increased risk of maternal infection, which is associated with neonatal infections.[86-89]

As a surrogate marker for disease severity, I looked at the number of specialist visits in the 3 months before pregnancy. I further assessed and controlled for serious infections occurring 3 months before pregnancy, as a prior infection is one of the most important risk factors for future infections.[90,91]

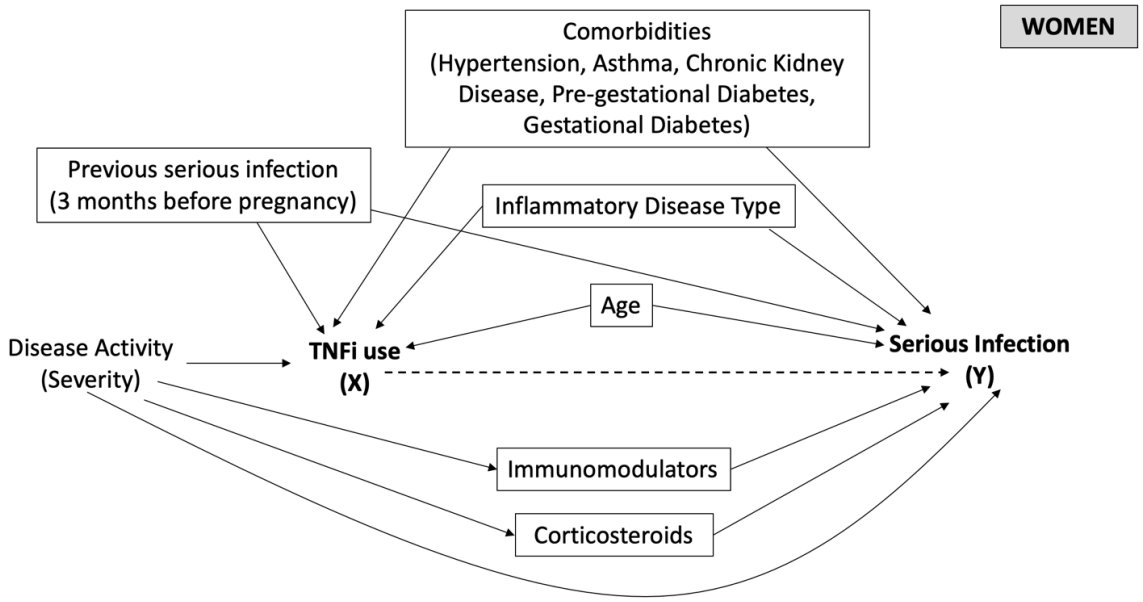

Figure 3.1.2 DAG of potential confounders of maternal analysis: risk of serious infections in women exposed to TNFi. X is the exposure, and Y is the outcome.

3.1.3 Identifying all use of TNFi prescriptions and procedures (TNFi exposure)

TNFi exposure was classified as time-varying. It was based on ≥1 filled prescription for adalimumab, certolizumab, etanercept, golimumab, and/or ≥1 infusion procedure claims for golimumab, infliximab filled before the outcome of interest. A time-varying exposure definition was used, where each person-day of follow-up was classified depending on which TNFi subtype was prescribed. Therefore, women who switched between TNFi subtypes had their person-time allocated to the exposure group they were exposed to at that specific time. After each prescription, I added a grace period based on five half-lives (Table 3.1.3) of each TNFi to determine if the prescriptions overlapped, ensuring constant exposure.

Table 3.1.3 TNFi half-lives

Name	Dosage form (injection type)	Half-life
infliximab	Intravenous	14 days
etanercept	Subcutaneous	4.5 days
adalimumab	Subcutaneous	10-20 days
certolizumab pegol	Subcutaneous	14 days
golimumab	Subcutaneous	13 days
golimumab	Intravenous	14 days

Grace periods are typically used to add time at the end of the prescription when the person is still under the influence of that drug. Once women were outside the grace period of 5 half-lives, they were classified as unexposed as the drug is no longer in their system; however, they can be reclassified as exposed if they start taking their drugs again (Figure 3.1.3). The timing of TNFi exposure during pregnancy was determined based on the onset of gestation. All drug exposures were identified based on prescriptions using NDC numbers in RED BOOK and J-codes (intravenous drugs). This strategy caught more instances of TNFi prescriptions compared to identifying the drugs with their individual NDC codes.

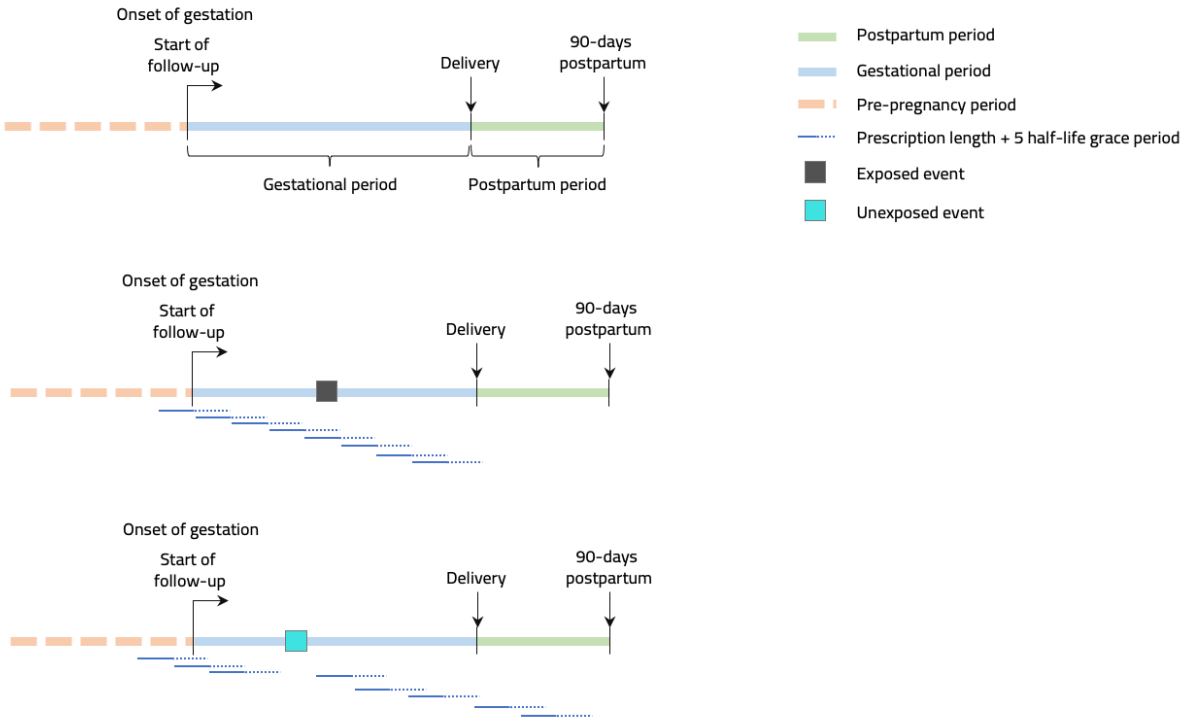

Figure 3.1.3 Schematic of TNFi prescription durations and event occurrence during gestation and postpartum periods in pregnant women

3.1.4 Outcome of interest

The outcome of interest (event) was serious infections, identified as the first primary hospital discharge diagnosis of infection during pregnancy and/or up to 90 days after delivery. Only the first occurrence in each period (gestational and postpartum) was considered. We ascertained serious infections based on ≥1 hospitalization with infection with a relevant diagnostic code listed as the primary reason for admission. Only the first serious infection during pregnancy

and postpartum was considered for each woman for the evaluation period. Once serious infection occurred, follow-up was terminated, and subsequent person-time was not included in the analysis. Women who remained event-free were right-censored at the end of the study period (December 31, 2021), end of commercial insurance coverage, or death. With respect to postpartum analysis, if a serious infection occurred in the gestational analysis, this was adjusted accordingly in the model. Additionally, as a time-varying exposure was used, if the event occurred while the woman stopped their medication and was outside of the 5-half-lives, it was classified as an unexposed event (Figure 3.1.3).

Infection codes were ascertained from multiple studies. Lo Re et al.'s ICD-10 algorithm had a positive predictive value of 80.2% (95% CI 75.1%, 84.6%) for hospitalization for serious infection events when compared with medical record review.[92] The study was conducted using the FDA's Sentinel Distributed Database. A non-validated cohort study looking at infection-related hospital admission in Australia provided a list of the ICD-9 diagnostic codes. [93] An additional non-validated Canadian population-based cohort study studying serious infections requiring hospitalization provided a list of ICD-9 codes.[94] These three studies were used to compile an extensive list of ICD-9/10 codes to identify serious infections and are available in Appendix A.

3.1.5 Statistical analysis

In addition to the Cox proportional hazards models performed in the following manuscript, numerous analyses were performed prior to settling on the final model. Importantly, I performed all of these checks for both the gestational period, as well as the postpartum period, as they were not the same. Firstly, I performed weighted cumulative exposure modelling to account for the differences in the time since exposure; however, the results from these models were null, indicating that time since exposure did not affect the results.

As I was using Cox proportional hazards models, I needed to ensure that the assumptions were not violated. As a reminder, the three assumptions are 1) multiplicative relation between covariates and hazard (linear with ln(hazard)), 2) hazard are proportional (i.e. hazard ratio is constant) over time, 3) baseline hazard is correctly specified (not technically needed)[95]. I checked for non-linear effects of covariates, including age, the number of specialist visits in the 90 days before delivery (range between 0 and 52 visits), and the number of hospitalizations in the 90 days before delivery (range between 0 and 5), using b-splines,quadratics, log transformations, and

categorizing the variable. I also looked at time-dependent effects of drug exposure and other covariates by looking at graphs and performing *cox.zph* in the R *Survival* package.[96] I further compared the difference between methods to account for the non-proportional hazards by adding a time interaction term to the model and stratifying on variables.[97] I also used flexible Cox models with regression splines to test whether any covariates are time-dependent and/or nonlinear using the CoxFlex extension.[98,99] I compared Akaike information criterion (AIC) and used the likelihood ratio test (LRT) to compare the different models.

I further performed sensitivity analyses of varying the grace period after each prescription. I looked at 3-, 4-, 6-, and 7- half-lives as sensitivity analyses alongside the primary model using 5-half-lives. Based on the results of this, 5-half-lives was a better fit for the data and represents the time when 97% of the drug should be eliminated from the body.[100]

Finally, I tested if frailties made a difference in the models. Frailty models are used to adjust for correlation in reproduction outcomes by accounting for dependence within multiple births from the same woman, as >1 pregnancy per woman might be included in the analyses.[101] I applied random effect models to the Cox models by adding a random effect term ("frailty") which is an unobserved random factor shared by all members (pregnancies) of the same cluster (mother). As the majority of the data is independent and the same mothers only account for 11% of the data (n=7,716), there was very little correlation; thus, the frailty models made no difference. As a result, they were excluded from the final models.

3.2 Manuscript #2: Tumour Necrosis Factor Inhibitors and Risk of Serious Infections in Pregnant Women with Chronic Inflammatory Diseases

3.2.1 Title Page

Running Head: Serious Infection Risk with TNFi in Pregnant Women

Tumour Necrosis Factor Inhibitors and Risk of Serious Infections in Pregnant Women with Chronic Inflammatory Diseases

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3.2.2 Abstract

Objectives. Tumour necrosis factor inhibitors (TNFi) are used by over 20% of pregnant women with chronic inflammatory diseases, which could further impede immune function and increase the risk of infections requiring hospitalization. We assessed the risk of serious infections during pregnancy and postpartum among TNFi-exposed and unexposed women with chronic inflammatory diseases.

Methods. Using MarketScan, we identified pregnant women with chronic inflammatory diseases and modelled TNFi exposure during pregnancy and postpartum as a time-varying variable. Cox proportional hazards models were used to estimate adjusted hazard ratios (HR) for TNFi and the risk of hospitalized infection.

Results. A total of 62,813 women contributed 70,529 pregnancies and 69,412 deliveries. Among these, 4,485 (7.1%) were exposed to ≥1 TNFi prescription during pregnancy and 3,559 during postpartum. Overall, 449 pregnancies were hospitalized for infection during pregnancy, including 31 TNFi-exposed cases. During postpartum, 205 pregnancies were associated with hospitalized infection, of which 17 were TNFi-exposed. Compared with no TNFi, TNFi use during pregnancy was associated with a HR of 1.39 (95% confidence interval, CI, 0.95, 2.05) for serious infections, while the HR during postpartum was 1.22 (95% CI 0.72, 2.06).

Conclusion. In this population-based study, TNFi-exposed pregnancies had a numerically higher rate of serious infections, though confidence intervals included the possibility of no increased risk. While our findings do not establish a clear association between TNFi use and infection risk, they suggest that an increased risk cannot be ruled out. Given the frequency of TNFi in pregnancy, these results may help provide counselling to guide its use during pregnancy and postpartum.

3.2.3 Introduction

Chronic inflammatory diseases, including rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriasis (PsO), psoriatic arthritis (PsA), and inflammatory bowel disease (IBD; Crohn's and ulcerative colitis), affect many women during their childbearing years.[1, 2] Tumour necrosis factor inhibitors (TNFi) are prescribed in approximately 22% of pregnant women with chronic inflammatory diseases, representing a 3-fold increase over the past 10 years, as studies have not shown fetal risk.[3-7]

In non-pregnant patients with chronic inflammatory diseases, a meta-analysis of observational studies showed that TNFi use was associated with an increased risk of serious infections compared to no TNFi use (odds ratio, OR, 1.72; 95% confidence interval, CI, 1.56-1.90).[8] Given the known immunosuppressive effects of TNFi, their use during pregnancy - a period of naturally reduced immune response - raises additional concerns about the risk of serious infections. TNFi could potentially exacerbate pregnancy-related immune suppression, further impairing the ability to respond to specific pathogens.

However, pregnant women are commonly excluded from TNFi clinical trials, and the largest studies on serious infections occurring in women with chronic inflammatory diseases during pregnancy are observational and population-based. Notably, two of the largest studies (n=776-1457) on the risk of serious infections during pregnancy excluded postpartum.[9, 10] These studies also classified TNFi as a fixed exposure, not time-varying, which likely introduced important exposure misclassification.

Given these limitations, further research is needed to clarify the risk of serious infections during pregnancy and postpartum. Including postpartum infections (including those related to delivery is important), as women with chronic inflammatory diseases have a 2-fold higher rate of caesarean delivery (~40% of affected women), and infection complicates up to 10% of caesarean deliveries, even among healthy women.[11-15] To address these gaps, we aimed to assess serious infection risk in women exposed to TNFi throughout pregnancy *and* postpartum to optimize management during these critical periods.

3.2.4 Patients and Methods

Data source. We used MarketScan, a United States health insurance claims database.[16] MarketScan contains de-identified medical and drug claims for >273 million individuals from

large companies (employees, spouses, and dependents) and includes data on physician office visits, hospitalizations, and drug prescriptions.[17] Medical diagnoses and procedures are recorded using the International Classification of Diseases 9th and/or 10th revisions (ICD-9/10) codes[18] and the American Medical Association Current Procedural Terminology (CPT) codes.[19]

Study population. A retrospective population-based cohort study was conducted consisting of all women between the ages of 15 and 45 with a primary diagnosis related to pregnancy within hospital diagnostic codes. This included women who were hospitalized for delivery (including stillbirth) or other pregnancy outcomes (i.e. spontaneous and induced abortions, ectopic pregnancy, molar pregnancy) between January 1, 2011, and December 31, 2021 (Supplemental Table 3.2.1). This captured most pregnancies but may have missed some pregnancy losses or terminations that occurred early in pregnancy. Pregnant women were required to have a chronic inflammatory disease (i.e. RA, AS, PsA, PsO, or IBD; Supplemental Table 3.2.2) before the onset of gestation and to be continuously enrolled within MarketScan with medical and pharmacy coverage for ≥12 months before the end of pregnancy. For the postpartum analysis, we excluded pregnancies that did not lead to delivery (i.e. spontaneous and induced abortions, ectopic pregnancy, molar pregnancy).

The onset of gestation was determined using published algorithms. For term deliveries (i.e. no preterm code), we followed Margulis et al.'s algorithm and subtracted 273 days (39 weeks) from the delivery date to establish the timing of conception.[20] For preterm deliveries, we also followed the algorithm of Margulis et al. if they had a preterm ICD diagnostic code and subtracted 245 days (35 weeks) from the delivery date.[20] In contrast, if they had a preterm code with a corresponding gestational age, GA, we used Li et al. and assigned the corresponding GA.[21] Stillbirth was defined as occurring at 28 weeks gestation[22], ectopic pregnancy and spontaneous abortion at 8 weeks gestation[22], molar pregnancy at 12 weeks gestation[23], and induced abortion at 10 weeks gestation.[22] The onset of gestation for these events was determined by subtracting the aforementioned number of weeks from the date of the outcome code. We excluded women with ≥1 prescription filled and/or infusion procedure code for non-TNFi biologics (i.e. rituximab, abatacept, tocilizumab, vedolizumab, ustekinumab, secukinumab) during pregnancy and/or postpartum. Ethics approval was obtained from the Research Ethics Office at McGill University (A11-M107-14A).

Exposure. Exposure to TNFi (i.e. infliximab, adalimumab, golimumab, etanercept, certolizumab) was defined as ≥1 filled prescription and/or ≥1 infusion procedure claims based on National Drug Codes from REDBOOK (source of prescription and over-the-counter pharmaceutical information) and J-codes (billing codes). Time-varying exposures were assigned, where each person-day of follow-up was classified depending on which TNFi subtype was prescribed. After each prescription, women were considered to still be exposed during a grace period of five half-lives, starting from the date of the prescription/injection date.[24]

Outcome. Based on ICD-9/10 codes, all incident events of a serious infection diagnosis occurring during the follow-up period were identified (Supplemental Table 3.3.3). These infections were further categorized based on organ systems or types of infection, such as abdominal, cardiovascular, central nervous system, respiratory, skin, muscles, and bones, urinary tract, and viral or systemic infections. Only the first occurrence of a primary hospital discharge diagnosis of infection in women during pregnancy and/or up to 90 days after delivery (postpartum) was considered. Administrative health data ICD diagnostic codes for infections leading to hospitalization have been validated against manual chart review and were found to have a positive predictive value (PPV) of 80.2%.[25]

Potential confounders or effect modifiers. For this study, the following co-morbidities were defined as present or absent (based on validated algorithms using ICD diagnostic codes) at any time before the onset of gestation: age, pre-gestational diabetes[26], asthma[27], and chronic kidney disease[28] (Supplemental Table 3.2.1). Pre-gestational use of systemic corticosteroids (methylprednisolone, prednisolone, prednisone, budesonide)[29-31] and non-biologic immunomodulators (sulfasalazine, chloroquine, hydroxychloroquine, leflunomide, methotrexate, azathioprine, 6-mercaptopurine, mesalamine, tacrolimus, cyclosporine, apremilast, tofacitinib, baricitinib)[32] were included based on ≥1 prescription filled during the 3 months before the onset of gestation. For the postpartum analysis, we additionally included gestational drug use (i.e. systemic corticosteroids and non-biologic immunomodulators) based on ≥1 prescription filled during the gestational period. We additionally assessed gestational diabetes[26] and infection during the gestational period for the postpartum analysis.

As a surrogate marker for disease severity, we looked at the number of chronic inflammatory disease specialist visits and hospitalizations in the 3 months before pregnancy. Regarding the type of disease, a woman may have more than one disease that could be an indication

for a TNFi. Thus, women were separated into four groups based on the following hierarchical definition: i) those diagnosed with any IBD code, regardless if they also have ICD diagnostic codes (billing and/or hospitalization) for other conditions of interest, ii) those diagnosed with any RA ICD diagnostic code but no IBD codes (though they may have AS, PsA, or PsO codes), iii) those diagnosed with any PsA code but neither IBD nor RA codes, and iv) those diagnosed with any AS or PsO code but none of the above disease codes.

Statistical analysis. Descriptive statistics were used to summarize the cohort characteristics of pregnancies with no TNFi use compared to any TNFi use during pregnancy. The crude incidence of serious infections and 95% confidence intervals (CI) based on the Poisson distribution for the entire cohort and each exposure group (TNFi/no-TNFi) were calculated for both pregnancy and postpartum. Multivariable proportional hazards regression was used to estimate the adjusted hazard ratios (HR) and corresponding 95% CI for serious infections associated with TNFi use, with separate models for pregnancy and postpartum. In these models, we controlled for maternal age, comorbidities, and medications listed earlier as potential confounders/effect modifiers. In the multivariable analysis pertaining to the postpartum, we further adjusted for serious infections during pregnancy. The pregnancy person-time spanned from the constructed time of gestation onset (time zero) to the first hospitalized infection or end of pregnancy. The postpartum person-time spanned from delivery (time zero) to the first hospitalized infection, end of commercial insurance eligibility, end of the study period (December 31, 2021), death, or 90 days after delivery, whichever occurred first.

We tested the proportional hazards assumption by assessing the independence between Schoenfeld residuals and time.[33] For the pregnancy analysis, as pre-gestational corticosteroid use and pre-gestational diabetes violated the proportional hazards assumption (i.e. the relationship between the covariates and the risk of hospitalized infection was not constant over time), we stratified on these covariates, allowing the baseline hazards to differ between strata.[34] For the postpartum analysis, we stratified by gestational diabetes as it violated the assumption. The non-linear effect of age was modelled by including its quadratic terms (age*age), as the effect of TNFi on serious infections was stronger for younger women during the pregnancy analysis. Similarly, the non-linear effect of the number of hospitalizations in the 90 days prior to the onset of gestation was modelled as a quadratic term during pregnancy. Cohort creation was done with SAS®

Enterprise Guide version 7.15 (SAS Institute, Cary, NC)[35] and analyses were conducted using R version 4.3.0.[36]

Secondary and sensitivity analyses. In a secondary analysis, we estimated the crude incidence of hospitalized infections for each type of TNFi to assess if the individual TNFi agent was associated with serious infections. In sensitivity analyses, for TNFi exposures, we first extended the period over which women were considered currently exposed increased from five half-lives to six- and seven half-lives. Second, we decreased this to three- and four-half-lives. We further considered using frailty models to adjust for the correlation between pregnancies from the same woman (11% of the sample), as multiple pregnancies per mother could introduce dependence in the data. Frailty models incorporate a random effect term to account for this clustering by including an unobserved random factor shared by all pregnancies from the same mother.[37] Finally, we included only those who received 2+ prescriptions for TNFi to determine if there is the possibility of TNFi exposure misclassification during pregnancy.

3.2.5 Results

A total of 70,529 pregnancies in 62,813 women met the inclusion criteria, corresponding to 69,412 deliveries. There were 16,266 person-years of follow-up during the 90-day postpartum period. The mean age at pregnancy onset was 32.3 (standard deviation 5.1) years. During 51,320 person-years of follow-up, 449 pregnancies were diagnosed with a serious infection during their pregnancy, of which 31 (6.9%) were TNFi-exposed. Overall, 4,485 (6.4%) pregnancies received at least one prescription for TNFi during pregnancy. During the postpartum period, 205 pregnancies had a hospitalized infection, of which 17 (8.3%) were exposed to TNFi. A total of 3,559 (4.8%) pregnancies leading to a delivery event were exposed to TNFi during the postpartum period.

Table 3.2.1 presents the characteristics of pregnancies stratified by the use of TNFi (at least one prescription) during pregnancy and postpartum. Pregnancies exposed to TNFi were associated with younger maternal age, higher likelihood of corticosteroid and non-biologic immunomodulator use, and lower prevalence of asthma and diabetes (gestational and pre-gestational). These pregnancies also had more specialist visits in the 90 days before the pregnancy and were more frequently associated with diagnoses of IBD and/or RA. In contrast, pregnancies

without TNFi use were more likely to have been associated with PsA diagnoses and the absence of IBD or RA codes.

Table 3.2.2 shows the results of the primary analyses. The absolute incidence of hospitalized infections during pregnancy was 8.5 per 1,000 person-years in unexposed pregnancies and 13.8 per 1,000 person-years in TNFi-exposed pregnancies (HR 1.39; 95% CI 0.95, 2.05). The incidence of hospitalized infection in the postpartum period was 12.0 per 1,000 person-years in TNFi-exposed pregnancies versus 27.1 per 1,000 person-years (HR 1.22; 95% CI 0.72, 2.06). Figure 3.2.1 displays the Kaplan-Meier survival curves for each exposure group during pregnancy and postpartum, illustrating the cumulative survival probability free of serious infections over the study period. We found no difference in our results after adjusting for frailties, so this was not implemented in the final analyses (HR 1.39; 95% CI 0.94, 2.06). Stratified analyses yielded similar effect estimates. Furthermore, the risk of serious infections among those who received 2+ prescriptions was similar compared to the overall analysis that included all pregnancies (HR 1.20; 95% CI 0.79, 1.82).

Figure 3.2.2 summarizes the results of the sensitivity analysis modifying the grace period for the definition of the time-varying current exposure to TNFi. During pregnancy, shortening the exposure grace period to four half-lives (HR 1.49; 95% CI 1.00, 2.20) did not change the estimate drastically, but when reduced to three half-lives (HR 1.05; 95% CI 0.65, 1.70), the effect was nearly null suggesting that more biologically exposed time was classified as unexposed. Lengthening the exposure grace period to six (HR 1.29; 95% CI 0.88, 1.90) and seven half-lives (HR 1.23, 95% CI 0.83, 1.81) also did not substantially change the estimate but instead diluted the effect by classifying biologically unexposed time as exposed. Overall, the varying grace periods produced consistent results with the primary analysis and showed a marginally non-significant association but with reduced precision.

When looking at the incidence rates of serious infections in pregnancies exposed to specific TNFi during pregnancy, we observed higher absolute rates of serious infections in those exposed to infliximab, adalimumab, etanercept, and certolizumab as opposed to those unexposed to TNFi (Table 3.2.3). During the postpartum period, similar results were found, except adalimumab had a slightly smaller incidence rate, but the 95% CIs overlapped.

The most common infections in those exposed to TNFi were maternal pregnancy-related infections (i.e., other viral diseases in the mother, antepartum condition; 39%) and urinary tract

infections (29%) during pregnancy and maternal pregnancy-related infections (i.e., major puerperal infection; 35%) and viral/systemic infections (18%) in postpartum. The most frequent infections for those unexposed to TNFi were viral/systemic infections (35%), urinary tract (29%), and maternal pregnancy-related infections (i.e., chorioamnionitis; 23%) in pregnancy and maternal pregnancy-related infections (i.e., major puerperal infection; 37%), digestive system infections (13%), and soft tissue infections (12%) in postpartum (Table 3.2.4). After January 1, 2020, there were only four serious infections during pregnancy and 11 during the postpartum period, none of which were associated with a hospital ICD diagnostic code corresponding to COVID-19. No fatal infections were observed, as no cases had an infection date that coincided with the date of death.

3.2.6 Discussion

In the largest real-world study to date, we did not find a statistically significant association between the use of TNFi and the risk of serious infections during pregnancy or postpartum. However, TNFi-exposed pregnancies had a numerically higher rate of serious infections, with an estimated 40% higher risk during pregnancy and 20% higher risk during postpartum, though confidence intervals included the possibility of no increased risk. While our findings do not establish a clear causal relationship, they suggest that an increased risk cannot be ruled out. Multiple observational studies have examined the association between TNFi use and the risk of serious infections and found an increased risk, but they had methodological limitations.[38]

One study identified 776 women with RA, AS, PsA, or IBD receiving TNFi during pregnancy.[9] Pregnancies using TNFi had a higher risk of serious infections, such as bacterial or opportunistic, requiring hospitalization compared to pregnancies exposed to non-biologics, but the 95% CI was wide (HR 1.36; 95% CI 0.47, 3.93) due to the limited power.[9] A similar study focusing on 1,457 pregnant women with IBD found that exposure to TNFi during pregnancy was associated with in-hospital infections (OR 1.25; 95% CI 1.04, 1.50).[10] These two studies restricted the analyses to only the gestational period and did not focus on all of the disease indications for which TNFi are prescribed.

Analyzing infectious events related to hospitalization for delivery is important. A study of 6,218 women with chronic inflammatory diseases by Tsao et al. focusing on the postpartum period could not find an association between biologics (including TNFi; n=90) and an increased risk of serious maternal postpartum infections (OR 0.79; 95% CI 0.24, 2.54).[39] However, despite

combining TNFi with other biologics, the exposure and outcome in their cohort was rare, resulting in potentially unstable estimates.

Our study was specifically designed to address the limitations of the previous studies. We utilized a time-varying exposure definition for TNFi use, eliminating the potential for exposure misclassification. Furthermore, we looked at both pregnancy and postpartum serious infection outcomes as the majority of studies primarily focused on the gestational period only. Our large sample size and number of events provided precision in our hazard ratio estimates.

Despite the strengths of our study, it has some limitations. First, there is the potential for misclassification of drug use since MarketScan records the filling of prescriptions; however, this does not mean that the patient took the medicine. Exposure to TNFi was defined based on filled prescriptions, except for infliximab and golimumab, which were identified by infusion procedure codes. Since infliximab is typically for patients with more severe diseases[40], knowing the accurate exposure status for these individuals, while potentially misclassifying those not on infusion TNFi, could have led to differential misclassification of exposure. This misclassification is likely related to the outcome, as we anticipated that patients on infliximab would be at a higher risk of infection.

Another limitation is that MarketScan (like most administrative databases) does not provide information on the onset of gestation, subsequently affecting our ability to identify the exact timing of TNFi exposure during pregnancy. Therefore, we estimated the gestational period by applying validated algorithms to term and preterm deliveries separately to determine the onset of gestation. To minimize potential misclassification and to ensure that exposure occurred during pregnancy, we performed a sensitivity analysis where we only included those exposed to TNFi who received 2 or more prescriptions during pregnancy. The results still showed a positive (also non-significant) association as the effect estimate decreased slightly with wider CIs. Additionally, only 539 patients on TNFi received fewer than 2 filled prescriptions during pregnancy (potentially excluding those who received prescriptions prior to the onset of gestation and one additional prescription during pregnancy), suggesting that the extent of exposure misclassification was likely minimal. Given that most individuals in MarketScan have out-of-pocket costs associated with filling prescriptions, it is reasonable to assume that the majority of women who filled a prescription for TNFi likely took ≥1 dose.[41]

With further regards to misclassification, although serious infections have been shown to be well recorded in MarketScan, as with any administrative database study, misclassification may

exist due to misclassifying non-infectious diseases as infections, not entering serious infections as such in the database, or admitting pregnant patients with moderate infections that would normally be cared for in an outpatient setting. A study strength is that by only including infections that were the primary reason for hospitalization, we reduced the risk of detection bias, as we did not include infections that were detected because of another reason for hospitalization. As well, there is the potential for surveillance bias as those taking TNFi may be more likely to be admitted to the hospital when presenting with an infection. However, we attempted to mitigate this bias by adjusting for healthcare utilization factors, including the number of specialist visits and baseline comorbidities.

Since MarketScan does not explicitly record chronic inflammatory disease activity measures, residual confounding by disease severity might be of concern, specifically due to the lack of lab results that could be used to assess maternal disease severity. However, in the absence of direct measures of disease severity, we adjusted for surrogate markers, including the use of other medications (i.e. immunomodulators and corticosteroids), and the number of specialist visits, which are likely to be associated with disease activity. In addition, there may be residual confounding from unmeasured variables, such as socioeconomic status, body mass index, or smoking.

Our results provide some reassurance, as we did not observe a statistically significant increased risk of serious infections during pregnancy or postpartum. While the number of infections was higher among TNFi-exposed pregnancies, the confidence intervals were wide, and an increased risk cannot be ruled out. These findings align with patterns seen in non-pregnant TNFi patients. Our results provide some evidence to help provide counselling and avoid unnecessary discontinuation of an important drug for disease control in pregnancy and postpartum for women with chronic inflammatory diseases.

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3.2.8 Tables

Table 3.2.1 Characteristics of pregnancies stratified by use of TNFi during pregnancy and postpartum.

	Pregnancy			Postpartum		
Variable*, n (%)	**Total (n=70,529)**	**No TNFi (n=66,044)**	**TNFi† (n=4,485)**	**Total (n=69,412)**	**No TNFi (n=65,853)**	**TNFi (n=3,559)**
Age, mean ± SD years	32.3 ± 5.1	32.4 ± 5.1	31.7 ± 4.8	32.3 ± 5.1	32.4 ± 5.1	31.7 ± 4.6
Asthma	7457 (11)	7114 (11)	343 (8)	7323 (11)	7041 (11)	282 (8)
Chronic kidney disease	445 (1)	409 (1)	36 (1)	430 (1)	403 (1)	27 (1)
Pre-gestational diabetes	5201 (7)	4959 (8)	242 (5)	5087 (7)	4905 (7)	182 (5)
Gestational diabetes	-	-	-	11718 (17)	11249 (17)	469 (13)
Corticosteroids						
Pre-gestational	8434 (12)	7467 (11)	967 (22)	-	-	-
Gestational	-	-	-	7752 (11)	6706 (10)	1046 (29)
Non-biologic immunomodulators						
Pre-gestational	5931 (8)	4963 (8)	968 (22)	-	-	-
Gestational	-	-	-	6222 (9)	5383 (8)	839 (24)
Any IBD diagnosis	15806 (22)	13243 (20)	2563 (57)	15553 (22)	13347 (20)	2206 (62)
Any RA diagnosis but no IBD	7004 (10)	5819 (9)	1185 (26)	6890 (10)	6035 (9)	855 (24)
Any PsA diagnosis but no IBD or RA	47086 (67)	46431 (70)	655 (15)	46346 (67)	45902 (70)	444 (13)
Any AS diagnosis or PsO diagnosis but no IBD, RA, or PsA	633 (1)	551 (1)	82 (2)	623 (1)	569 (1)	54 (2)
Gestational infection	-	-	-	409 (1)	378 (1)	31 (1)
Hospitalizations, mean ± SD	0.01 ± 0.1	0.02 ± 0.1	0.03 ± 0.2	0.02 ± 0.1	0.02 ± 0.1	0.03 ± 0.2
Specialist visits, mean ± SD	0.6 ± 1.3	0.5 ± 1.3	1.3 ± 1.8	0.6 ± 1.3	0.5 ± 1.3	1.3 ± 1.9

* Characteristics measured before pregnancy onset include age, asthma, chronic kidney disease, pre-gestational diabetes, corticosteroids (pre-gestational), non-biologic immunomodulators (pre-gestational), chronic inflammatory disease diagnosis, and the number of hospitalizations and the number of specialist visits in the 90 days prior to the onset of gestation. Characteristics measured during pregnancy include gestational corticosteroid and non-biologic immunomodulator use, and gestational infection.

† "TNFi" is for at least 1 prescription of TNFi during the relevant study period, and "No TNFi" is for none.

Table 3.2.2 Crude and adjusted hazard ratios for the association between time-varying current use of tumour necrosis factor inhibitors and risk of serious infections

Exposure*	Serious infection events	Person-years	Incidence rate (95% CI)†	Hazard ratio (95% CI)	
				Crude	Adjusted
Pregnancy‡ (n=70,529)					
No-TNFi (n=66,044)	418	49,071	8.5 (7.7, 9.4)	1.00	1.00 (reference)
TNFi (n=4,485)	31	2,249	13.8 (9.4, 19.6)	1.79 (1.24, 2.58)	1.39 (0.95, 2.05)
Postpartum§ (n=69,412)					
No-TNFi (n=65,853)	188	15,638	12.0 (10.4, 13.9)	1.00	1.00 (reference)
TNFi (n=3,559)	17	628	27.1 (15.8, 43.4)	2.34 (1.42, 3.84)	1.22 (0.72, 2.06)

Abbreviations. TNFi, tumour necrosis factor inhibitor; CI, confidence interval

*Current TNFi usage was modelled as a time-varying variable as patients could move from a period of non-exposure to a period of exposure (allowing them to contribute both exposed and unexposed person-time)

†per 1000 person-years

‡Adjusted for age, pre-gestational comorbidities (asthma, pre-gestational diabetes), pre-gestational use of corticosteroids and non-biologic immunomodulators, number of specialist visits and hospitalizations in the 90 days prior to the onset of gestation, and disease type with an indication for TNFi.

§Also adjusted for gestational diabetes, gestational infections, and gestational use of corticosteroids and non-biologic immunomodulators.

Table 3.2.3 Incidence rates of serious infections according to type of TNFi for time-varying current exposure during pregnancy and postpartum.

Exposure	Person-years	Number of pregnancies*	Number of events	Incidence rate (95% CI)†
Pregnancy				
Infliximab	838	1,384	11	13.1 (6.6, 23.5)
Adalimumab	949	1,839	13	13.7 (7.3, 23.4)
Golimumab	44	105	0	N/A
Etanercept	130	703	2	15.4 (1.9, 55.6)
Certolizumab	286	588	5	17.5 (5.7, 40.8)
Unexposed	49,037	68,893	418	8.5 (7.7, 9.4)
Postpartum				
Infliximab	223	1,150	7	31.4 (12.6, 64.7)
Adalimumab	250	1,339	3	12.0 (2.5, 35.0)
Golimumab	13	75	0	N/A
Etanercept	47	507	1	21.5 (0.5, 119.8)
Certolizumab	95	512	6	63.4 (23.3, 138.1)
Unexposed	15,627	67,759	188	12.0 (10.4, 13.9)

*Since individuals can contribute to multiple exposure groups, the total across categories may sum to more than the actual study population.

†per 1000 person-years

Table 3.2.4 Most frequent types of serious infections across exposure categories of current TNFi use.

Types of serious infection		Cases of serious infection (%)			
		Pregnancy (n=449)		Postpartum (n=205)	
		TNFi exposure (n=31)	No-TNFi exposure (n=418)	TNFi exposure (n=17)	No-TNFi exposure (n=188)
ABD	Abdominal	1 (3)	4 (1)	2 (12)	4 (2)
LRT	Lower respiratory tract	0	7 (2)	1 (6)	4 (2)
SMB	Skin, muscles and bones	0	5 (1)	1 (6)	22 (12)
MAT	Maternal pregnancy-related infections	12 (39)	96 (23)	6 (35)	69 (37)
URI	Urinary tract	9 (29)	123 (29)	0	14 (7)
URT	Upper respiratory tract	0	1 (0.2)	0	0
VRS	Viral/Systemic	4 (13)	148 (35)	3 (18)	10 (5)
COP	Certain conditions originating in the perinatal period	0	1 (0.2)	0	0
DDS	Diseases of the digestive system	0	8 (2)	2 (12)	25 (13)
DEA	Diseases of the eye and adnexa	0	0	0	6 (3)
DEM	Diseases of the ear and mastoid process	0	0	0	1 (1)
DGS	Diseases of the genitourinary system	0	2 (1)	0	7 (4)
DNS	Diseases of the nervous system	0	2 (1)	0	0
DRS	Diseases of the respiratory system	1 (3)	3 (1)	0	3 (2)
DST	Diseases of the skin and subcutaneous tissue	1 (3)	7 (2)	0	2 (1)
IPD	Infectious and parasitic diseases (A00-B99)	3 (10)	11 (3)	2 (12)	21 (11)

3.2.9 Figures

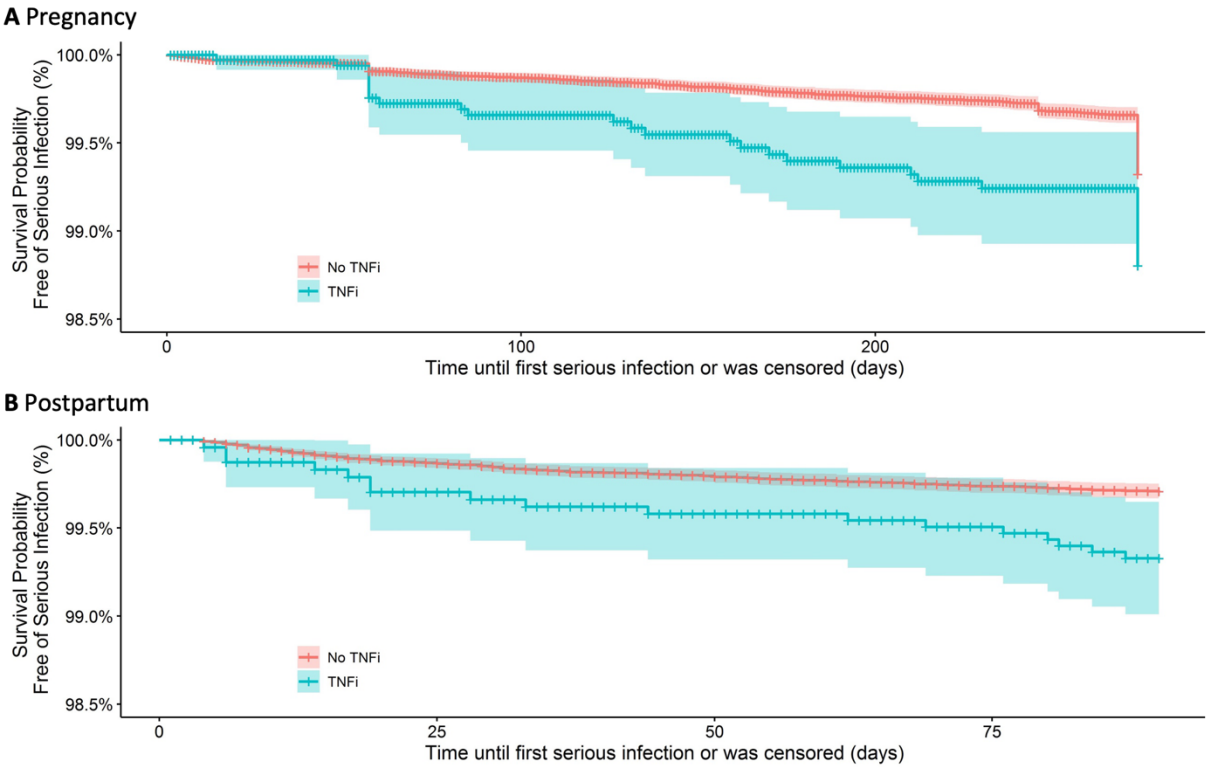

Figure 3.2.1 Survival Analysis: Kaplan-Meier Curves for TNFi exposure. The two panes show the Kaplan-Meier survival curves for each exposure group during pregnancy (Panel A) and postpartum (Panel B), illustrating the cumulative survival probability free of serious infections over the study period. The y-axis is scaled to display a range from 98.5% to 100%, as survival probabilities do not drop below this threshold, highlighting differences within the upper range.

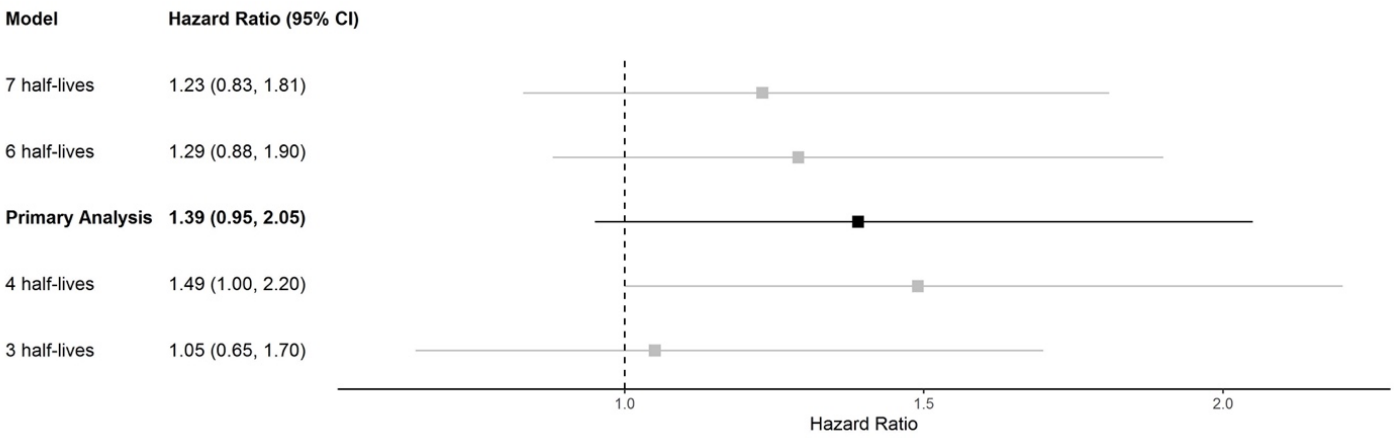

Figure 3.2.2 Forest plot displaying adjusted hazard ratios and 95% confidence intervals (CI) from the results of the primary (5 half-lives) and sensitivity analyses to assess the association between current use of tumour necrosis factor inhibitor and the incidence of serious infections during pregnancy. In sensitivity analyses, the grace period after the prescription date over which the pregnancies were considered currently exposed was modified from 5 half-lives used for the primary analysis.

3.2.10 Supplemental

Supplemental Table 3.2.1 Definitions used within MarketScan databases, based on diagnostic and procedure codes

Definitions	ICD-9	ICD-10	Diagnosis-Related Group (DRG) codes	CPT Procedure codes
Vaginal delivery	650, V27.0, V27.2, 72.0-72.9, 73.22, 73.59, 73.6	O60.1-3, O68, O69, O70, O80, O81, O83	v28-v35: 767, 768, 774, 775 v36-v39: 796-798, 805-807	59400, 59409, 59410, 59610, 59612, 59614
Caesarean section delivery	669.7, 74.0-74.2, 74.4, 74.4, 74.99	Z38.01, O82	v28-v35: 765, 766 v36-v39: 783-788	59510, 59514, 59515, 59618, 59620, 59622
Stillbirth	V27.1, 632, 656.4, 768.0, 768.1, 779.9	O02.1, O36.4, Z37.1, Z37.4, Z37.7		
Ectopic pregnancy	633.x	O00, O08 (ectopic & molar)	DRGv28-35: 777 Deleted after v35	
Molar pregnancy	630	O01, O08 (ectopic & molar)		
Spontaneous abortion	634.x	O03		
Legally induced abortion	635, 69.01, 69.51, 69.6, 74.91, 75.0, V25.3	O04, O07	DRGv28-39: 770, 779	59840, 59841, 59850-59852, 59855, 59857
Other	631, 632, 638.x, 639.x,			
Multiple gestation	651.x, V27.2-V27.7, V91.x	O30, O84, Z37.2- Z37.7, Z38.3-Z38.8		
Inflammatory bowel diseases (Crohn's disease & Ulcerative colitis)	555.xx, 556.xx	K50.x, K51.x		
Psoriasis or Psoriatic Arthritis	696.0, 696.1	L40.0-L40.4, L40.5x, L40.8, L40.9, M07.0-M07.3, M09.0		
Rheumatoid Arthritis	714	M05, M06		
Ankylosing Spondylitis	720.0	M45, M08.1		
Preterm delivery	644.0x-644.1x, 644.2x (765.0, 765.1 in offspring)	O60	DRGv28-35: 791, 792 DRGv36-39: 791, 792	
Maternal asthma	493	J45		
Maternal chronic kidney disease	585, 403, 404	N18, I12, I13		
Pre-gestational diabetes	250-250.93, 648.00-648.04	O24.0-24.3, E10-E14		
Gestational diabetes	648.8	O24.4, O24.9		
COVID-19 Infection		U07.1		

Supplemental Table 3.2.2 Chronic inflammatory disease validation studies

Disease	Cohort	Algorithm	Reference Standard	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive Predictive Value, % (95% CI)	Negative Predictive Value, % (95% CI)
rheumatoid arthritis	Ontario Health Insurance Plan database [57]	1 hospitalization RA diagnosis code OR **2** physician RA diagnosis codes with ≥1 by a specialist over 1 year ICD-9 714; ICD-10 M05-M06	Physician-reported diagnoses based on chart review	80 (70-89)	100 (100-100)	66 (56-76)	100 (100-100)
ankylosing spondylitis	Minneapolis Veterans Affairs Medical Center [58]	≥2 ICD codes ICD-9: 720.0 ICD-10: M45, M08.1 (not included in paper)	Chart review by rheumatologist	82 (76, 87)	100 (NA)	100 (NA)	99 (97, 100)
psoriasis	Ontario Health Insurance Plan database [59]	≥1 diagnosis in hospitalization records OR ≥2 psoriasis diagnostic codes ever assigned by any physician ICD-9: 696.1 ICD-10: L40.0, L40.1, L40.2, L40.3, L40.4, L40.5, L40.8, L40.9	Chart abstraction (clinician diagnosis based on chart review)	52	99	62	100
psoriatic arthritis	Ontario Health Insurance Plan database [59]	≥1 diagnosis in hospitalization records OR [≥1 psoriasis diagnosis code (above) ever assigned by a physician AND ≥2 diagnosis codes of spondyloarthritis (ICD-9 721; ICD-10 M47) ever assigned with ≥1 assigned by a rheumatologist or internal medicine specialist] ICD-9: 696.0 ICD-10: M07.0-M07.3, M09.0	Chart abstraction (clinician diagnosis based on chart review)	51	100	65	99

inflammatory bowel disease (ulcerative colitis and Crohn's disease)	United Kingdom General Practice Research Database [60]	Any hospitalization CD: ICD-9 555.x; ICD-10 K50.x UC: ICD-9 556.x; ICD-10 K51.x	Manual chart review and a large cohort of patients from Ontario	82.2	96.1	78.6	96.8
	Kaiser Permanente California administrative claims data [60]	≥2 physician visits (outpatient) CD: ICD-9 555.x; ICD-10 K50.x UC: ICD-9 556.x; ICD-10 K51.x	Manual chart review and a large cohort of patients from Ontario	86.5	91.6	62.9	97.6

Supplemental Table 3.2.3 Serious infection ICD-9 and ICD-10 codes

	ICD-9	ICD-10
Infectious and parasitic disease	001–139.9	A00-B99
Further separated into organ involvement		
Abdominal		A00.9, A01.1, A02.0, A03.8, A04.3, A04.5, A04.7, A04.8, A04.9, A05.9, A08.0, A08.1, A08.2, A08.3, A08.4, A08.5, A09, A09.9, B67.0, K35.0, K35.0A, K35.1, K35.1A, K35.9, K57.2B, K57.3, K57.3A, K57.3B, K57.3F, K57.9A, K65.0,K65.0A, K65.0G, K65.0J, K65.8, K65.8I, K65.9, K75.0, K80.3, K80.4, K81.0, K81.9, K83.0
Cardiovascular	421	I30.0, I30.1, I30.8, I30.9, I33.0, I33.9, I38.9, I39.8
Central nervous system	320, 323, 324	A39.0, A39.2A, A86.9, A87.0, A87.9, B00.3, B00.4, B02.0, B02.2, B02.2A, B02.2B, B91.9, G00.1, G00.8, G00.9, G00.9A, G01.9, G04.0, G04.2, G06.0, G06.0F, G06.2, G07.9
Respiratory system	460-466, 473, 480-487, 510	Pneumonia: A31.0A, A48.1, B37.1, J12.0, J13.9, J14.9, J15, J15.0, J15.1, J15.2, J15.4, J15.5, J15.7, J15.8, J15.9, J17.0, J17.8C, J18, J18.0, J18.1, J18.8, J18.9, J20.9, J20.9A, J21.9, J22.9, J69.0, J69.8, J69.8A Other: A15.0, A15.1, A15.2, A15.9, B90.9, J40.9, J44.0, J85.1, J85.2, J86.0, J86.9
Other sites of infection	790.7	B00.2A, B02.3G, B37.3A, B37.4, B37.8C, E06.0, E06.1, H65.1, H66.0, H66.9, J00.9B, J01.0, J01.1, J01.2, J01.8, J01.9, J02.0, J02.9, J02.9B, J03.0, J03.9, J03.9A, J04.0, J05.1, J06.9, J36.9, J39.0C, K04.0A, K05.3A, K10.2C, K11.2C, K12.1, K62.8L, N41.2, N45.0B, N45.9, N45.9A, N76.4A, O86.8
Skin, muscles, and bones	681-686, 711.0, 730	A46.9, B00.1A,B00.1B, B37.2, K61.0, K61.0A, K61.1, K61.2, L02.2, L02.2T, L02.4, L02.4F, L02.4K, L02.9, L02.9A, L03.1, L03.1E, L03.3, L08.8, L08.9, M00.0, M00.2, M00.2A, M00.8, M00.9, M46.3, M46.4, M46.5, M46.5A, M46.9, M71.1, M86.1, M86.8, M86.9
Unknown		A40.1, A40.3, A40.8, A40.9, A41.0, A41.1, A41.1A, A41.2, A41.3, A41.4, A41.5, A41.8, A41.9, A49.9A, B37.7, A32.9, A41.9A, A42.9, A44.9, A48.2, A49.0, A49.1, A49.3, A49.8, A49.9, A68.9, A70.9, A81.2, B00.8, B02.9, B34.0, B34.9, B36.9, B37.0, B37.8, B80.9, B89.9, B95.5, B95.6, B95.6A, B96.4, B96.5, B96.8, B99.9, R50, R50.0, R50.8, R50.9, T81.4D, T84.6, T89.9
Urinary tract	590	A41.9B, N10.9, N12.9, N13.6, N30.0, N30.8, N30.9, N39.0, N39.0B
Viral/Systemic		A51.5, A79.9, B00.1, B05.9, B20.4, B20.6, B20.8, B23.0, B23.2, B24.9, B25.8, B25.9, B27.0, B27.9, B50.9, B52.9, B54.9, B55.0, B58.9, J09.1, J09.9, J10.0, J10.8, J11, J11.0, J11.1, J11.8

CHAPTER 4 - MANUSCRIPT #3

4.1 Preamble to Manuscript #3

In manuscript #3, I used the maternal cohort that was created in Chapter 3 and descriptively analyzed the trends surrounding the use and discontinuation of TNFi among pregnant women. Since the decision to continue or discontinue TNFi during pregnancy is highly individualized, depending on both patient preferences and provider recommendations, the patterns of use can vary widely. Therefore, we aimed to descriptively explore and analyze these trends in TNFi use throughout pregnancy over time, and compare corticosteroid use in those who discontinued TNFi at specific gestational time points versus those who continued throughout gestation.

This manuscript, entitled "Patterns of Use and Discontinuation for Tumor Necrosis Factor Inhibitors in Pregnant Women: Insights from a Real-World Sample," is under review as a brief communication with the *Journal of Rheumatology* (14 January 2025). Conference abstracts based on similar contents of this manuscript were presented at the Canadian Rheumatology Association Annual Scientific Meeting (Winnipeg, 2024), the American College of Rheumatology Convergence (San Diego, 2023), the European Alliance of Associations for Rheumatology (Milan, 2023), and the Conference of Medications and Pregnancy (Montreal, 2023) as poster presentations, and as an oral presentation at the Laurentian Conference of Rheumatology (Estérel, 2023). At the latter, I was awarded the Carol Yeadon Award for Best Research Presentation.

4.2 Manuscript #3: Patterns of Use and Discontinuation for Tumour Necrosis Factor Inhibitors in Pregnant Women: Insights from a Real-World Sample

4.2.1 Title Page

Running Head: TNFi Use in Pregnancy

Patterns of Use and Discontinuation for Tumour Necrosis Factor Inhibitors in Pregnant Women: Insights from a Real-World Sample

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Conflict of interest: The authors have no conflicts to declare.
Ethics: Ethics approval was obtained from the Research Ethics Office at McGill University (A11-M107-14A)

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Key indexing terms:

Tumour necrosis factor inhibitors; pregnancy; autoimmune diseases

4.2.2 Abstract

Objective: To evaluate tumour necrosis factor inhibitor (TNFi) usage patterns in pregnant women with rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), psoriasis (PsO), and inflammatory bowel diseases (IBD), and to compare corticosteroid use in those discontinuing TNFi at specific gestational time points versus those continuing throughout gestation.

Methods: We analyzed pregnancies resulting in a live birth among women aged 15-45 with RA, AS, PsA, PsO, and/or IBD, hospitalized for delivery between January 2011 and December 2021, using MarketScan commercial claims database. TNFi exposure was defined as at least one filled prescription or infusion procedure claim for a TNFi. Timing of exposure was categorized by the gestational period and specific trimesters, with a grace period of five half-lives added to each prescription to account for ongoing biological activity.

Results: We identified 3,711 pregnancies exposed to TNFi among 49,925 women with RA, AS, PsA, PsO, and/or IBD. Of the 3,711 pregnancies, 64% had continuous TNFi use throughout all three trimesters. Most (89%) of TNFi-exposed pregnancies had preconception exposure, and 68% continued TNFi postpartum. The proportion of pregnancies with TNFi use throughout all trimesters increased from 55% in 2011-2013 to 73% in 2020-2021 (p-value for trend <0.0001). Corticosteroid use during pregnancy/postpartum was less frequent in pregnancies exposed to TNFi throughout gestation versus those exposed in the first +/- second trimester only.

Conclusion: We observed trends towards increased continuous TNFi use throughout gestation (and fewer corticosteroids in this group), suggesting growing confidence in the safety and effectiveness of TNFi use in pregnancy.

4.2.3 Introduction

Reproductive-age women with chronic inflammatory diseases, including rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), psoriasis (PsO), and inflammatory bowel diseases (IBD), are frequently prescribed tumour necrosis factor inhibitors (TNFi). These medications cross the placenta via neonatal Fc receptors, entering the fetal bloodstream around gestational week 20, with adalimumab, infliximab, and golimumab crossing in higher proportions than etanercept and certolizumab (1,2). Early guidelines recommended discontinuing TNFi during pregnancy due to limited safety evidence (3,4), but more recent guidelines, including those from the American College of Rheumatology (2020) and the European Alliance of Associations for Rheumatology (2024), recommend against discontinuation (5,6).

Despite these updates, concerns about infections in offspring lead some patients and physicians to stop TNFi during late pregnancy (late second or early third trimester), partly to reduce the risk of immunosuppression in the offspring, which raises concerns regarding live-vaccine immunization of the infant. Due to certolizumab's low placental transfer ability, guidelines recommend continuing treatment before and during pregnancy. The choice to stop TNFi preconception or during pregnancy might be patient-dependent.

While observational studies have evaluated the use of disease-modifying anti-rheumatic drugs (DMARDs) during pregnancy, few have focused on TNFi continuation and discontinuation. Understanding trends and predictors of TNFi discontinuation during gestation may help optimize maternal and fetal outcomes. Therefore, we examined TNFi prescriptions in pregnant women with chronic inflammatory diseases, identifying patterns of use and the characteristics of those who discontinued at specific time points compared to those who continued throughout pregnancy.

4.2.4 Methods

We evaluated pregnancies resulting in live births among women aged 15 to 45 with RA, AS, PsA, PsO, and/or IBD who were hospitalized for delivery between January 2011 and December 2021, using the MarketScan database. Delivery-related hospitalizations were identified using the International Classification of Diseases, 9th and 10th Revisions (ICD-9/10) codes. Women could contribute multiple pregnancies and were required to be continuously enrolled within MarketScan for ≥12 months before the end of pregnancy. Deliveries were identified using a validated algorithm by Margulis et al. (7), where if gestational age was unknown, we estimated it

by subtracting 39 weeks (273 days) from the delivery date for term deliveries and 35 weeks (245 days) for preterm cases. When preterm birth ICD codes included a gestational age range, we used an algorithm by Li et al. (8).

TNFi use was defined as ≥1 filled prescription or infusion procedure claim for TNFi medications during the preconception, gestation, or postpartum period. Preconception was defined as the 90 days before gestation, and postpartum as 90 days after delivery. The first trimester spanned from gestation onset to 84 days, the second from 85 to 183 days, and the third from 184 days to delivery. TNFi medications were categorized by placental transfer ability: high (infliximab, golimumab, adalimumab) or low (etanercept or certolizumab), identified using national drug codes and procedure codes.

TNFi exposure timing was based on prescription or infusion dates relative to the gestational period. A grace period of five half-lives was added after each TNFi prescription, specific to each TNFi (ranging from 4.5 days for etanercept to 20 days for adalimumab), to account for biological exposure. A woman was classified as exposed during a trimester if she received at least one prescription or an overlapping grace period within that trimester. Continuous exposure was defined as at least one day of exposure in each trimester. Switchers were classified as women who received a prescription for one drug and then received a prescription for another drug during the grace period.

We examined trends in TNFi use over calendar years, stratified by trimester, using the extended Mantel Haenszel Chi-Square test for linear trends. Concomitant drug use, systemic corticosteroids (methylprednisolone, prednisolone, prednisone, budesonide) and non-biologic DMARDs (sulfasalazine, chloroquine, hydroxychloroquine, leflunomide, methotrexate, azathioprine, 6-mercaptopurine, mesalamine, tacrolimus, cyclosporine, apremilast, tofacitinib, baricitinib), was assessed by prescription filled during pregnancy and stratified by trimester. Comorbidities, such as diabetes, asthma, hypertension, and/or chronic kidney disease, were identified at any time before the onset of gestation using ICD-9/10 codes. Cohort creation was done with SAS® Enterprise Guide version 7.15 (SAS Institute, Cary, NC). Ethics approval was obtained from the Research Ethics Office at McGill University (A11-M107-14A).

4.2.5 Results

We identified 49,925 women who had 56,866 pregnancies over 2011-2021 (Table 4.2.1, Figure 4.2.1). Overall, there were 144 pregnancies who were only exposed to TNFi preconception and did not continue treatment during pregnancy, and 282 who were exposed to TNFi only during postpartum. Among these 381 pregnancies, 45 were exposed to TNFi preconception, discontinued during pregnancy, and restarted postpartum. In total, there were 3,711 pregnancies exposed to TNFi at some point during gestation. Within these TNFi-exposed pregnancies, 64% were exposed to TNFi continuously through all three trimesters, 17% during a single trimester only, and 18% during two trimesters (Figure 4.2.2A). Specifically looking at late pregnancy discontinuation, 15% (573/3711) were exposed only during the first trimester and another 15% (546/3711) only during the first and second trimesters.

The majority of TNFi pregnancies were exposed to TNFi preconception (89%), and over half were exposed to TNFi postpartum (68%) (Figure 4.2.1). Among TNFi-exposed pregnancies who also took TNFi preconception, the majority continued their treatment into the first trimester (95%; 543/573) or the second trimester (88%; 480/546). Interestingly, among pregnancies where TNFi was used preconception and continued only during the first trimester, 30% (174/573) resumed TNFi treatment postpartum. Similarly, for pregnancies that used TNFi during both the first and second trimesters but stopped before the third trimester, 35% (185/546) resumed TNFi treatment postpartum. The vast majority (94%) of mothers exposed to TNFi in all three trimesters were using TNFi preconception, and most (84%) continued postpartum.

Pregnancies in IBD accounted for 56% of all TNFi pregnancies, of which 84% of IBD pregnancies (1749/2094) continued TNFi throughout all trimesters (Table 4.2.1). Compared to those with IBD, more pregnancies with RA (difference of 15%, 95% confidence interval, CI 13-18%), PsA (24%, 95% CI 21-29%), and AS/PsO (24%, 95% CI 14-36%) had TNFi use during the first and second trimester but discontinued before the third. Pregnancies in women with additional co-morbidities (i.e. diabetes, asthma, hypertension, and/or chronic kidney disease) were more likely to stay on TNFi through all three trimesters.

The temporal exposure of TNFi stratified by timing during gestation from 2011 to 2021 is shown in Figure 4.2.2B. Over calendar years, a higher proportion of pregnancies were exposed to TNFi throughout all three trimesters (55% in 2011-2013 vs 62% in 2014-2016 vs 69% in 2017-

2019 vs 73% in 2020-2021; p-value for trend <0.0001). The proportion of those only exposed to TNFi during the first trimester decreased over the years (p-value for trend <0.0001).

Focusing on concomitant drug use, 22% of TNFi-exposed pregnancies used non-biologic DMARDs at any time during pregnancy (18% first trimester, 15% second trimester, 14% third trimester), 22% preconception, and 17% postpartum (Figure 4.2.1). Among pregnancies where TNFi was stopped after the first trimester, 4% (24/573) were given DMARDs postpartum, even though they did not use these medications during pregnancy or before conception. Additionally, 3% (14/546) of those exposed to TNFi during only the first and second trimesters were prescribed DMARDs postpartum, even though they had not used DMARDs during gestation or preconception. DMARD use through pregnancy was higher among those who were exposed to TNFi during all three trimesters compared to those taking TNFi in the first trimester only (Figure 4.2.2C).

Regarding corticosteroids, the proportion of TNFi-exposed pregnancies who received corticosteroids increased from 22% during preconception to 28% at any time during gestation and back down to 21% during postpartum (Figure 4.2.1). Corticosteroid prescriptions during pregnancy among those exposed to TNFi at any point during gestation (3,711) were further broken down to 16% (604) receiving a prescription during the first trimester, 16% (605) during the second trimester, and 14% (536) during the third trimester. Corticosteroid use during pregnancy was slightly lower in those exposed to TNFi in all three trimesters (26%; 618/2380) versus those using TNFi only during a single trimester (range of 31-80%; 215/646) (difference of 7%; 95% CI 3-11%) or those using TNFi only in two trimesters (range of 29-48%; 221/685) (difference of 6%; 95% CI 2-10%) (Figure 4.2.2D). Similarly, women who used TNFi only in a single trimester had a higher percentage of postpartum corticosteroid use (range of 24-40%; 166/646) vs. compared to those exposed in all three trimesters (19%; 451/2380) (difference of 7%; 95% CI 3-10%). Specifically, there was less corticosteroid use postpartum among IBD patients using TNFi throughout gestation than among those exposed in the first trimester (difference of 4%, 95% CI -2-10%) or first and second trimesters (difference of 3%, 95% CI -3-8%). Among pregnancies where TNFi was used during the first and second trimesters but not the third trimester, 11% (61/546) did not use corticosteroids during pregnancy but were given postpartum corticosteroids. Additionally, 12% (68/573) of those who stopped taking TNFi after the first trimester received a

new prescription for corticosteroids postpartum after not taking any corticosteroids during pregnancy.

Among the 3,711 pregnancies exposed to TNFi at least once during pregnancy, 2,699 (73%) were on a high placental transfer TNFi (infliximab, golimumab, adalimumab) at some point, and 1,012 (27%) were only ever on low placental transfer TNFi (etanercept or certolizumab). Specifically, among the 3,528 pregnancies exposed to TNFi during the first trimester, 74% were exposed to a high placental transfer TNFi. Results were similar among the 3,041 exposed to TNFi during the second trimester, with 78% taking a high placental transfer TNFi. Finally, 76% of the 2,587 pregnancies exposed to TNFi during the third trimester took high placental transfer TNFi. Interestingly, 53 (1.4%) women switched from a high placental transfer drug to a low placental transfer drug during their pregnancy, with 26 of them switching from a high to low placental drug in the third trimester. Only 8 (0.2%) women switched from low to high transfer TNFi during pregnancy.

4.2.6 Discussion

In our study, 7% of chronic inflammatory disease pregnancies were exposed to TNFi, with 64% exposed during all three trimesters. This substantial portion of continuous TNFi use (and the trend of increasing use over calendar years) suggests growing confidence in TNFi safety during pregnancy, along with the uptake of updated guidelines.

Interestingly, a survey was performed in 2017 among inflammatory arthritis patients who had at least one pregnancy to evaluate how women's beliefs and interactions with healthcare providers influenced their decision to continue their medication during pregnancy (9). Among the 29 women on TNFi, 22 women discontinued during pregnancy, and 7 continued. The women mainly discontinued based on physician advice but also because of a lack of consensus between providers. Additionally, 24% of women reported that their healthcare providers had differing opinions about the safety of their medications during pregnancy. The difference between our data and this survey possibly reflects the calendar year effect of updated guidelines starting in 2020 promoting the continuation of TNFi throughout all trimesters. This was evident as the proportion of pregnancies continuing TNFi through all three trimesters between 2020-2021 increased compared to earlier years. Alternatively, 17% of pregnancies used TNFi during a single trimester only and 18% during two trimesters, suggesting some level of concern or precaution regarding

prolonged TNFi exposure during pregnancy, specifically among those only using it in the first trimester and then stopping or using it in the first and second trimesters and stopping. We suspect that many of those who used TNFi only in the third trimester likely had a flare during pregnancy that required treatment.

In each trimester, the majority of TNFi pregnancies were taking a drug with high placental transfer (a process which increases during late pregnancy); there were only a small number of pregnancies that switched from a high placental transfer drug to a low placental transfer drug during pregnancy. Of note, the risk of serious infection in children exposed to high-placental transfer TNFi has not been shown to be substantially greater than in those exposed to low-placental transfer TNFi (10). Thus, the overall body of evidence does not support the practice of switching from a high- to low-placental transfer drug, with guidelines updated in 2022 to reflect this (11).

The majority of pregnancies were exposed to TNFi preconception and postpartum. There was a higher continuation rate of TNFi among pregnancies with IBD (84% used TNFi during all three trimesters) than RA pregnancies (42%, 426/1017). Although both IBD and RA carry an increased risk of flare in the postpartum (12,13), this difference may reflect the greater risk of disease flare observed in IBD during both pregnancy and postpartum periods, as IBD activity has been shown to increase relative to non-pregnant periods (14). In contrast, a prospective Dutch study found that among RA patients, nearly half achieved low disease activity by the third trimester, with approximately 25% reaching remission (15). These findings highlight the distinct changes in disease activity of IBD and RA during pregnancy and postpartum, which likely influence patterns of TNFi use.

Interestingly, gestational and postpartum corticosteroid use was less frequent in pregnancies exposed to TNFi throughout gestation as opposed to those exposed in the first +/- second trimester only. In the subgroup of IBD patients, using TNFi throughout gestation was associated with less postpartum corticosteroid use than in those who only took TNFi in the first +/- second trimesters. This aligns with current literature suggesting that about one-third of IBD patients who discontinue therapy during pregnancy will flare in the first 3 weeks postpartum; therefore, an increase in corticosteroid use postpartum would be expected after flaring postpartum (16).

Our study has several strengths, including its large sample size (3,711 TNFi-exposed pregnancies) and its focus on multiple chronic inflammatory conditions, providing valuable

insights into treatment patterns across diverse populations who are prescribed TNFi. The categorization of TNFi exposure by trimester and placental transfer further enhances our understanding of prescription patterns. Additionally, the inclusion of corticosteroid and non-biologic DMARD use enriches our analysis of treatment patterns.

However, our study also has limitations. As a retrospective analysis, it is subject to residual confounding, due to the inherent limitations of using administrative data. The lack of detailed clinical data, such as disease activity levels and reasons for TNFi discontinuation, limits our ability to fully understand treatment decisions. There is also the potential for misclassification of TNFi exposure and gestational timing due to the reliance on claims data. Another limitation is that we excluded pregnancies resulting in stillbirths, despite these cases involving delivery. This exclusion may limit the generalizability of our findings, as it prevents us from capturing the full spectrum of pregnancy outcomes associated with TNFi exposure. Similarly, since MarketScan only includes commercially insured women, the findings may not be generalizable to women with public or no insurance. Despite these limitations, our study provides valuable insights into TNFi use during pregnancy and its association with corticosteroid use, highlighting important trends over time.

In conclusion, our findings suggest a trend towards increased TNFi continuation throughout gestation. As new TNFi drugs enter the market, ongoing evaluation of their safety and long-term outcomes during pregnancy will be critical, notably related to immunization response in offspring. This information will inform future guidelines and help optimize the health of mothers with chronic inflammatory disease and their children.

4.2.7 References

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4.2.8 Tables

Table 4.2.1 Characteristics of chronic inflammatory disease pregnancies by tumour necrosis factor inhibitor use

Variable, n (%)		TNFi exposure (n=3,711)*	Only exposed in a single trimester (n=646)†		Exposed in two trimesters (n=685)			Exposed in all three trimesters (n=2,380)
			1st only (n=573)	3rd only (n=68)	1st and 2nd only (n=546)	1st and 3rd only (n=29)	2nd and 3rd only (n=110)	
Disease state	IBD	2094 (56)	117/2094 (6)	32/2094 (2)	137/2094 (7)	3/2094 (0)	56/2094 (3)	1749/2094 (84)
	RA (no IBD)	1017 (27)	288/1017 (28)	25/1017 (2)	222/1017 (22)	17/1017 (2)	34/1017 (3)	426/1017 (42)
	PsA (no IBD, RA)	530 (14)	151/530 (28)	8/530 (2)	165/530 (31)	8/530 (2)	17/530 (3)	181/530 (34)
	PsO/AS (no IBD, RA, PsA)	70 (2)	17/70 (24)	3/70 (4)	22/70 (31)	1/70 (1)	3/70 (4)	24/70 (34)
TNFi	Preconception	3302 (89)	543/573 (95)	8/68 (12)	480/546 (88)	26/29 (90)	16/110 (15)	2228/2380 (94)
	Postpartum	2522 (68)	174/573 (30)	46/68 (68)	189/546 (35)	22/29 (76)	82/110 (75)	2007/2380 (84)
Corticosteroids								
Preconception		800 (22)	115/573 (20)	11/68 (16)	118/546 (22)	5/29 (17)	31/110 (28)	520/2380 (22)
During pregnancy		1054 (28)	179/573 (31)	32/68 (47)	156/546 (29)	12/29 (41)	53/110 (48)	618/2380 (26)
	1st trimester	604 (16)	95/573 (17)	12/68 (18)	89/546 (16)	5/29 (17)	28/110 (26)	373/2380 (16)
	2nd trimester	605 (16)	102/573 (18)	22/68 (32)	95/546 (17)	8/29 (28)	41/110 (37)	336/2380 (14)
	3rd trimester	536 (14)	99/573 (17)	24/68 (35)	73/546 (13)	8/29 (28)	20/110 (18)	310/2380 (13)
Postpartum		787 (21)	148/573 (26)	16/68 (24)	139/546 (26)	8/29 (28)	23/110 (21)	451/2380 (19)
Non-biologic DMARDs								
Preconception		801 (22)	92/573 (16)	19/68 (28)	84/546 (15)	5/29 (17)	26/110 (24)	574/2380 (24)
During pregnancy		811 (22)	79/573 (14)	23/68 (34)	79/546 (14)	3/29 (10)	32/110 (29)	593/2380 (25)
	1st trimester	672 (18)	60/573 (11)	19/68 (28)	64/546 (12)	2/29 (7)	23/110 (21)	503/2380 (21)
	2nd trimester	562 (15)	39/573 (7)	14/68 (21)	46/546 (8)	3/29 (10)	22/110 (20)	438/2380 (18)
	3rd trimester	509 (14)	43/573 (8)	14/68 (21)	34/546 (6)	1/29 (3)	13/110 (12)	402/2380 (17)
Postpartum		615 (17)	71/573 (12)	16/68 (24)	63/546 (12)	5/29 (17)	12/110 (11)	447/2380 (19)
Diabetes	Pre-gestational	202 (5)	33/202 (16)	4/202 (2)	35/202 (17)	0/202 (0)	11/202 (5)	119/202 (59)
	Gestational	547 (15)	103/547 (19)	8/547 (1)	93/547 (17)	3/547 (1)	21/547 (4)	318/547 (58)
Asthma		265 (7)	33/265 (12)	11/265 (4)	44/265 (17)	1/265 (0)	13/265 (5)	163/265 (62)
Hypertension		404 (11)	67/404 (17)	6/404 (1)	67/404 (17)	5/404 (1)	13/404 (3)	246/404 (61)
Chronic kidney disease		26 (1)	5/26 (19)	0/26 (0)	1/26 (4)	0/26 (0)	1/26 (4)	19/26 (73)
Delivery year								
2011-2013	All	985 (27)	223/985 (23)	24/985 (2)	166/985 (17)	8/985 (1)	18/985 (2)	544/985 (55)
	IBD	549 (15)	46/549 (8)	12/549 (2)	45/549 (8)	0/549 (0)	13/549 (2)	433/549 (79)
	RA (no IBD)	280 (8)	109/280 (39)	10/280 (4)	70/280 (25)	6/280 (2)	4/280 (1)	79/280 (28)
	PsA (no IBD or RA)	138 (4)	59/138 (43)	2/138 (1)	43/138 (31)	2/138 (1)	1/138 (1)	31/138 (22)
	PsO/AS (no IBD, RA, PsA)	18 (0)	9/18 (50)	0/18 (0)	8/18 (44)	0/18 (0)	0 /18 (0)	1/18 (6)
2014-2016	All	1026 (28)	171/1026 (17)	18/1026 (2)	152/1026 (15)	10/1026 (1)	36/1026 (4)	638/1026 (62)
	IBD	617 (17)	36/617 (6)	11/617 (2)	46/617 (7)	2/617 (0)	21/617 (3)	501/617 (81)
	RA (no IBD)	265 (7)	90/265 (34)	5/265 (2)	54/265 (20)	5/265 (2)	13/265 (5)	97/265 (37)

	PsA (no IBD or RA)	122 (3)	41/122 (34)	1/122 (1)	43/122 (35)	2/122 (2)	1/122 (1)	34/122 (28)
	PsO/AS (no IBD, RA, PsA)	22 (1)	4/22 (18)	1/22 (5)	9/22 (41)	1/22 (5)	1/22 (5)	6/22 (27)
2017-2019	All	1004 (27)	129/1004 (13)	10/1004 (1)	148/1004 (15)	4/1004 (0)	25/1004 (2)	688/1004 (69)
	IBD	562 (15)	26/562 (5)	3/562 (1)	34/562 (6)	0/562 (0)	11/562 (2)	488/562 (87)
	RA (no IBD)	274 (7)	64/274 (23)	4/274 (1)	60/274 (22)	3/274 (1)	9/274 (3)	134/274 (49)
	PsA (no IBD or RA)	153 (4)	36/153 (24)	2/153 (1)	49/153 (32)	1/153 (1)	5/153 (3)	60/153 (39)
	PsO/AS (no IBD, RA, PsA)	15 (0)	3/15 (20)	1/15 (7)	5/15 (33)	0/15 (0)	0/15 (0)	6/15 (40)
2020-2021	All	696 (19)	50/696 (7)	16/696 (2)	80/696 (11)	7/696 (1)	31/696 (4)	510/696 (73)
	IBD	366 (2)	9/366 (2)	6/366 (2)	12/366 (3)	1/366 (0)	11/366 (3)	327/366 (89)
	RA (no IBD)	198 (13)	25/198 (13)	6/198 (3)	38/198 (19)	3/198 (2)	8/198 (4)	116/198 (59)
	PsA (no IBD or RA)	117 (13)	15/117 (13)	3/117 (3)	30/117 (26)	3/117 (3)	10/117 (9)	56/117 (48)
	PsO/AS (no IBD, RA, PsA)	15 (7)	1/15 (7)	1/15 (7)	0/15 (0)	0/15 (0)	2/15 (13)	11/15 (73)

*Denominator = 3,711

†The 'Second only' column (n=5) was removed due to small cell sizes to protect patient confidentiality

Abbreviations: AS, ankylosing spondylitis; DMARDs, disease-modifying anti-rheumatic drugs; IBD, inflammatory bowel disease; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; SD, standard deviation.

Note: Percentages may not add up to 100 due to rounding.

4.2.9 Figures

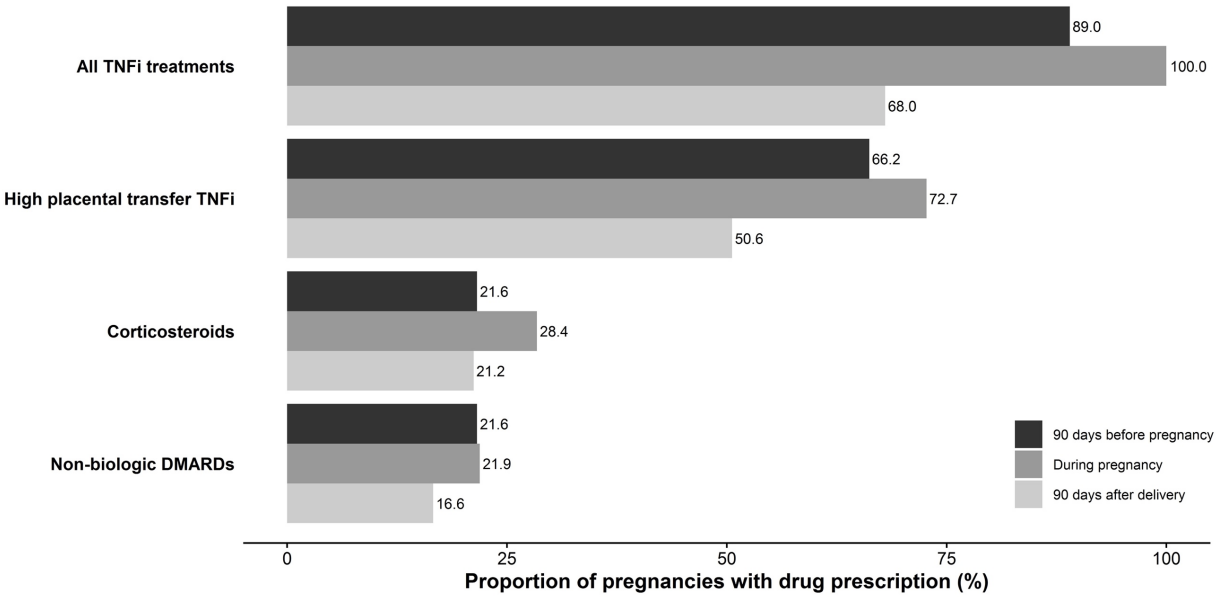

Figure 4.2.1 Proportion of pregnancies prescribed tumour necrosis factor inhibitors (stratified by high placental transfer ability), corticosteroids, and non-biologic DMARDs during the 90 days before, during, and 90 days after delivery, 2011-2021.

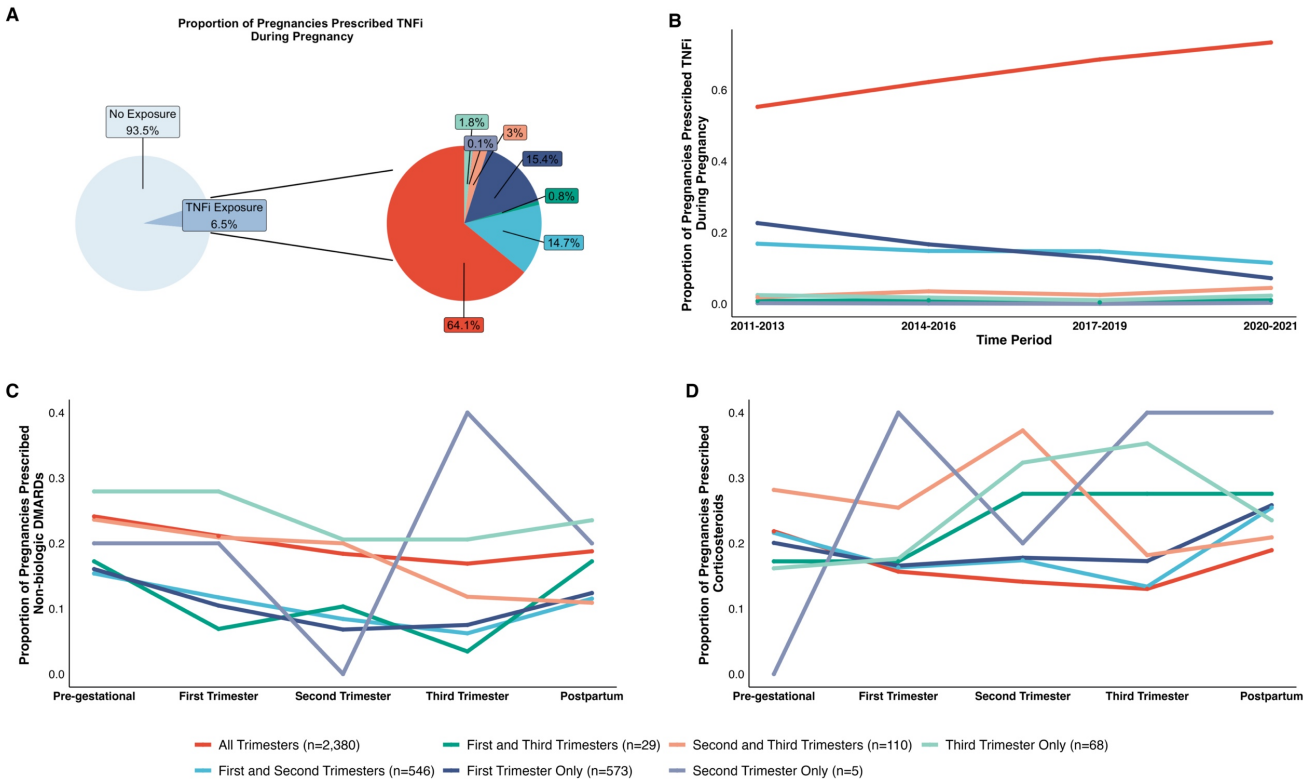

Figure 4.2.2 Proportion and Trends of Medication Prescriptions During Pregnancy, 2011-2021. Panel A shows the proportion of total pregnancies (n=56,866) prescribed tumour necrosis factor inhibitors (TNFi) during pregnancy (n=3,711) and the breakdown of the timing of TNFi usage during pregnancy. Panel B shows the trend between the proportion of pregnancies prescribed TNFi during pregnancy and time, stratified by trimester of pregnancy. Panel C shows the trend over time (before, during, and after pregnancy) of the proportion of patients prescribed non-biologic DMARDs, stratified by trimester of pregnancy. Panel D shows the trend over time (before, during, and after pregnancy) of the proportion of patients prescribed corticosteroids, stratified by trimester of pregnancy.

CHAPTER 5 - MANUSCRIPT #4

5.1 Preamble to Manuscript #4

As mentioned in Chapter 2, during pregnancy, there is active trans-placental transport of maternal circulating immunoglobulins G (IgG) proteins through their fragment crystallizable (Fc) region.[102] Transfer begins around gestational week 16 and increases throughout pregnancy.[103] Most TNFi (i.e. adalimumab, infliximab, golimumab) are monoclonal IgG with an Fc region.[18] Etanercept is a fusion protein comprised of a TNF receptor and the IgG Fc region, and certolizumab is a pegylated Fab fragment of an anti-TNF monoclonal antibody without an Fc region (Figure 5.1.1).[18,19]

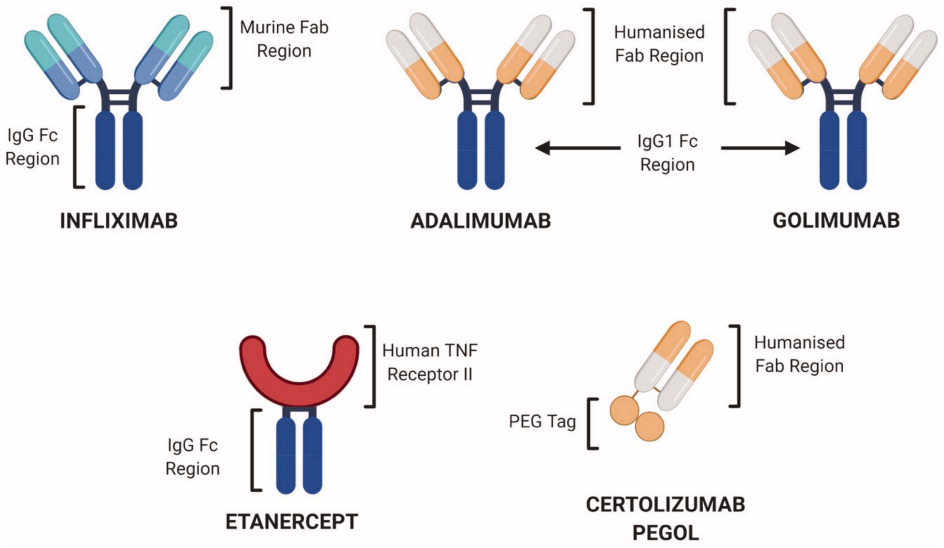

Figure 5.1.1 Structures of tumour necrosis factor inhibitors
Challenges for biosimilars: focus on rheumatoid arthritis. Akram, MS, et al. Critical Reviews in Biotechnology[104] **© copyright 2020**, reprinted by permission of Informa UK Limited, trading as Taylor & Taylor & Francis Group, http://www.tandfonline.com

Therefore, most TNFi are actively transported across the placenta via neonatal Fc receptors, enter the fetus' bloodstream, and may reach higher blood levels in the fetus than in the mother due to the biological half-life being longer in newborns than in adults.[12] Infliximab, adalimumab, and golimumab have the highest trans-placental transfer (reaching cord blood levels of, respectively, 160%, 150%, and 121% of maternal blood levels), while etanercept and certolizumab display the lowest passage (cord blood levels of, respectively, 4% and <0.25% of maternal blood levels).[15,18-20,105,106] As fetuses can be exposed to therapeutic (and potentially supra-therapeutic) TNFi doses, TNFi could cause changes in the offspring's immune system.[14]

There is currently limited data on the risk of serious infections in children exposed *in utero* to TNFi. Furthermore, due to differences in placental transfer ability, evaluating the potential risks of each subtype is critical for delivering appropriate care to mother and child. Similarly, due to the fear of excessive immunosuppression in the offspring, many rheumatology experts recommend cessation of TNFi (primarily infliximab, adalimumab, and golimumab) during late pregnancy (late second or early third trimester).[2,3,107] As a result of certolizumab's low placental transfer ability, guidelines recommend continuing treatment during conception and pregnancy.[2,3,107]

In manuscript #4, I discuss findings surrounding exposure to TNFi *in utero* and the risk of serious infections in offspring born to mothers with chronic inflammatory diseases. This manuscript, entitled "Tumour Necrosis Factor Inhibitors and Risk of Serious Infections in Offspring Exposed in utero to TNFi", will be submitted to *Annals of Rheumatic Diseases*. Conference abstracts based on similar contents of this manuscript were presented as oral presentations at the European Alliance of Associations for Rheumatology (Copenhagen, 2022), the American College of Rheumatology Convergence (Philadelphia, 2022), and the Canadian Rheumatology Association Annual Scientific Meeting (Quebec City, 2023), as well as a poster tour at the Canadian Rheumatology Association Annual Scientific Meeting (Virtual, 2022). My abstract at EULAR was selected as part of the EULAR Clinical Highlights which presents the top 10 most impactful research presented at the meeting. I was also awarded the Best Abstract by a Post-Graduate Research Trainee Award by the Canadian Rheumatology Association (Quebec City, 2023) for my abstract on this objective.

5.1.1 Creating the study cohort

Using the maternal cohort and the variables created in Objective 1 (section 3.1.2), we created a cohort of live births by linking the mothers with their infants using family identifiers (EFAMID) and delivery dates. This method is commonly used with MarketScan data and has been shown to link 81% of mothers with their live births.[108] All maternal demographic variables extracted in Objective 1, as well as chronic inflammatory disease diagnosis, TNFi use, and covariates, were used in this objective (Figure 5.1.2). The original exclusion and inclusion criteria were also used (sections 3.1.2.2, 3.1.2.3). The unit of analysis was the offspring. Cohort entry (time zero) was defined as the date of birth (delivery), with follow-up being the time axis (Figure 5.1.3). Follow-up was from delivery up to 12 months after birth, the first event of interest (i.e.

serious infection or diarrhea-associated health care event), end of commercial insurance eligibility, or death, whichever came first.

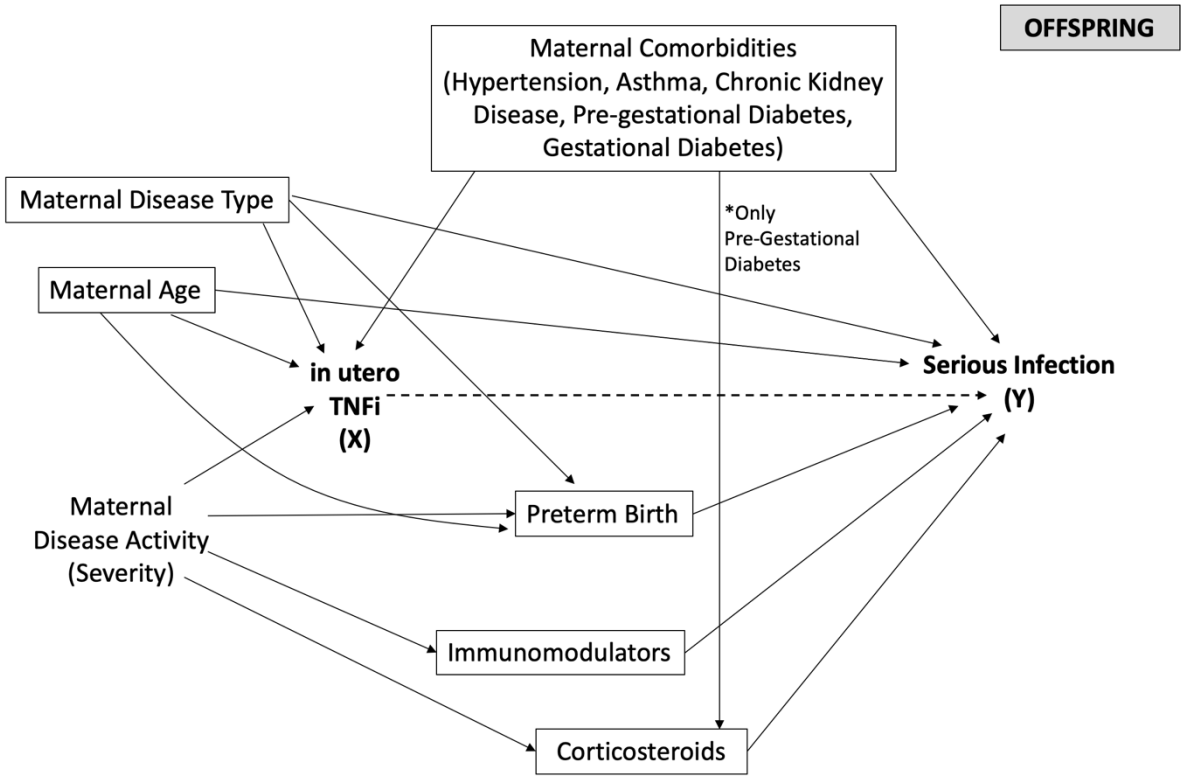

Figure 5.1.2 DAG of potential confounders of offspring analysis: risk of serious infections in offspring exposed *in utero* to TNFi. X is the exposure, and Y is the outcome. Variables adjusted for are in boxes.

Figure 5.1.3 Timeline of follow-up for offspring, TNFi and serious infections

5.1.1.1 Identifying offspring born to women with chronic inflammatory diseases

We identified all *live singleton* births based on women with ≥1 hospitalization for delivery between January 1, 2011 and December 31, 2021. Delivery was defined using any inpatient hospital admission record including a pregnancy-related diagnosis or procedure code for vaginal or caesarean delivery identified by the ICD-9 codes 650, 669.7, V27.x, or procedure codes 72.0-72.9, 73.22, 73.59, 73.6, 74.0-74.2, 74.4, 74.99; ICD-10 codes O60.1-3, O68, O69, O70, O80-O83, Z38.01; Diagnosis Related Group codes for vaginal or caesarean delivery, for version 28 –

version 35 codes 765, 766, 767, 768, 774, 775; for version 36 - version 39: 783-788, 796-798, 805-807; and CPT codes 59400, 59409, 59410, 59610, 59612, 59614 for vaginal delivery and 59510, 59514, 59515, 59618, 59620, 59622 for caesarean delivery. Deliveries were excluded if they were identified as multiple gestation using one or more of the following codes: ICD-9 codes 651.x, V27.2-V27.7, V91.x; ICD-10 codes O30x, O84, Z37.2- Z37.7, Z38.3-Z38.8.

5.1.2 Exposure definition

We defined TNFi exposure in the offspring based on mothers having ≥1 filled prescription and/or infusion procedure code during pregnancy. Fetal TNFi exposure was initially classified as time-varying, as was done in the maternal cohort (section 3.1.3). This allowed us to determine the timing of fetal exposure during pregnancy. Specifically, maternal TNFi exposure was classified based on the timing of prescriptions relative to recorded gestational age and date of birth of each offspring (section 3.1.2.4). After each TNFi prescription, a grace period of 5 half-lives was added to account for the pregnancy's biological exposure to the medication.

Using this information, we then created fixed exposure variables for the offspring. Offspring were classified as exposed to TNFi during all three trimesters if their mother had overlapping prescriptions spanning the entire pregnancy. If no prescriptions were recorded during an entire trimester, and the grace period from prior prescriptions did not extend into that trimester, the offspring were considered unexposed for that trimester. Exposure status could change depending on the timing of prescriptions: offspring classified as unexposed in one trimester could be classified as exposed in another trimester, and vice versa. We further refined TNFi exposure based on the potential for high (i.e. infliximab, adalimumab, golimumab) versus low (i.e. certolizumab, etanercept) placental transfer.[15,18-20,105,106]

5.1.3 Outcome definition

The outcome of interest was the first serious infection in the first year of life, defined as the first admission with a primary hospital discharge diagnosis of infection, from birth to their first birthday. For children with >1 recorded serious infection, I only considered the time to the first event (i.e. age at the first event). Follow-up ended at the time of the first serious infection, and subsequent person-time was not included in the analysis. Follow-up was right-censored for

offspring who remained event-free but reached the end of insurance eligibility, death, or end of the study period (12/2021).

Infection codes were ascertained from both validated and unvalidated studies. Lo Re et al.'s ICD-10 algorithm had a positive predictive value of 80.2% (95% CI 75.1%, 84.6%) for hospitalization for serious infection events among patients prescribed biologics when compared with medical record review.[92] The study was conducted using the FDA's Sentinel Distributed Database.

In addition to Lo Re et al.'s study in adults, one cohort study of infection-related hospital admission in Australia[93] among infants and one Canadian[94] population-based cohort study of serious infections requiring hospitalization in mothers and babies provided a list of ICD-9 diagnostic codes for infection, though neither validated their code list. Another cohort study by Miller et al.[109] studied neonatal infections utilizing previously validated hospitalization data from Henriksen et al., which was done in an adult population.[110] Henriksen et al.'s cross-sectional study was conducted across a range of infection subtypes (i.e., bacterial, viral) in an adult (≥15 years old) Danish database. They estimated ICD-10 discharge diagnosis codes of infection for patients admitted to the medical emergency department to have a sensitivity of 79.9% (95% CI 78.1%, 81.3%), specificity of 83.9% (95% CI 82.6%, 85.1%), positive predictive value of 78.2% (95% CI 76.6%, 79.9%), and negative predictive value of 85.1% (95% CI 83.9%, 86.3%).[110]

These prior studies were used to compile an extensive list of ICD-9/10 codes used to identify serious infections and are available in Appendix A (Table 9.1.2).

5.1.4 Statistical analysis

As I was using Cox proportional hazards models, I needed to ensure that the assumptions were not violated. I checked for non-linear effects of maternal age using quadratics. Using AIC, Bayesian information criterion (BIC), and LRT, I compared the linear model (AGE) with the quadratic model (AGE*AGE). The quadratic model had worse AIC/BIC than the standard linear Cox model; therefore, maternal age was included as a linear variable. I further looked at the time-dependent effects of drug exposure and other covariates by performing *cox.zph*.[96,111] This test evaluates the null hypothesis that a predictor's coefficient remains constant over time, meaning the effect of the variable does not change as time progresses. As none of the variables were

significant, this indicated no apparent violation of the proportional hazards assumption in these variables.

5.2 Manuscript #4: Serious Infections in Offspring Exposed to Tumour Necrosis Factor Inhibitors During Pregnancy: Comparison of Timing During Pregnancy and Placental Transfer

5.2.1 Title Page

Serious Infections in Offspring Exposed to Tumour Necrosis Factor Inhibitors During Pregnancy: Comparison of Timing During Pregnancy and Placental Transfer

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5.2.2 Abstract

Objectives. We evaluated serious infections in offspring exposed to tumour necrosis factor inhibitors (TNFi) *in utero,* separated by timing and placental transfer ability.

Methods. Using MarketScan, we identified offspring born to mothers with chronic inflammatory diseases between 2011 and 2021. TNFi exposure was defined as ≥1 filled prescription during pregnancy, further subdivided by trimesters and placental transfer. Serious infections were based on ≥1 hospitalization with infection in the offspring's first year of life. We performed multivariable survival analysis using a Cox proportional hazards model, adjusting for maternal demographics, disease type, comorbidities, pregnancy complications, and *in utero* drug exposure.

Results. We identified 56,866 offspring; 3,711 (6.5%) were exposed to TNFi during pregnancy. Overall, TNFi exposure was not associated with an increased risk of serious infections compared to unexposed offspring (hazard ratio, HR, 0.85; 95% confidence interval, CI, 0.68, 1.07). However, when focusing on timing, offspring exposed during the third trimester had an 80% higher risk of serious infections compared to those exposed only in the first and/or second trimesters (HR 1.80; 95% CI 1.01, 3.22). Additionally, we observed potential trends for increased risk with TNFi having higher placental transfer ability (infliximab, adalimumab, golimumab) overall (HR 1.50; 95% CI 0.83, 2.69) and during the third trimester (HR 1.32, 95% 0.66, 2.63), compared to low placental transfer TNFi (certolizumab, etanercept).

Conclusions. Our findings suggest that both the timing of TNFi exposure and the drug's placental transfer characteristics may influence the risk of serious infections in offspring.

5.2.3 Introduction

Infections contribute to over one-third of maternal and fetal deaths worldwide [1]. These adverse events are decreasing in frequency in the developed world but remain a concern in vulnerable individuals, including those with chronic inflammatory diseases. Conditions like rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), psoriasis (PsO), and inflammatory bowel diseases (IBD) together affect approximately 10% of pregnant people [2]. In pregnant women with chronic inflammatory diseases, flares are common and may be associated with adverse pregnancy outcomes [3, 4]. Thus, controlling the disease with effective drugs, such as tumour necrosis factor inhibitors (TNFi), is often necessary, with up to 20% of pregnant women with chronic inflammatory diseases being prescribed TNFi [5, 6].

Studies in non-pregnant women have shown that TNFi are associated with a 2- to 4- fold increase in the risk of serious infections compared to non-users with chronic inflammatory diseases [7-9]. In addition to the risk of infections in mothers, there is also a risk of serious infections in the offspring [10]. During pregnancy, TNFi are actively transported across the placenta and enter the fetal bloodstream at different levels depending on the TNFi subtype prescribed (high vs low placental transfer) [11-15]. Infliximab and adalimumab have the highest trans-placental transfer (reaching cord blood levels of, respectively, 160% and 150% of maternal blood levels), while etanercept and certolizumab display the lowest passage (cord blood levels of, respectively, 4-7% and <0.25% of maternal blood levels) [11-15]. As fetuses can be exposed to supratherapeutic TNFi doses, there are concerns that TNFi could cause immunosuppression in the offspring [16].

Chronic inflammatory diseases are highly prevalent in pregnant women; therefore, assessing the risk of infection in their offspring is crucial for guiding the management of women requiring TNFi during pregnancy to minimize offspring complications. We aimed to determine whether TNFi exposure during pregnancy, categorized by timing and placental transfer subtype, increases the risk of serious infections in exposed offspring after birth.

5.2.4 Methods

Data source. We conducted a retrospective population-based cohort study using IBM MarketScan commercial claims data from January 2011 to December 2021 [17]. MarketScan is a large United States database of >250 million individuals with employer-provided health insurance

and contains claims for commercially insured individuals from numerous health plans and employers. It includes data on hospitalizations, outpatient visits, and drug prescription claims.

Study population. We identified all offspring born to women between January 1, 2011, and December 31, 2021, who were between the ages of 15 and 45 and were diagnosed with a chronic inflammatory disease (i.e. RA, AS, PsA, PsO, IBD) before pregnancy (Supplemental Table 5.2.1). Term deliveries were identified through maternal or child International Classification of Diseases 9th and/or 10th revisions (ICD-9/10) codes using a validated algorithm by Margulis et al. [18]. If gestational age was unknown and no preterm code was present, the onset of gestation was estimated by subtracting 39 weeks (273 days) from the delivery date. For cases with a preterm code, 35 weeks (245 days) were subtracted from the birth date to estimate the timing of conception. When preterm birth ICD codes included a gestational age range, we used an algorithm by Li et al. [19]. Offspring were linked with their mothers using family identifiers and delivery dates. This method is commonly used with MarketScan data and has been shown to link 81% of mothers with their live births [20]. Cohort entry was the date of birth and continued until 12 months of age, first serious infection, end of insurance eligibility, death, or end of the study period (12/2021), whichever came first.

Exposure. Offspring were categorized based on *in utero* TNFi exposure, determined through maternal prescription records. TNFi exposure was defined as the mothers having a prescription of any TNFi (infliximab, adalimumab, golimumab, etanercept, certolizumab) established using ≥1 filled prescription and/or ≥1 infusion procedure claims based on National Drug Codes from REDBOOK (source of prescription and over-the-counter pharmaceutical information) and J-codes (billing codes). The timing of the prenatal TNFi exposure was further classified based on the trimester of pregnancy and was calculated using the onset of gestation, accounting for gestational age and offspring's date of birth. The first trimester was defined from gestation onset to 84 days, the second trimester from 85 days to 183 days, and the third from 184 days to delivery.

After each prescription, a grace period of 5 half-lives was added to account for the mother's biological exposure to the medication. Offspring were classified as exposed to TNFi during all three trimesters if the mother had overlapping prescriptions spanning the entire pregnancy. If no prescriptions were recorded during an entire trimester, and the grace period from prior prescriptions did not extend into that trimester, the offspring were considered unexposed for that

trimester. We further refined TNFi exposure by creating two separate groups based on the potential for (i) high (i.e. infliximab, adalimumab, golimumab) versus (ii) low (i.e. certolizumab, etanercept) placental transfer. If a mother took both high and low placental transfer TNFi in the same trimester, they were categorized as high.

Outcome. Our outcome of interest was serious infections occurring in the offspring. We ascertained serious infections based on ≥1 hospitalization with infection as a primary diagnosis (based on relevant diagnostic codes) within the first 12 months of life (Supplemental Table 5.2.2). This approach to identifying serious infections has been shown to have a positive predictive value of >80% [7, 21, 22]. The event's timing was determined based on the date of the first hospitalization for a serious infection. For children with >1 recorded serious infection, we only considered the time to the first event.

Assessment of covariates. Baseline covariates were assessed before delivery and included (i) maternal comorbidities (pre-gestational diabetes, asthma) and pregnancy complications (gestational diabetes, preterm birth) based on ≥1 physician billing and/or hospitalization with relevant diagnostic codes (Supplemental Table 5.2.1), as well as (ii) *in utero* drug exposures to systemic corticosteroids and non-biologic immunomodulators (e.g. sulfasalazine, methotrexate, azathioprine, 6-mercaptopurine, cyclosporine, etc.), based on ≥1 prescription filled by the mother during the gestational period. We additionally included maternal age at delivery and chronic inflammatory disease diagnosis. Maternal disease diagnosis was subdivided into four groups based on severity: (i) those mothers diagnosed with any IBD code, (ii) those mothers diagnosed with any RA code but no IBD code, (iii) those mothers diagnosed with any PsA code but neither IBD nor RA codes, and (iv) those mothers diagnosed with any AS code or PsO code but neither IBD, RA, nor PsA codes.

Statistical analyses. Descriptive statistics were used to summarize the cohort characteristics of offspring with no *in utero* TNFi exposure compared to those exposed to TNFi. We calculated crude incidence rates with 95% confidence intervals (CI) for each exposure group. We ran a standard multivariable Cox proportional hazards model to estimate the adjusted hazard ratio (aHR) for serious infections in children, comparing first those exposed to TNFi to those with no exposure. Then, in those exposed to TNFi during pregnancy, we performed a multivariable Cox proportional hazards model to estimate the adjusted HR for serious infections based on TNFi timing (early vs late pregnancy) and placental transfer of TNFi (high vs low placental transfer).

These models were adjusted for maternal covariates, including age at delivery, chronic inflammatory disease diagnosis, pre-gestational diabetes, and gestational diabetes, as well as preterm birth and maternal use of medications during pregnancy (corticosteroids and non-biologic immunomodulators). Cohort creation was done with SAS® Enterprise Guide version 7.15 (SAS Institute, Cary, NC) [23]. All analyses for this study were conducted using R version 4.3.0 [24]. Ethics approval was obtained from the Research Ethics Office at McGill University (A11-M107-14A).

5.2.5 Results

We identified 56,866 offspring linked to mothers with chronic inflammatory diseases between 2011 and 2021, including 12,775 born to mothers with any IBD diagnosis, 5,643 with any RA diagnosis but no IBD, 37,954 with any PsA diagnosis but no IBD or RA, and 494 with any AS diagnosis or PsO diagnosis but no IBD, RA, or PsA. Among these, 3,711 (6.5%) were exposed to TNFi during pregnancy. Over 46,064 person-years of follow-up, 1,347 children were diagnosed with a serious infection, 86 (6.4%) of whom had been exposed to TNFi *in utero*.

Table 5.2.1 summarizes maternal demographic characteristics, stratified by TNFi exposure status, timing of exposure during pregnancy, and placental transfer subtype in the third trimester. The TNFi-unexposed group includes all pregnancies without recorded TNFi use, while the TNFi-exposed group is divided into those exposed during the 1st and/or 2nd trimesters only and those exposed at some point during the 3rd trimester. Third-trimester TNFi exposures were further classified by placental transfer as low or high.

Compared with unexposed offspring, TNFi-exposed offspring had younger mothers, who were more likely to have used corticosteroids and non-biologic immunomodulators during pregnancy and less likely to have asthma or diabetes (gestational and pre-gestational). TNFi-exposed offspring were also more likely to have mothers diagnosed with IBD and/or RA, while TNFi-unexposed offspring were more likely to have mothers diagnosed with PsA and not IBD or RA.

The incidence rate of serious infections among TNFi-exposed offspring was 28.7 (95% CI 23.0, 35.5) cases per 1,000 person-years and 29.3 (95% CI 27.7, 31.0) cases per 1,000 person-years in TNFi-unexposed offspring (Table 5.2.2). TNFi-exposed offspring did not have an increased risk of serious infections (aHR 0.85; 95% CI 0.68, 1.07) compared to unexposed

offspring. Overall, the most common infections in offspring exposed and unexposed to TNFi were respiratory tract (Supplemental Table 5.2.3).

Among TNFi-exposed offspring, 1,124 (30%) were exposed during the first and/or second trimesters only, and 2,587 (70%) were exposed during the third trimester, regardless of whether they were also exposed in earlier trimesters. Compared to offspring exposed during the first and/or second trimesters only, offspring exposed during the third trimester (+/- other trimesters) were more likely to have been born to mothers with IBD, have been exposed to non-biologic immunomodulators in utero, and less likely to have been born prematurely. Offspring exposed in the third trimester had a significantly higher risk of serious infections than those exposed in the first and/or second trimesters only (33.5 vs 18.2 per 1,000 person-years; aHR 1.80; 95% CI 1.01, 3.22).

Of TNFi-exposed offspring, 2,699 (73%) were exposed to TNFi agents with high placental transfer, while 1,012 (27%) were exposed to agents with low placental transfer. Overall, 70% of pregnancies exposed to high placental transfer TNFi were among IBD mothers, while 54% of pregnancies exposed to low placental transfer TNFi were among RA mothers. In the third trimester, 1,962 (76%) were exposed to high placental transfer TNFi and 625 (24%) were exposed to low placental transfer TNFi. Among offspring born to IBD mothers who were exposed to TNFi during the third trimester (n=1,840), 90% (n=1,661) were exposed to high placental transfer TNFi during this period. These offspring accounted for 85% of all those exposed to high placental transfer at any point during the third trimester.

There was a potential trend toward increased risk of serious infections with high placental transfer TNFi overall (32.3 vs 20.5 per 1,000 person-years; aHR 1.50; 95% CI 0.83, 2.69) and during the third trimester (34.9 vs 29.0 per 1,000 person-years; aHR 1.32; 95% CI 0.66, 2.63) compared to low placental transfer TNFi, although both CI included the null.

5.2.6 Discussion

In this cohort of offspring born to mothers with chronic inflammatory diseases, overall TNFi exposure during pregnancy (i.e., at any time) was not associated with a significant increased risk of serious infections compared to TNFi-unexposed offspring as shown in prior studies. However, among TNFi-exposed offspring, the timing of TNFi exposure during pregnancy was an important factor. Specifically, offspring exposed during the third trimester had an 80% higher risk

of serious infections compared to those exposed only in the first and/or second trimester exposure. We also identified a potential trend toward increased infection risk among offspring exposed to high placental transfer TNFi compared to those exposed to low placental transfer TNFi. This was particularly noticeable (albeit still not statistically significant) during the third trimester.

Although we adjusted for preterm birth, maternal disease type, and other drug exposures (including corticosteroids), residual confounding by maternal disease characteristics, including severity, might be possible. For example, mothers who can stop using TNFi during pregnancy may have milder disease and/or lower disease activity than those who continue the drug. Maternal disease severity may be associated with adverse outcomes other than preterm birth, such as small for gestational age status, which can increase the risk of infection in offspring, as observed in mothers with RA [25]. Notably, the vast majority (71%) of pregnancies exposed to TNFi in the third trimester occurred in mothers with IBD, as opposed to 23% in those exposed in the first and/or second trimester only. Also, most pregnancies (70%) exposed to high placenta transfer TNFi were in mothers with IBD, compared to 21% of pregnancies exposed solely to low placental transfer TNFi.

It is important to emphasize that, despite the increased relative risk of infections in offspring, the absolute risk remains relatively small - approximately 30 events per 1000 infants followed for 1 year. This absolute risk should be considered in the context of potential adverse outcomes in mothers and offspring resulting from sub-optimally treated disease.

A few previous studies on the risk of serious infections in offspring exposed to biologics, including TNFi, have been published [10]. A systematic review and meta-analysis found a small increased risk of newborn infections (odds ratio, OR, 1.12, 95% CI 1.00, 1.27) among TNFi-exposed offspring born to mothers with IBD and RA compared to children born to diseased controls [26]. Studies featured in that meta-analysis included our prior MarketScan commercial data analyses, which were unable to detect a clear increase of hospitalized infection among the 380 offspring born to mothers with RA exposed to TNFi at any time during pregnancy (OR, 1.4; 95% CI 0.7, 2.8) or among the 156 exposed during the third trimester (OR 1.4; 95% CI 0.5, 3.6) compared to RA offspring who were unexposed [27]. Also included, Luu et al. did not find an increase in hospital infections among offspring with IBD mothers (n=797) in their retrospective study using a French national health system database (adjusted OR 0.85; 95% CI 0.64, 1.13) [28].

Some studies included in that systematic review, but not among the newborn infection meta-analysis, reported mixed findings. For example, Chambers et al., analyzing prospectively US and Canadian pregnancy registry data, found no significant differences in the risk of serious infections in offspring born to mothers with RA and Crohn's disease, comparing those exposed to adalimumab versus unexposed children (n= 229; relative risk 0.97; 95% CI 0.34, 2.77) [29]. Bröms et al. found a significant association between TNFi exposure and an increased risk of hospital admissions due to infections during the offspring's first year of life with an incidence rate ratio (IRR) of 1.29 (95% CI 1.11, 1.50; n=1,027) compared to the general population in their population-based study using registries [30]. They further looked at TNFi compared to non-biologic immunomodulators and found that the IRR for hospital admissions for infection in the infant's first year was 1.25 (95% CI 1.05, 1.48). The risk associated with TNFi exposure was actually larger when exposure occurred in the first and/or second-trimester exposure only, with an IRR of 1.32 (95% CI 1.07, 1.61) compared to non-biologic immunomodulator exposure in this period. In contrast, TNFi exposure during the third trimester only was associated with a smaller, non-significant IRR of 1.15 (95% CI 0.87, 1.50) compared to non-biologic immunomodulator exposure. Finally, a study by Nørgård et al., which was not included in the systematic review due to its publication date, used Danish health registries and found an elevated risk of hospital-diagnosed infection in children less than one year who had been born to mothers treated with TNFi (in the 3 months before conception or during pregnancy) compared to unexposed children (n=493; HR 1.44, 95% CI 1.19, 1.74) [31]. Key limitations in all these studies arose from low power and other issues, such as variability in the type of TNFi, grouping TNFi with other biologics, the timing of TNFi exposure, and the choice of the comparison group (e.g. general population, offspring born to non-diseased mothers).

Our own study has some potential limitations. As our study is retrospective in nature and uses administrative data, it might suffer from potential residual confounding due to unmeasured confounders or effect modifiers (e.g. body mass index, smoking, disease activity) as mentioned previously. The covariates used in our study all relate to the mother, except for premature birth. We were unable to adjust for small for gestational age status (data we didn't have), which could be associated with an increased risk of serious infections in the offspring. This is a limitation of most studies done with administrative health data. Future studies could consider these issues, where possible.

Our study has important strengths. We used a large administrative health database that has been extensively used to conduct pharmacoepidemiologic studies in chronic inflammatory diseases, particularly related to biologic drugs such as TNFi, as well as in studies on drug safety in pregnancy. Furthermore, MarketScan data allowed us to assess the rare outcome of serious infections in offspring exposed to TNFi, stratified by trimester of exposure. Additionally, using an administrative database limited risk of recall bias as all data (exposure, outcome, and covariates) were obtained from prospectively recorded administrative records. It also mitigated the potential for selection bias by providing a comprehensive, population-based sample. Finally, our case definitions for maternal chronic inflammatory disease diagnoses have been previously validated [32-38].

Similarly, the outcome of interest in our study was serious infections, which were diagnosed using ICD-9 and ICD-10 discharge diagnosis codes. These infection codes were previously evaluated by Henriksen et al. in a general population of adult Danish patients admitted to the hospital, and compared to chart review as the gold standard; ICD-10 infection codes had a sensitivity of 79.9% (95% CI 78.1%, 81.3%) and a specificity of 83.9% (95% CI 82.6%, 85.1%) [22]. An advantage of using these validated codes is that the authors included both viral and bacterial infections. However, we cannot rule out residual non-differential outcome misclassification due to errors in physicians' diagnoses of the offspring (or in the hospital clerks' recording of discharge diagnoses using ICD). Non-differential misclassification would make our effect estimates more conservative, meaning that the true effect may be stronger than what we observed.

Our study is the first to compare the risk of serious infections according to TNFi subtypes. Other studies have primarily compared exposed children to either unexposed offspring born to mothers with autoimmune diseases or the general population. In contrast, we focused specifically on offspring born to mothers with chronic inflammatory diseases, stratified by TNFi exposure, and uniquely categorized TNFi usage into two groups based on placental transfer ability: high versus low. The findings from our study will guide clinicians when counselling and/or prescribing TNFi to women who are pregnant or plan to get pregnant. Despite the potential relative increased risk of serious infections associated with third trimester exposure and/or high placental transfer, the absolute risk was small, with up to 35 cases per 1,000 person-years. This small absolute risk should be emphasized in counselling patients who often fear that their medications will harm their fetus.

The reassurance may potentially result in better compliance during pregnancy, thus reducing the risk of flares, which have been associated with adverse pregnancy outcomes [3, 4].

In conclusion, in this cohort of offspring born to mothers with chronic inflammatory diseases, overall TNFi exposure during pregnancy was not clearly associated with a significant increase in serious infections compared to unexposed offspring. However, among TNFi-exposed offspring the timing of exposure was important. Offspring exposed during the third-trimester, particularly to TNFi agents with high placental transfer, appear to heighten the risk of serious infections during the first year of life compared to those exposed only in the first and/or second trimesters. These findings highlight the importance of considering both the timing and type of TNFi therapy during pregnancy to balance maternal disease management with minimizing potential risks to the offspring. Notably, controlling disease activity with TNFi may enable some women to carry their pregnancies to term, making a potentially increased risk of neonatal infections an acceptable trade-off in cases where these women might not have otherwise been able to have children. Further research is needed to explore the long-term health outcomes of TNFi-exposed children; in particular, directly measuring TNFi levels in infants, and determining correlation with infection risk, would be a novel future addition to the literature.

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5.2.9 Tables

Table 5.2.1 Maternal demographic data stratified by TNFi exposure, gestational timing, and placental transfer in the third trimester.

Variable, n (%)	Overall Total (n=56,866)	TNFi-unexposed (n=53,155)	TNFi				
			TNFi-exposed (n=3,711)		3rd trimester		
				1st and/or 2nd trimesters only (n=1,124)	3rd trimester exposure (n=2,587)	Low placental transfer only during 3rd trimester (n=625)	High placental transfer at some point during 3rd trimester (n=1,962)
Age, mean ± SD years	33.2 ± 4.3	33.3 ± 4.3	32.4 ± 4.2	32.7 ± 4.3	32.3 ± 4.1	32.5 ± 4.1	32.2 ± 4.1
Asthma	5708 (10)	5443 (10)	265 (7)	77 (7)	188 (7)	38 (6)	150 (8)
Chronic kidney disease	321 (1)	295 (1)	26 (1)	6 (1)	20 (1)	3 (1)	17 (1)
Pre-gestational diabetes	4218 (7)	4016 (8)	202 (5)	68 (6)	134 (5)	34 (5)	100 (5)
Gestational diabetes	10101 (18)	9554 (18)	547 (15)	197 (18)	350 (14)	92 (15)	258 (13)
Corticosteroids	6439 (11)	5385 (10)	1054 (28)	339 (30)	715 (28)	240 (38)	475 (24)
Non-biologic immunomodulators	5296 (9)	4485 (8)	811 (22)	160 (14)	651 (25)	143 (23)	508 (26)
Any IBD diagnosis	12775 (23)	10681 (20)	2094 (56)	254 (23)	1840 (71)	179 (29)	1661 (85)
Any RA diagnosis but no IBD	5643 (10)	4626 (9)	1017 (27)	515 (46)	502 (19)	322 (52)	180 (9)
Any PsA diagnosis but no IBD or RA	37954 (67)	37424 (70)	530 (14)	316 (28)	214 (8)	103 (17)	111 (6)
Any AS diagnosis or PsO diagnosis but no IBD, RA, or PsA	494 (1)	424 (1)	70 (2)	39 (4)	31 (1)	21 (3)	10 (1)
Premature rupture of membranes	7240 (13)	6781 (13)	459 (12)	128 (11)	331 (13)	95 (15)	236 (12)
Prolonged labour	969 (2)	917 (2)	52 (1)	14 (1)	38 (2)	9 (1)	29 (2)
Preterm delivery	8999 (16)	8392 (16)	607 (16)	217 (19)	390 (15)	100 (16)	290 (15)

Variable, n (%)	Overall Total (n=56,866)	TNFi-unexposed (n=53,155)	TNFi				
			TNFi-exposed (n=3,711)	1st and/or 2nd trimesters only (n=1,124)	3rd trimester		
					3rd trimester exposure (n=2,587)	Low placental transfer only during 3rd trimester (n=625)	High placental transfer at some point during 3rd trimester (n=1,962)
Placental transfer, high anytime during pregnancy	2699 (5)	-	2699 (73)	696 (62)	2003 (77)	-	-
Adalimumab	1501 (3)	-	1501 (40)	504 (45)	997 (39)	-	-
Infliximab	1131 (2)	-	1131 (31)	156 (14)	975 (38)	-	-
Golimumab	94 (0.1)	-	94 (3)	41 (4)	53 (2)	-	-
Certolizumab	497 (1)	-	497 (13)	95 (9)	402 (16)	-	-
Etanercept	610 (1)	-	610 (16)	342 (30)	268 (10)	-	-

Abbreviations. AS, ankylosing spondylitis; IBD, inflammatory bowel disease; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; SD, standard deviation; TNFi, tumour necrosis factor inhibitor.

Table 5.2.2 Crude and adjusted hazard ratios for the association between tumour necrosis factor inhibitors and the risk of serious infections, separated by TNFi exposure, gestational timing, and placental transfer in the third trimester.

Exposure	Serious infection events	Person-years	Incidence rate (95% CI)*	Hazard ratio (95% CI)	
				Crude	Adjusted[†]
Overall TNFi exposure (n=56,866)					
No-TNFi (n=53,155)	1261	43,052	29.3 (27.7, 31.0)	1.00	1.00 (reference)
TNFi (n=3,711)	86	2,994	28.7 (23.0, 35.5)	0.98 (0.79, 1.22)	0.85 (0.68, 1.07)
Early vs late TNFi exposure (n=3,711)					
$1^{st}/2^{nd}$ trimesters only (n=1,124)	17	934	18.2 (10.6, 29.2)	1.00	1.00 (reference)
3^{rd} trimester (n=2,587)	69	2,060	33.5 (26.1, 42.4)	1.82 (1.07, 3.09)	1.80 (1.01, 3.22)
Placental transfer (n=3,711)					
Low placental transfer (n=1,012)	18	879	20.5 (12.1, 32.4)	1.00	1.00 (reference)
High placental transfer (n=2,699)	68	2,115	32.2 (25.0, 40.8)	1.51 (0.89, 2.57)	1.50 (0.83, 2.69)
Placental transfer, third trimester (n=2,587)					
Low placental transfer (n=625)	14	483	29.0 (15.9, 48.7)	1.00	1.00 (reference)
High placental transfer (n=1,962)	55	1,578	34.9 (26.3, 45.4)	1.22 (0.68, 2.19)	1.32 (0.66, 2.63)

Abbreviations. TNFi, tumour necrosis factor inhibitor; CI, confidence interval

*per 1000 person-years

[†]Adjusted for maternal covariates (i.e., age, pre-gestational diabetes, gestational diabetes, chronic inflammatory disease state), preterm birth, and *in utero* drug exposure (i.e., corticosteroids and non-biologic immunomodulators).

5.2.10 Supplemental

Supplemental Table 5.2.1 Definitions used within MarketScan databases, based on diagnostic and procedure codes.

Definitions	ICD-9	ICD-10	Diagnosis-Related Group (DRG) codes	CPT Procedure codes
Included deliveries: Vaginal	650, V27.0, V27.2, 72.0-72.9, 73.22, 73.59, 73.6	O60.1-3, O68, O69, O70, O80, O81, O83	v28-v35: 767, 768, 774, 775 v36-v39: 796-798, 805-807	59400, 59409, 59410, 59610, 59612, 59614
Included deliveries: Caesarean section	669.7, 74.0-74.2, 74.4, 74.4, 74.99	Z38.01, O82	v28-v35: 765, 766 v36-v39: 783-788	59510, 59514, 59515, 59618, 59620, 59622
Premature rupture of membranes	658.1, 658.2	O42.1, O42.9		
Prolonged labour	662.01, 662.11,	O63.0, O63.1, O63.9		
Multiple gestation	651.x, V27.2-V27.7, V91.x	O30, O84, Z37.2-Z37.7, Z38.3-Z38.8		
Inflammatory bowel diseases (Crohn's disease & Ulcerative colitis)	555.xx, 556.xx	K50.x, K51.x		
Psoriasis or Psoriatic Arthritis	696.0, 696.1	L40.0-L40.4, L40.5x, L40.8, L40.9, M07.0-M07.3, M09.0		
Rheumatoid Arthritis	714	M05, M06		
Ankylosing Spondylitis	720.0	M45, M08.1		
Preterm delivery	644.0x-644.1x, 644.2x (765.0, 765.1 in offspring)	O60	DRGv28-35: 791, 792 DRGv36-39: 791, 792	
Maternal asthma	493	J45		
Maternal chronic kidney disease	585, 403, 404	N18, I12, I13		
Pre-gestational diabetes	250-250.93, 648.00-648.04	O24.0-24.3, E10-E14		
Gestational diabetes	648.8	O24.4, O24.9		

Supplemental Table 5.2.2 Serious infection ICD-9 and ICD-10 codes used within IBM MarketScan databases

	ICD-9	ICD-10
Infectious and parasitic disease	001–139.9	A00-B99
Further separated into organ involvement		
Abdominal		A00.9, A01.1, A02.0, A03.8, A04.3, A04.5, A04.7, A04.8, A04.9, A05.9, A08.0, A08.1, A08.2, A08.3, A08.4, A08.5, A09, A09.9, B67.0, K35.0, K35.0A, K35.1, K35.1A, K35.9, K57.2B, K57.3, K57.3A, K57.3B, K57.3F, K57.9A, K65.0,K65.0A, K65.0G, K65.0J, K65.8, K65.8I, K65.9, K75.0, K80.3, K80.4, K81.0, K81.9, K83.0
Cardiovascular	421	I30.0, I30.1, I30.8, I30.9, I33.0, I33.9, I38.9, I39.8
Central nervous system	320, 323, 324	A39.0, A39.2A, A86.9, A87.0, A87.9, B00.3, B00.4, B02.0, B02.2, B02.2A, B02.2B, B91.9, G00.1, G00.8, G00.9, G00.9A, G01.9, G04.0, G04.2, G06.0, G06.0F, G06.2, G07.9
Respiratory system	460-466, 473, 480-487, 510	Pneumonia: A31.0A, A48.1, B37.1, J12.0, J13.9, J14.9, J15, J15.0, J15.1, J15.2, J15.4, J15.5, J15.7, J15.8, J15.9, J17.0, J17.8C, J18, J18.0, J18.1, J18.8, J18.9, J20.9, J20.9A, J21.9, J22.9, J69.0, J69.8, J69.8A Other: A15.0, A15.1, A15.2, A15.9, B90.9, J40.9, J44.0, J85.1, J85.2, J86.0, J86.9
Other sites of infection	790.7	B00.2A, B02.3G, B37.3A, B37.4, B37.8C, E06.0, E06.1, H65.1, H66.0, H66.9, J00.9B, J01.0, J01.1, J01.2, J01.8, J01.9, J02.0, J02.9, J02.9B, J03.0, J03.9, J03.9A, J04.0, J05.1, J06.9, J36.9, J39.0C, K04.0A, K05.3A, K10.2C, K11.2C, K12.1, K62.8L, N41.2, N45.0B, N45.9, N45.9A, N76.4A, O86.8
Skin, muscles, and bones	681-686, 711.0, 730	A46.9, B00.1A,B00.1B, B37.2, K61.0, K61.0A, K61.1, K61.2, L02.2, L02.2T, L02.4, L02.4F, L02.4K, L02.9, L02.9A, L03.1, L03.1E, L03.3, L08.8, L08.9, M00.0, M00.2, M00.2A, M00.8, M00.9, M46.3, M46.4, M46.5, M46.5A, M46.9, M71.1, M86.1, M86.8, M86.9
Unknown		A40.1, A40.3, A40.8, A40.9, A41.0, A41.1, A41.1A, A41.2, A41.3, A41.4, A41.5, A41.8, A41.9, A49.9A, B37.7, A32.9, A41.9A, A42.9, A44.9, A48.2, A49.0, A49.1, A49.3, A49.8, A49.9, A68.9, A70.9, A81.2, B00.8, B02.9, B34.0, B34.9, B36.9, B37.0, B37.8, B80.9, B89.9, B95.5, B95.6, B95.6A, B96.4, B96.5, B96.8, B99.9, R50, R50.0, R50.8, R50.9, T81.4D, T84.6, T89.9
Urinary tract	590	A41.9B, N10.9, N12.9, N13.6, N30.0, N30.8, N30.9, N39.0, N39.0B
Viral/Systemic		A51.5, A79.9, B00.1, B05.9, B20.4, B20.6, B20.8, B23.0, B23.2, B24.9, B25.8, B25.9, B27.0, B27.9, B50.9, B52.9, B54.9, B55.0, B58.9, J09.1, J09.9, J10.0, J10.8, J11, J11.0, J11.1, J11.8

Supplemental Table 5.2.3 Most frequent types of serious infections across categories of TNFi exposure

Types of serious infection		Cases of serious infection (%)							
		Overall TNFi exposure (n=56,866)		Early vs late TNFi exposure (n=3,711)		Placental transfer (n=3,711)		Placental transfer, third trimester (n=2,587)	
		No-TNFi (n=1261)	TNFi (n=86)	1st/2nd trimesters only (n=17)	3rd trimester (n=69)	Low placental transfer (n=18)	High placental transfer (n=68)	Low placental transfer (n=14)	High placental transfer (n=55)
ABD	Abdominal	22 (2)	2 (2)	0 (0)	2 (3)	0 (0)	2 (3)	0 (0)	2 (4)
LRT	Lower respiratory tract	329 (26)	23 (27)	7 (41)	16 (23)	7 (39)	16 (24)	4 (29)	12 (22)
SMB	Skin, muscles and bones	19 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
UNK	Unknown	44 (3)	3 (3)	1 (6)	2 (3)	1 (6)	2 (3)	0 (0)	2 (4)
URI	Urinary tract	33 (3)	8 (9)	2 (12)	6 (9)	3 (17)	5 (7)	3 (21)	3 (5)
URT	Upper respiratory tract	36 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
VRS	Viral/Systemic	90 (7)	8 (9)	0 (0)	8 (12)	1 (6)	7 (10)	1 (7)	7 (13)
NE9	Necrotizing enterocolitis in newborn	6 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
COP	Certain conditions originating in the perinatal period	69 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
DDS	Diseases of the digestive system	3 (0)	1 (1)	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	1 (2)
DEA	Diseases of the eye and adnexa	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
DEM	Diseases of the ear and mastoid process	0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
DGS	Diseases of the genitourinary system	34 (3)	1 (1)	0 (0)	1 (1)	1 (6)	0 (0)	1 (7)	0 (0)
DMT	Diseases of the musculoskeletal	3 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

	system and connective tissue								
DNS	Diseases of the nervous system	7 (1)	1 (1)	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	1 (2)
DRS	Diseases of the respiratory system	402 (32)	26 (30)	6 (35)	20 (29)	3 (17)	23 (34)	4 (29)	16 (29)
DST	Diseases of the skin and subcutaneous tissue	22 (2)	3 (3)	1 (6)	2 (3)	1 (6)	2 (3)	0 (0)	2 (4)
IPD	Infectious and parasitic diseases (A00-B99)	112 (9)	8 (9)	0 (0)	8 (12)	1 (6)	7 (10)	1 (7)	7 (13)
NEC	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	29 (2)	2 (2)	0 (0)	2 (3)	0 (0)	2 (3)	0 (0)	2 (4)

CHAPTER 6 - MANUSCRIPT #5

6.1 Preamble to Manuscript #5

In utero exposure to TNFi could result in a delay in administering the rotavirus vaccine to offspring due to fear of immunosuppression, as TNFi can be present in infants for up to six months.[12,112] Consequently, adverse effects may occur in early life, including those associated with routine childhood immunizations. In manuscript #5, I used survival analysis to explore the risk of diarrhea-associated healthcare events in offspring exposed to TNFi *in utero* compared to those who were unvaccinated. This manuscript, entitled "Diarrhea Events in Offspring Exposed to TNF Inhibitors & Rotavirus Vaccine," will be submitted to *Annals of Rheumatic Diseases.* Conference abstracts based on the contents of this manuscript were presented at the Infectious Diseases and Immunity in Global Health (IDIGH) Research Day (Montreal, 2024), the Laurentian Conference of Rheumatology (Estérel, 2024), and at the American College of Rheumatology Convergence (Washington DC, 2024) as oral presentations. It was also presented at the European Alliance of Associations for Rheumatology (Vienna, 2024) as a poster tour presentation and was presented as a poster at the Canadian Rheumatology Association Annual Meeting (Calgary, 2025). Additional information regarding cohort creation is presented below. I was awarded the Emerging Investigator Excellence Award for Reproductive Issues in Rheumatic Disorders (which recognizes outstanding abstracts presented by investigators at an early stage of their career [only one award is given per abstract category]) by the American College of Rheumatology for this research (Washington DC, 2024). I was also awarded the Best Abstract by a Post-Graduate Research Trainee Award by the Canadian Rheumatology Association (Calgary, 2025) for my abstract on this objective.

6.1.1 Background on rotavirus vaccination

In North America, the rotavirus vaccine is the only live vaccine administered before 6 months of age as part of the routine immunization schedule (Figure 6.1.1). Two oral live attenuated vaccines (with similar efficacy and safety) have been available for the prevention of rotavirus disease, the pentavalent (RV5)[113] and the monovalent (RV1)[114] rotavirus vaccines, since they were introduced in the US in 2006 and 2008, respectively. RV5 is administered at 2, 4, and 6 months of age, while RV1 is administered at 2 and 6 months, and both vaccines are highly effective in preventing rotavirus disease, reducing diarrhea-related events by >90%.[53,54]

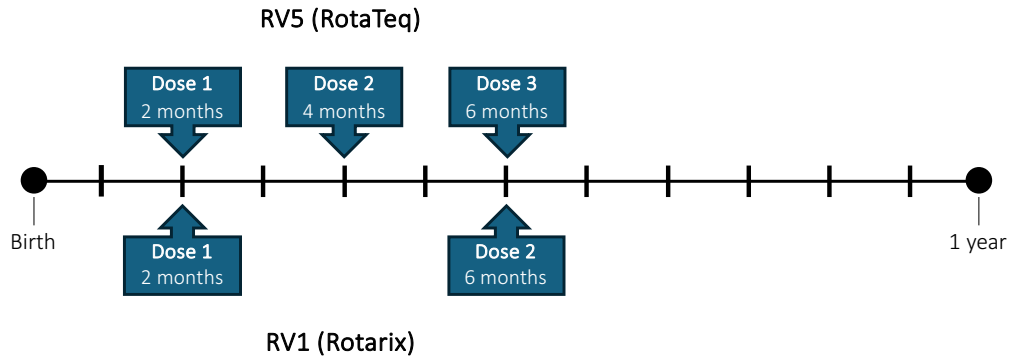

Figure 6.1.1 Rotavirus vaccine schedule

6.1.2 Creating the study cohort

Using the offspring cohort created in Chapter 5 by identifying all *live singleton* births based on women with ≥1 hospitalization for delivery, we further excluded infants born in the 13 US states with a state-funded universal rotavirus vaccine program (i.e. Alaska, Idaho, Maine, Massachusetts, New Hampshire, New Mexico, North Dakota, Oregon, Rhode Island, Vermont, Washington, Wisconsin, and Wyoming).[115] There would be no private insurer claims for the rotavirus vaccine among these children; therefore, commercial databases would not capture them. These 13 states represent 25% of the overall MarketScan database.[116] We used the MarketScan identifiers Metropolitan Statistical Area (MSA), State of employee (STATE), Geographic Location Employee (EGEOLOC), and Geographic Region of employee residence (REGION) to identify and exclude the aforementioned states.

As I wanted to examine the risk of diarrhea-associated events in children exposed to TNFi who received the vaccine before 6 months of age, I further restricted the analysis to include only children exposed *in utero* to TNFi. Children were required to have continuous insurance enrollment during the study period unless they died, in which case a shorter eligibility period was allowed. Children were followed from birth until 6 months, death, or end of the study period (12/2021) (Figure 6.1.2).

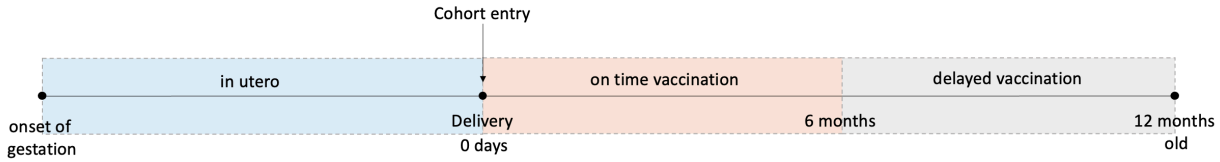

Figure 6.1.2 Timeline of follow-up for offspring, rotavirus vaccine

6.1.3 Exposure definition

The exposure was rotavirus vaccine (RV1 and RV5) and was based on ≥1 CPT code for RV5 (90681) and/or RV1 (90680), which have been previously validated in commercially insured US infant populations with positive predictive values of 86.7% - 88.5%.[117,118] Rotavirus vaccination was classified as time-varying, allowing a child to be switched from a period of no exposure to a period of exposure (i.e. vaccinated) only after receiving the first dose of rotavirus vaccine.

6.1.4 Outcome definition

The outcome was the first instance of diarrhea-associated health care use via relevant diagnostic codes at hospitalizations and/or outpatient visits: ICD-9 008.6-008.8, 001.0-005.9, 008.0-008.5, 006.0-007.9, 009.0-009.3, 558.9, 787.9; ICD-10 A00-A09. This approach has been previously used to assess the effect of the rotavirus vaccine on diarrhea-associated events within MarketScan.[52,53] Outpatient events were identified based on 1 of the 2 diagnosis fields in the outpatient services table.[53] Events were classified as emergency department visits (not hospitalizations or outpatient visits) if "urgent care facility" or "emergency room" was specified in either the inpatient services table or the outpatient services table.[53]

6.1.5 Covariates

Additional covariates used in this analysis included geographic region, calendar year of birth, and birth season (Figure 6.1.3). Studies have shown that there is a global seasonality of rotavirus disease, including in the United States.[119] Specifically, in the US, rotavirus is prevalent during the fall and winter months.[120] One study from the US found that children born in the winter had the highest hazard of hospitalization compared to children born in spring, summer, or fall.[121] Another study found considerable geographic variation in rotavirus vaccination rates in the US.[122] As a result of these geographic differences and the seasonality, I adjusted for the geographic region of birth as well as the season of birth (October-March vs. April-September). Furthermore, calendar year of birth has been shown to be associated with the risk of hospitalization due to rotavirus, with odd calendar years being classified as having high activity.[121] Therefore, the calendar year of birth was grouped into three categories (2011-2014, 2015-2018, 2019-2021) and was included in the models.

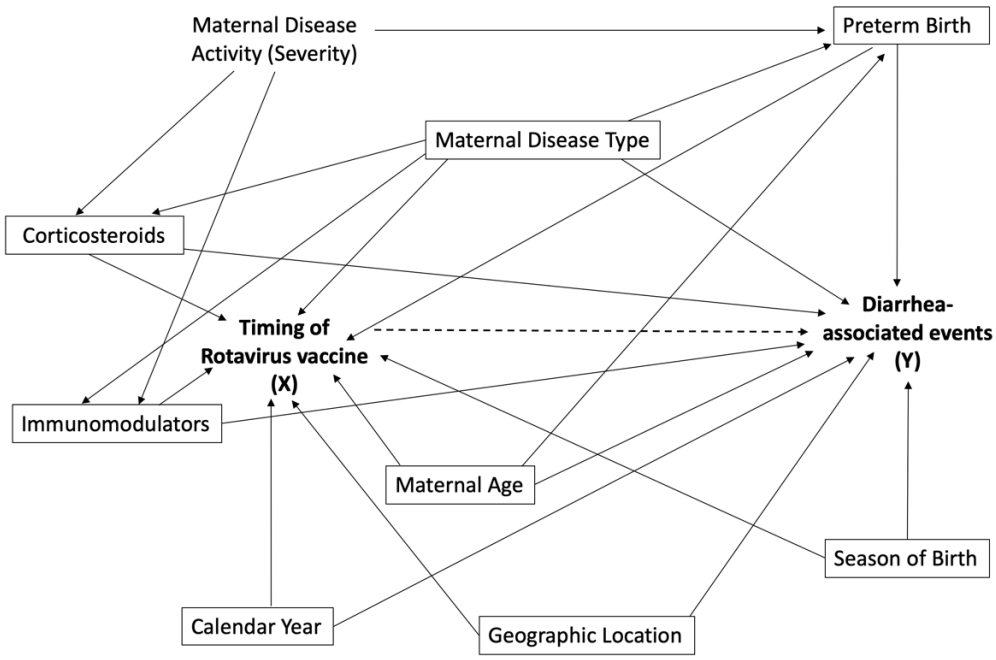

Figure 6.1.3 DAG of potential confounders of offspring rotavirus analysis: risk of diarrhea-associated events in TNFi-exposed offspring receiving the rotavirus vaccine. X is the exposure and Y is the outcome. Available variables to adjust are in boxes.

6.1.6 Descriptive analysis

As offspring exposed to TNFi *in utero* are recommended to receive their rotavirus vaccines on a delayed schedule, I first looked at the distribution of the first vaccine among TNF-exposed and TNFi-unexposed offspring to see if those exposed to TNFi are indeed on a delayed schedule. The median length of time from birth to the first vaccine for both TNFi groups was 64 days (Table 6.1.1). According to guidelines, the vaccines can be administered as early as 42 days old.[113,114] Thirty-six offspring were excluded from the dataset as their date of vaccine was less than that (e.g., some had their vaccine date a day after birth). The pattern of time to the first vaccine among TNFi-exposed and TNFi-unexposed was very similar (Figure 6.1.4), showing that the vaccination patterns are very similar among both groups of offspring.

Table 6.1.1 Time to first rotavirus vaccine after birth among TNFi-exposed and TNFi-unexposed offspring

TNFi exposure	N	Mean	Median	Std Dev	Minimum	Maximum	P25	P75	P90
0	38763	67.3	64.0	15.0	42.0	183.0	62.0	68.0	77.0
1	2240	67.9	64.0	15.9	42.0	182.0	62.0	68.0	78.0

Abbreviations: N, number of offspring; P25, 25th percentile; P75, 75th percentile; P90, 90th percentile; Std Dev, standard deviation.

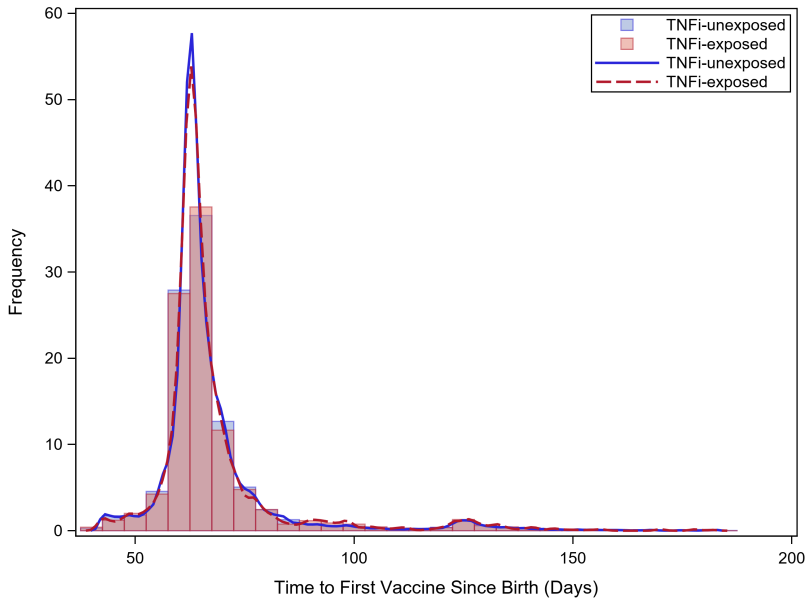

Figure 6.1.4 Distribution of time from birth until first rotavirus vaccine administration among TNFi-exposed (red) and TNFi-unexposed (blue) offspring

I further checked to see how many offspring became sick within two weeks after receiving the rotavirus vaccine. According to the FDA reports for the vaccines, an efficacy study found that the protective effect of the vaccine after one dose was 89.8% (95% CI 8.9, 99.8).[114] Similarly, the report also mentioned that peak viral shedding in stool was 7 days after Dose 1 and that median viral shedding was 10 days. As a result, I assumed that by 14 days after vaccination, the diarrhea-associated healthcare events I witnessed were no longer vaccine-associated events. The smallest duration between vaccination and diarrhea-associated healthcare events was 0 days in both the TNFi-unexposed group and the TNFi-exposed group (Table 6.1.2; Figure 6.1.5). Overall, 127 offspring (120 in TNFi-unexposed (11.2%) and 7 in TNFi-exposed (11.9%)) had a diarrhea-associated healthcare use event within 14 days of receiving the vaccine.

Table 6.1.2 Time to first diarrhea-associated healthcare use event after receiving the rotavirus vaccine among TNFi-unexposed and TNFi-exposed offspring (n=1129)

TNFi exposure	N	Mean	Median	Std Dev	Minimum	Maximum	P25	P75	P90
0	1070	59.3	59.0	34.4	0.0	140.0	30.0	89.0	106.0
1	59	61.7	62.0	34.4	0.0	122.0	33.0	93.0	104.0

Abbreviations: N, number of offspring; P25, 25th percentile; P75, 75th percentile; P90, 90th percentile; Std Dev, standard deviation.

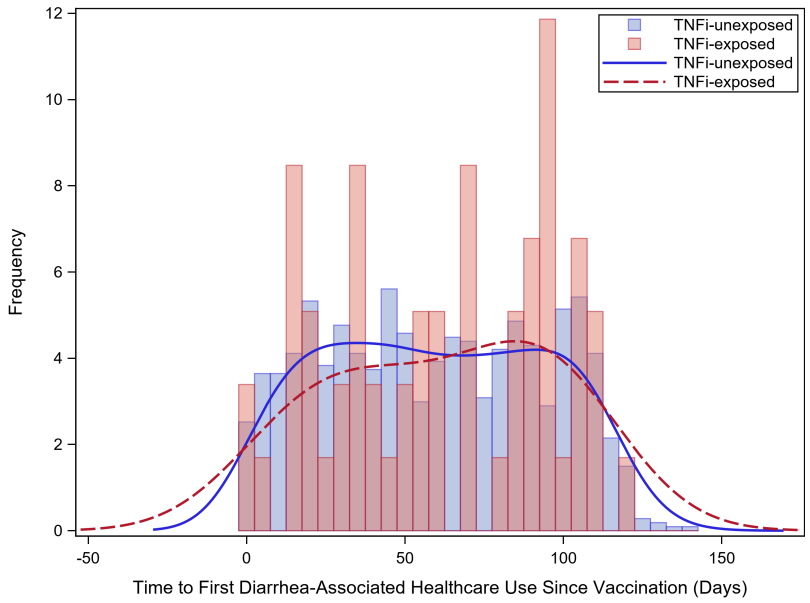

Figure 6.1.5 Distribution of time to first diarrhea-associated healthcare use event after receiving the rotavirus vaccine among TNFi-unexposed (blue) and TNFi-exposed (red) offspring

6.1.7 Statistical analysis

Prior to finalizing the Cox proportional hazards model, I conducted several additional analyses to ensure robustness. Specifically, I reran the models with varying exposure definitions to verify that maternal TNFi exposure, particularly TNFi with high placental transfer during late pregnancy, was accurately captured. Importantly, I relaxed the number of events per variable to fewer than 10, following the guidance of Vittinghoff and McCulloch's paper, which suggests that the traditional threshold of 10 events per variable can be relaxed to 5 to 9 in the context of confounder adjustment.[123]

As I was using Cox proportional hazards models, I needed to ensure that the proportional hazards assumptions were not violated. I checked for time-dependent effects of vaccine exposure and other variables, including year of birth, using the CoxFlex extension.[98,99] This method tests the time-dependent assumption using flexible Cox models with regression splines. While no time-dependent effect was found for the rotavirus vaccine, a time-dependent effect for sex was detected. As a result, I stratified the model by sex to allow for the proportional hazards to vary across males and females.[97] Since there were no linear covariates included, I did not need to test for non-linear effects. I used the AIC and LRT to compare the different models. Additionally, I performed *cox.zph* tests[96] to confirm the proportionality of sex before and after stratification, further validating the CoxFlex results.

Finally, to examine the effect of the rotavirus vaccination among TNFi-exposed and TNFi-unexposed offspring *post hoc*, I included an interaction term between rotavirus vaccination and TNFi exposure. This approach enabled me to assess whether the vaccine's effect differed based on TNFi exposure status. By incorporating this interaction term, I was able to estimate the differential effect of vaccination in each group, highlighting any potential modifying influence of TNFi exposure on vaccine efficacy and the risk of diarrhea-associated healthcare use. The results of this post hoc analysis were not included in the manuscript, as the TNFi-unexposed analysis was not planned *a priori*.

6.2 Manuscript #5: Diarrhea Events in Offspring Exposed to TNF Inhibitors & Rotavirus Vaccine

6.2.1 Title Page

Diarrhea Events in Offspring Exposed to TNF Inhibitors & Rotavirus Vaccine

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6.2.2 Abstract

Objectives. Guidelines previously recommended withholding rotavirus vaccine in tumour necrosis factor inhibitor (TNFi)-exposed infants until 6 months due to infection risk. However, delaying vaccination may increase diarrhea-associated morbidity compared to routine immunization starting at 2 months. We compared the risk of diarrhea-associated healthcare events during the first 6 and 24 months in TNFi-exposed infants based on vaccination status.

Methods. Using MarketScan (2011-2021), we identified 3,167 offspring born to mothers with chronic inflammatory diseases who took TNFi. Rotavirus vaccine exposure was defined as receiving ≥1 dose between 2 and 6 months of age. Cox proportional hazards models estimated hazard ratios (HR) and 95% confidence intervals (CI) for diarrhea-associated healthcare use in vaccinated versus unvaccinated infants.

Results. Among TNFi-exposed offspring, no statistically significant association was found between vaccination and diarrhea event risk during the first 6 months (HR 1.02; 95% CI 0.64, 1.63) or 24 months (HR 1.18; 95% CI 0.89, 1.58). This pattern remained consistent in those exposed to TNFi during the third trimester, with no association during the first 6 months (HR 1.06; 95% CI 0.61, 1.83) or 24 months (HR 1.12; 95% CI 0.81, 1.56). Similarly, no association was observed among offspring exposed to high placental-transfer TNFi in the third trimester during the first 6 months (HR 0.93; 95% CI 0.51, 1.70) or 24 months (HR 1.12; 95% CI 0.79, 1.59).

Conclusions. Our findings suggest no increased diarrhea risk from rotavirus vaccination during the first 6 months of life in TNFi-exposed offspring, even with late TNFi pregnancy exposure.

6.2.3 Introduction

Chronic inflammatory diseases often affect individuals during their reproductive years and are mainly female-predominant [1]. Ongoing immune suppression is needed for many of these diseases, which means these women, in their pregnancy, are often exposed to immune-suppressive drugs, including tumour necrosis factor inhibitors (TNFi).

Rotavirus is the most important cause of severe gastroenteritis, particularly in unvaccinated infants, but the highly effective rotavirus vaccines, which reduce diarrhea-related events by over 90%, avert approximately 45,000 infant hospitalizations annually in the United States (US) [2-4]. In North America, the rotavirus vaccine is the only live vaccine administered before 6 months of age as part of the routine immunization schedule [3, 4]. Two oral live attenuated vaccines are available: the pentavalent (RV5) and the monovalent (RV1) rotavirus vaccines. RV5 is administered at 2, 4, and 6 months of age, while RV1 is administered at 2 and 6 months, and both vaccines are highly effective in preventing rotavirus disease, reducing diarrhea-related hospitalizations by >87% [5, 6].

As TNFi can be detected in infants exposed *in utero* for up to 6 months [7, 8], adverse effects may occur in early life, including those linked with routine childhood immunizations. This was seen in a 2010 case report [9] of a child exposed *in utero* to TNFi who developed a fatal Bacillus Calmette–Guérin infection, which caused rheumatology guidelines to recommend withholding rotavirus vaccine in offspring exposed *in utero* to any TNFi until 6 months of age, instead of routine immunization starting at 2 months [10, 11]. However, this places the infants at risk for serious diarrhea-associated illness, especially as the most severe rotavirus disease, which can be fatal, occurs primarily among unvaccinated children aged 3-12 months [2, 12, 13].

In 2022, the American College of Rheumatology vaccination guidelines conditionally recommended administering the rotavirus vaccine to infants within the first 6 months of life based on only 3 very small observational studies (combined n=58 TNFi-exposed offspring) [14] and in 2024, the European Alliance of Associations for Rheumatology updated their guidelines mentioning that live vaccines can be administered during the first 6 months, depending on the timing of maternal exposure during pregnancy, transplacental passage, and type of vaccine. For rotavirus, they recommended that it be administered according to the vaccine schedule [15]. Seeing the need for larger studies, we leveraged administrative data to examine the risk of diarrhea-

associated healthcare events in TNFi-exposed infants according to rotavirus vaccine exposure in the first 6 months of life.

6.2.4 Methods

Data source. This study used MarketScan commercial claims, a US employer-provided private health insurance claims database [16]. MarketScan contains de-identified medical and drug claims for >273 million individuals from large companies (employees, spouses, and dependents) and includes data on physician office visits, hospitalizations, and drug prescriptions [17]. Medical diagnoses and procedures are recorded using the International Classification of Diseases 9th and/or 10th revisions (ICD-9/10) codes [18] and American Medical Association Current Procedural Terminology (CPT) procedure codes [19].

Study population. We identified all TNFi-exposed offspring born between January 1, 2011, and December 31, 2021, to women between the ages of 15 and 45 who were diagnosed before pregnancy with a chronic inflammatory disease (i.e. rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriasis (PsO), psoriatic arthritis (PsA), and inflammatory bowel disease (IBD; Crohn's and ulcerative colitis)). *In utero* TNFi exposure was determined through maternal prescription records, defined as the mothers having at least one filled prescription or infusion procedure claims for any TNFi (i.e. infliximab, adalimumab, golimumab, etanercept, certolizumab). Prescription records were identified using National Drug Codes from REDBOOK (a source of prescription and over-the-counter pharmaceutical information) and J-codes (billing codes).

The timing of TNFi exposure was determined based on prescription or infusion dates in relation to the gestational period and trimester, calculated from the onset of gestation. Term deliveries were identified through maternal or child ICD-9/10 codes using a validated algorithm by Margulis et al.[20]. If gestational age was unknown and no preterm code was present, the onset of gestation was estimated by subtracting 39 weeks (273 days) from the delivery date. For cases with a preterm code, 35 weeks (245 days) were subtracted from the birth date to estimate conception. When preterm birth ICD codes included a gestational age range, we used an algorithm by Li et al.[21]. After each prescription, a grace period of 5 half-lives was added to account for the mother's biological exposure to the medication. Offspring were classified as exposed to TNFi during all three trimesters if the mother had overlapping prescriptions spanning the entire

pregnancy. If no prescriptions were recorded during an entire trimester, and the grace period from prior prescriptions did not extend into that trimester, the offspring were considered unexposed for that trimester. Exposure status could change depending on the timing of prescriptions: offspring classified as unexposed in one trimester could later be reclassified as exposed if the mother resumed TNFi use, and vice versa.

Offspring were linked with their mothers using family identifiers and delivery dates. This method is commonly used with MarketScan data and has been shown to link 81% of mothers with their live births [22]. Infants were excluded if they were born in the 13 US states with a state-funded universal rotavirus vaccine program (i.e. Alaska, Idaho, Maine, Massachusetts, New Hampshire, New Mexico, North Dakota, Oregon, Rhode Island, Vermont, Washington, Wisconsin, and Wyoming) [23]. There would be no private insurer claims for the rotavirus vaccine among these children; therefore, commercial databases would not capture them. These 13 states represent 25% of the overall MarketScan database [24].

Exposure. Rotavirus vaccine exposure was based on ≥1 procedure billing code for providing the pentavalent human-bovine reassortant (RV5; 90681) and/or the attenuated human (RV1; 90680) rotavirus vaccines (both live vaccines) administered between 6 weeks and 6 months of age. These codes have been previously validated in commercially insured US infant populations with positive predictive values of 86.7% - 88.5% [25, 26]. Rotavirus vaccination was classified as time-varying; therefore, a child contributed person-time as unexposed from 6 weeks up to their first rotavirus vaccine dose, after which they contributed person-time as exposed to the vaccine. In order to be fully protected, RV5 requires 3 doses and RV1 requires 2 doses; however, for this study, we looked at just the first dose as the vaccines have shown >90% protective effects after just one dose [5, 6].

Outcome. The first instance of diarrhea-associated healthcare use was defined via relevant ICD-9/10 diagnostic billing codes at hospitalizations, outpatient visits, or emergency department visits (i.e. emergency room or urgent care facility). The codes included ICD-9 008.6-008.8, 001.0-005.9, 008.0-008.5, 006.0-007.9, 009.0-009.3, 558.9, 787.9 and ICD-10 A00-A09, which encompass a range of intestinal infections and diarrhea-related diagnoses. This definition also specifically includes rotavirus infections (ICD-9 008.61; ICD-10 A08.0). This approach has been previously used to evaluate the effect of the rotavirus vaccine on diarrhea-associated events within MarketScan [3, 27]. For the primary analysis, this was assessed during the first 2 to 6 months of

life. In an extended analysis, diarrhea-associated hospitalizations and/or outpatient physician visits were also assessed in offspring from age 6 months to age 24 months.

Statistical analyses. We evaluated the risk of diarrhea-associated hospitalizations and/or outpatient physician visits in vaccinated and unvaccinated TNFi-exposed offspring. Descriptive statistics were used to summarize the cohort characteristics. To estimate adjusted hazard ratios (HR) and corresponding 95% confidence intervals (CI), we performed Cox proportional hazards models. For the primary analysis, follow-up began at 6 weeks, the earliest time a child could receive their first vaccine dose, and continued until 6 months of age. For the expanded 24-month analysis, follow-up was extended to 24 months of age. However, infants vaccinated after 6 months were censored at the time of vaccination, as the focus was on those vaccinated within the first 6 months of life. Until the date of their first vaccination, these offspring contributed unexposed person-time. Offspring who experienced a diarrhea-associated healthcare event within the first 6 months were excluded from this expanded analysis.

The models were adjusted for potential confounders and/or effect modifiers, including *in utero* exposures to corticosteroids (i.e. methylprednisolone, prednisolone, prednisone, budesonide) and non-biologic immunomodulators (i.e. sulfasalazine, chloroquine, hydroxychloroquine, leflunomide, methotrexate, azathioprine, 6-mercaptopurine, mesalamine, tacrolimus, cyclosporine, apremilast, tofacitinib, baricitinib), sex, geographic region (Northern [Northeast and North Central] or Southern & Western United States), year of birth (2011-2014, 2015-2018, 2019-2021), season of birth (October-March, April-September), and high TNFi placental transfer (adalimumab, infliximab, golimumab) at any point during pregnancy. All of the TNFi medications were available prior to the start of the study, except intravenous golimumab, which was available starting in July 2013.

We verified the proportional hazards assumption for all variables and stratified our analyses on sex, allowing the hazards to differ between strata, as the relationship of the outcome with this variable violated the proportional hazards assumption [28]. We included both calendar year and season of birth because of the possibility that year (due to certain calendar years having higher rotavirus activity) and season (due to seasonal variations in diarrheal-associated illness) could potentially be effect modifiers. We also calculated the crude incidence of diarrhea-associated healthcare use with 95% CI, based on the Poisson distribution, stratified by TNFi exposure status and vaccination status.

Additional secondary analyses. We performed two additional secondary analyses of diarrheal illnesses in the offspring, with the same model covariates, with variations on how TNFi exposure was characterized. In the first secondary analysis, TNFi exposure was characterized by timing: exposure during the first and/or second trimesters only, versus exposure anytime during the third trimester (+/- other trimesters). A multivariate Cox proportional hazards model was used, including an interaction term between TNFi exposure and rotavirus vaccination. This approach allowed us to estimate the effect of rotavirus vaccination separately for offspring exposed to TNFi in the first and/or second trimesters only and for those exposed in the third trimester (+/ other trimesters).

In the second secondary analysis, we focused on TNFi-exposed infants during the third trimester regardless of additional trimester exposures. TNFi exposure was classified based on the degree of placental transfer (high versus. low transfer). Using a multivariate Cox proportional hazards model, we included an interaction term between TNFi placental transfer and rotavirus vaccination. This allowed us to estimate the vaccine effect separately for offspring exposed to high placental transfer TNFi and low placental transfer TNFi during the third trimester.

Sensitivity analysis. We performed a sensitivity analysis where we added a lag period between the date of the vaccine and when the infant was classified as exposed; this was to account for the possibility that some of the vaccines' effects may be delayed by several days. We varied the lag period to be between 2 days and 14 days.

To assess the potential impact of seasonal variation on our findings, we conducted another sensitivity analysis restricting follow-up to infants whose observation period (starting at 42 days of age and continuing until 6 months of age) included at least 50% of the follow-up within a fall/winter season, defined as October 1 to March 31 of the same or following calendar year. We then repeated our primary analysis within this restricted cohort to evaluate whether seasonal factors influenced the association of interest.

Cohort creation was done with SAS® Enterprise Guide version 7.15 (SAS Institute, Cary, NC) [29]. All analyses for this study were conducted using R version 4.3.0 [30]. Ethics approval was obtained from the Research Ethics Office at McGill University (A11-M107-14A).

Patient and public involvement. Patient advocates from the Canadian Arthritis Patient Alliance (CAPA) were involved in developing the research question and grant applications. Our dissemination plan includes presentations of the research to relevant patient communities (e.g.,

CAPA, the Arthritis Society, the Arthritis Foundation, CreakyJoints, and the Arthritis Power patient registry).

6.2.5 Results

Between 2011 and 2021, a total of 3,167 offspring were born to mothers with chronic inflammatory diseases who took TNFi during pregnancy. Specifically, 981 offspring were only exposed to TNFi during the first and/or second trimesters, while 2,186 were exposed at some point during the third trimester (+/- earlier trimesters). Among those exposed in the third trimester, 1,665 (76%) were exposed to TNFi with high placental transfer. The majority (41%) of TNFi-exposed offspring were exposed to adalimumab at some point, with infliximab making up 30%. Overall, 71% received at least one dose of the rotavirus vaccine between 2-6 months of age. The median time to vaccination since birth was 64 days. During the first 6 months, there were 101 diarrhea-associated events that occurred among the cohort. When expanded to 24 months, 283 diarrhea-associated events occurred among the reduced cohort of 2,583. The median time to the first event after receiving the rotavirus vaccine among the TNFi-exposed offspring was 62 days. Overall, 7 offspring (6.9%) had a diarrhea-associated healthcare event within 14 days of receiving the vaccine.

Table 6.2.1 presents the baseline characteristics for the entire cohort according to vaccination status during the first 6 months. Compared with unvaccinated offspring, vaccinated offspring were less likely to have been exposed to non-biologic immunomodulators during gestation, more likely to have been born prematurely, and more likely to have been born between April and September.

Among TNFi-exposed offspring, no statistically significant associations were observed between rotavirus vaccination and the risk of diarrhea-associated healthcare events during the first 6 months (HR 1.02; 95% CI 0.64, 1.63) or the first 24 months (HR 1.18; 95% CI 0.89, 1.58) (Table 6.2.2). Focusing on the timing of TNFi exposure, offspring exposed to TNFi during the first and/or second trimesters only experienced 37 diarrheal events in the first 6 months and 97 events by 24 months. We identified no statistically significant associations between vaccination and the risk of diarrhea-associated healthcare use during either time frame (6 months: HR 0.93; 95% CI 0.44, 1.94; 24 months: HR 1.45; 95% 0.77, 2.73) (Table 6.2.3). Similarly, when looking at the vaccine's effect among those exposed during the third trimester (+/- first or second trimesters), 64 events

were observed during the first 6 months and 186 during the first 24 months. Again, no statistically significant associations with vaccination were found (6 months: HR 1.06; 95% CI 0.61, 1.83; 24 months: HR 1.12; 95% CI 0.81, 1.56).

Further looking at the third-trimester exposure, among those exposed to high placental-transfer TNFi in the third trimester, we found no statistically significant association during the first 6 months (HR 0.93; 95% CI 0.51, 1.70) or 24 months (HR 1.12; 95% CI 0.79, 1.59). As only 10 diarrheal events were observed among the 521 offspring who were exposed to low placental transfer in the third trimester, this translated into a large effect estimate with very wide CI overlapping with the null during the first 6 months (HR 4.45; 95% CI 0.54, 36.46), but somewhat stabilized during 24 months (HR 1.23; 95% CI 0.48, 3.14), as there were 42 events among 411 exposed. Including a lag period (i.e. 2 days, 5 days, or 14 days) between the date of vaccine and being classified as exposed did not change the effect estimates drastically; therefore, no lag period was included in the final models.

6.2.6 Discussion

In our study, the largest such study to date, in infants exposed to TNFi *in utero* between 2 and 6 months of age, administration of the rotavirus vaccine was not clearly associated with an increase in diarrhea-associated healthcare visits early in life. Results were similar when looking specifically at exposures during the third trimester, even in those exposed to high placental transfer TNFi.

Our study adds to a recent systematic review by Schell et al. that assessed the safety of rotavirus vaccination in biologic-exposed infants; that review identified only 10 studies with a total of 162 TNFi-exposed infants who received the vaccine [32]. Their review concluded that rotavirus vaccination was safe in all 162 infants, with a significant portion of children (64%, n=103) drawn from a single study by Fitzpatrick et al. [33].

While these studies provide potentially reassuring early safety data, our research substantially expands on earlier findings in several ways. First, our cohort is much larger, offering greater evidence of the safety of rotavirus vaccination in TNFi-exposed infants, with respect to diarrhea-associated healthcare visits. Second, our study examined outcomes over a longer follow-up period, investigating the risk of diarrhea-associated healthcare events within the first 6 months of life and then extended to 24 months, as opposed to Fitzpatrick et al.'s focus on the first 24 hours

post-vaccination. Additionally, our study is unique as it considers TNFi exposure during pregnancy by assessing both high placental transfer and third-trimester exposure, which were not differentiated in prior studies. This more detailed exposure assessment allowed us to explore whether *in utero* exposure to TNFi influences the infant's risk of post-vaccination diarrheal events.

Recently, rheumatology guidelines have been updated to conditionally recommend rotavirus vaccination during the first 6 months of life for TNFi-exposed offspring [13, 14]. Our study provides valuable new data on the longer-term risks associated with rotavirus vaccination in this population, with a significantly larger sample size than previous studies. Our more comprehensive assessment of safety confirms the updated guidelines and offers reassurance to both clinicians and parents regarding rotavirus vaccine administration in TNFi-exposed infants.

An earlier study by Cortes et al. [3] included children aged 3-23 months old who had had in-utero TNFi exposure and received at least one RV5 dose before the start of the rotavirus season. That study found a 44% reduction in diarrhea-associated hospitalization (rate reduction of 44%; 95% CI 33% to 53%), also based on administrative health care ICD codes. A key difference compared to our study is the age range and time frame studied. We examined diarrhea-related healthcare use for offspring between 2-6 months of age and then 6-24 months. Also, we examined a longer calendar period, while Cortes et al. focused only on two post-vaccine rotavirus seasons, January to June of 2008 and 2009. Rotavirus disease follows a seasonal pattern, peaking in the fall and winter months [2, 31], and children born in the winter have the highest risk of hospitalization for rotavirus [32].

Our study has some potential limitations. First, as mentioned, we only assessed outcomes following the first dose of the rotavirus vaccine, while a full series is 2 or 3 doses, depending on the vaccine type. The Food and Drug Administration (FDA) reported that the vaccine's protective effect after one dose is 89.8% (95% CI 8.9, 99.8) [6]. Most offspring in our study should have completed the full series by the extended 24-month follow-up, as the final doses are to be administered by 24 weeks (RV1) and 32 weeks (RV5) [5, 6]. As another potential limitation, using diarrhea-associated healthcare use as our outcome may not capture all cases of post-vaccination diarrhea, especially mild cases not requiring medical attention. However, our study is designed to capture the more severe cases of diarrhea, that are most clinically significant.

In conclusion, among *in utero* TNFi-exposed offspring, our findings suggest no increased risk of diarrhea-related healthcare use related to rotavirus vaccination during age 6 weeks to 6

months of life (nor when the analyses were extended to 24 months). In vaccinated versus non-vaccinated offspring, we further found no clear increased risk of diarrhea-related healthcare use when comparing early (first/second trimester only) versus late (third trimester +/- first/second trimesters) TNFi exposure, nor with late pregnancy high placental transfer TNFi exposure. These results provide compelling evidence to support early rotavirus vaccination in TNF-exposed infants, offering additional reassurance that may help successfully disseminate and reinforce the recent guideline changes recommending rotavirus vaccination in this population.

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6.2.8 Key messages

What is already known on this topic: Prior to this study, limited data existed on the safety of rotavirus vaccination in infants exposed to TNFi during pregnancy. Recently, rheumatology guidelines have been updated to conditionally recommend exposed offspring to receive the vaccine; however, they are based on small studies.

What this study adds: Rotavirus vaccination administered to infants exposed to TNFi *in utero* between 2 and 6 months of age was not associated with an increase in diarrhea-associated healthcare visits during the first 6 and 24 months of life. This result held even for infants exposed to TNFi in the third trimester and those exposed to TNFi with high placental transfer during the third trimester.

How this study might affect research, practice or policy: Our study will provide stronger evidence to current guidelines conditionally recommending rotavirus vaccination for infants exposed to TNFi in utero.

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6.2.10 Tables

Table 6.2.1 Baseline characteristics of infants exposed *in utero* to tumour necrosis factor inhibitors (TNFi), stratified by rotavirus vaccination status during the first 6 months of life

Variable, n (%)		No Rotavirus Vaccine (N=927)	Rotavirus Vaccine (N=2,240)	Total (N=3,167)
TNFi exposure				
	1st/2nd trimesters only	185 (20)	796 (36)	981 (31)
	3rd trimester exposure	742 (80)	1444 (65)	2186 (69)
Adalimumab		371 (40)	925 (41)	1296 (41)
Infliximab		384 (41)	567 (25)	951 (30)
Golimumab		24 (3)	61 (3)	85 (3)
Certolizumab		85 (9)	327 (15)	412 (13)
Etanercept		94 (10)	434 (19)	528 (17)
TNFi, high placental transfer*				
	Any trimester	770 (83)	1541 (69)	2311 (73)
	Third trimester	631 (68)	1034 (46)	1665 (53)
Corticosteroid exposure, *in utero*		258 (28)	663 (30)	921 (29)
Non-biologic immunomodulator exposure,		227 (25)	471 (21)	698 (22)
Preterm delivery		137 (15)	379 (17)	516 (16)
Biological sex, male		482 (52)	1153 (52)	1635 (52)
Gestational diabetes		139 (15)	344 (15)	483 (15)
Season of birth, October - March		465 (50)	1042 (47)	1507 (48)
Year of delivery				
2011-2014		292 (32)	829 (37)	1121 (35)
2015-2018		332 (36)	778 (35)	1110 (35)
2019-2021		303 (33)	633 (28)	936 (30)
Geographic region				
Northeast and North Central United		517 (56)	1356 (61)	1873 (59)
Southern & Western United States		12 (2)	11 (1)	23 (1)
Unknown		398 (43)	873 (39)	1271 (40)

*TNFi with high placental transfer: adalimumab, golimumab, infliximab

Table 6.2.2 Adjusted hazard ratios for the effect of rotavirus vaccination on the risk of diarrhea-related healthcare events during the first 6 and 24 months of life in TNFi-exposed offspring (exposed during any trimester), comparing vaccinated vs. unvaccinated.

Age of TNFi-Exposed Offspring at Follow-Up	Diarrheal Events	Vaccine Effect Hazard Ratio (95% CI)	
		Crude	Adjusted*
2-6 months (n=3,167)	101	1.06 (0.66, 1.68)	1.02 (0.64, 1.63)
6-24 months (n=2,583)	283	1.24 (0.93, 1.64)	1.18 (0.89, 1.58)

*Adjusted for TNFi trimester of exposure, *in utero* drug exposures (i.e. corticosteroids, non-biologic immunomodulators), sex, gestational diabetes, geographic region, year of birth, birth season (October-March vs April-September), high TNFi placental transfer at any point during pregnancy.

Table 6.2.3 Adjusted hazard ratios for the effect of rotavirus vaccination on the risk of diarrhea-related healthcare events during the first 6 and 24 months of life in TNFi-exposed offspring, stratified by trimester of exposure (first/second vs. third trimester) and placental transfer during the third trimester (high vs. low), comparing vaccinated vs. unvaccinated.

Follow-Up Period	TNFi Exposure Group	Diarrheal Events	Vaccine Effect Hazard Ratio (95% CI)*
2-6 months (n=3,167)	Exposed to TNFi during first and/or second trimesters only (n=981)	37	0.93 (0.44, 1.94)
	Exposed to TNFi during third trimester (n=2,186)	64	1.06 (0.61, 1.83)
	Exposed to low TNFi during third trimester (n=521)[†]	10	4.45 (0.54, 36.46)
	Exposed to high TNFi during third trimester (n=1,665)[†]	54	0.93 (0.51, 1.70)
6-24 months (n=2,583)	Exposed to TNFi during first and/or second trimesters only (n=813)	97	1.45 (0.77, 2.73)
	Exposed to TNFi during third trimester (n=1,770)	186	1.12 (0.81, 1.56)
	Exposed to low TNFi during third trimester (n=411)[†]	42	1.23 (0.48, 3.14)
	Exposed to high TNFi during third trimester (n=1,359)[†]	144	1.12 (0.79, 1.59)

*Adjusted for TNFi trimester of exposure, *in utero* drug exposures (i.e. corticosteroids, non-biologic immunomodulators), sex, gestational diabetes, geographic region, year of birth, birth season (October-March vs April-September), high TNFi placental transfer at any point during pregnancy.
[†]In models evaluating low vs. high TNFi exposure during the third trimester, TNFi placental transfer was not included as an adjustment variable since it defines the exposure groups.

CHAPTER 7 - DISCUSSION

7.1 Summary of Findings

This thesis provided novel insights into (1) the relationship between gestational use of TNFi and the risk of serious infections in mothers and their offspring and (2) the risk of rotavirus vaccine administration within 6 months after the birth of offspring exposed to TNFi *in utero*, areas that were previously underexplored in the literature. By examining not only the immediate effects of TNFi use on the health of pregnant women with chronic inflammatory diseases but also the postnatal outcomes for their offspring, this work offers a comprehensive evaluation of the safety of TNFi in mothers and their offspring. While most prior studies focused narrowly on maternal outcomes, this thesis expands the scope to consider how *in utero* exposure to TNFi affects the immune system of offspring, particularly in relation to serious infections and responses to vaccinations, providing much-needed insight into these important outcomes.

Chapter 2 (manuscript #1) gave a comprehensive overview of the existing literature on serious infections in women of reproductive age and their offspring associated with the use of TNFi during pregnancy.

Chapter 3 (manuscript #2) presented the largest real-world analysis on TNFi use and serious infection risks in women with chronic inflammatory diseases during pregnancy and postpartum. Using data from over 62,000 women with chronic autoimmune diseases and 70,000 pregnancies, this chapter used careful methodology to estimate that pregnancies exposed to TNFi tended to have a higher risk of hospitalized infections during gestation, although not with perfect precision; however, the absolute risk remained low.

Chapter 4 (manuscript #3) described the most comprehensive analysis to date regarding TNFi use during pregnancy. This documented a rise between 2011 and 2021 in TNFi use throughout gestation, suggesting increasing confidence in the safety of at least some TNFi drugs during pregnancy. We also demonstrated a decrease in corticosteroid use during pregnancy/postpartum among women exposed to TNFi throughout gestation versus those exposed in the first and/or second trimester only.

Chapter 5 (manuscript #4) introduced novel findings on the risk of serious infections in offspring exposed to TNFi *in utero*, focusing on the differential impact of exposure during various trimesters. It was the first large-scale study to explore the role of TNFi agents with high versus

low placental transfer, showing that third-trimester exposure, particularly to high-transfer agents, may increase the risk of serious infections compared to earlier exposures.

Chapter 6 (manuscript #5) contributed new evidence on the safety of rotavirus vaccination in infants exposed to TNFi *in utero*. As the largest study on this topic, it demonstrated that TNFi-exposed infants, including those exposed in the third trimester and to high placental transfer agents, did not have an elevated risk of diarrhea-associated healthcare visits following vaccination. These findings reinforced updated rheumatology guidelines conditionally recommending rotavirus vaccination in TNFi-exposed offspring during the first 6 months of life, providing reassurance to both clinicians and parents.

By covering both the maternal and child impacts of TNFi, this thesis contributes a dual perspective that has been missing from much of the earlier literature. The ability to link maternal treatment decisions to offspring outcomes in the first year of life is a key strength, providing clinicians with a fuller picture of the safety profile of these medications.

7.2 Strengths and Clinical Implications

My doctoral thesis has multiple strengths and produced novel evidence to help establish clinical guidelines and policies for women with chronic inflammatory conditions to improve reproductive outcomes. A major strength of this thesis is its use of real-world data from the MarketScan database. The large sample size and long follow-up period enabled more precise risk estimates, contributing substantially to the robustness of the findings. It also provided details on medication use, such as use of TNFi and concomitant corticosteroids and non-biologic immunomodulators during pregnancy.

In comparison to clinical trials, my thesis filled key knowledge gaps about how medications used during pregnancy can affect the user and their offspring as pregnant women are commonly excluded from clinical trials (due to the potential harm to fetuses and the need to demonstrate fetal safety before including them[124-127]) and are often underrepresented in clinic-based observational studies (due to possible challenges surrounding the recruitment and retention of pregnant women[128]). As pregnancy is a state of limited time duration which does not occur in all individuals, sampling pregnant individuals is difficult, especially within a diverse population. Therefore, my studies are the largest cohort studies conducted on the subject. Previously, the largest study on serious infection outcomes in women taking TNFi during pregnancy included 1,457 exposed

women[129], the largest on serious infections in TNFi-exposed offspring included 3,399 exposed infants[130], and the largest examining TNFi-exposed offspring who received the rotavirus vaccine included 133 infants.[131]

My project generated urgently needed evidence so that patients, prescribers, and regulatory agencies could better understand the risks of TNFi use during pregnancy. This was an essential addition to the literature as there were limited data on TNFi and serious infections in pregnant women and exposed offspring, as identified in manuscript #1.[132]

The incorporation of time-varying exposure definitions further strengthens the analyses. By accounting for changes in TNFi exposure over the course of pregnancy, this thesis provides a more nuanced understanding of how the timing of exposure influences outcomes, both for mothers and their offspring. For instance, the ability to differentiate between first-, second-, and third-trimester exposure enabled the identification of trimester-specific risks, offering greater insight into when TNFi use is safest. This level of detail is essential for clinical decision-making, as it supports more personalized treatment strategies for pregnant women which might be influenced by disease activity while weighing the specific risks associated with TNFi during different stages of pregnancy.

In terms of clinical implications, this thesis provides reassurance for physicians and patients regarding the use of TNFi during pregnancy. Historically, TNFi use has been a source of concern due to potential immunosuppressive effects, but the evidence generated by this thesis shows that these drugs pose minimal risk of serious infections, both for mothers and their offspring. Even when a relative increase in risk was observed, the absolute risk remained very small. For instance, among offspring exposed to high placental transfer TNFi in the third trimester, the absolute risk was up to 35 cases of serious infections per 1,000 person-years. These findings help alleviate some of the hesitations around continuing TNFi treatment during pregnancy, especially in women with severe inflammatory disease. For these individuals, discontinuing TNFi may lead to disease flare-ups, which themselves are associated with adverse maternal and fetal outcomes. Overall, this work provides reassurance that maintaining TNFi therapy during pregnancy is a reasonable option, especially when weighed against the potentially much greater risks of uncontrolled maternal disease. Importantly, the findings related to rotavirus vaccination in TNFi-exposed infants further strengthen this reassurance, reinforcing the safety of vaccination practices in this vulnerable population.

As well, the real-world generalizability of these findings is another strength. By analyzing healthcare use data that reflects actual prescribing patterns, medication adherence, and infection risks, this thesis provides insights that are directly transferable to clinical practice. This makes the findings relevant regarding decision-making shared by healthcare providers and pregnant women with chronic diseases that require TNFi. This research will be used by Canadian and international clinical groups responsible for updating drug-use guidelines during pregnancy.

7.3 Potential Limitations

7.3.1 Imperfect case ascertainment within administrative health data

Outcomes defined by ICD or procedure codes within administrative data are not necessarily clinically confirmed, potentially leading to imperfect ascertainment of disease status. To address this, I used previously validated definitions of chronic inflammatory diseases, serious infections, comorbidities and obstetrical outcomes; these definitions have been shown to have high sensitivities and specificities (sections 3.1.2.2, 3.1.2.5, 3.1.4). Regarding ascertainment of covariates, to alleviate the potential for observation bias caused when an adverse event may lead to differential ascertainment/coding of comorbidities, I ensured that all covariates were recorded before outcome assessment by measuring them at the onset of gestation for fixed variables and any time before the infectious event for time-varying variables.

If residual disease misclassification occurred and was unrelated to TNFi exposure (i.e. non-differential misclassification), then the bias would typically be toward the null, thus underestimating the true association. An example would be if individuals with mild autoimmune conditions (e.g. psoriasis) are misclassified as having severe conditions (e.g. rheumatoid arthritis), thus the cohort would appear more homogenous and potentially underestimate the true association between TNFi exposure and outcome. However, if disease misclassification differs between exposed and unexposed groups, then there may be an overestimation or underestimation of the effect estimate. For example, if patients receiving TNFi are more likely to be correctly identified as having severe diseases due to increased medical attention (e.g. frequent specialist visits), it could lead to an overestimation of the association between TNFi exposure and serious infections as the exposed group would disproportionately include higher-risk individuals. Alternatively, if there is under-ascertainment in the TNFi group (perhaps because these patients are more likely to feel unwell and miss a clinical follow-up), a true association between TNFi exposure and the outcome

may be underestimated. Importantly, our cohort consists of MarketScan members with health insurance, and both TNFi-exposed and unexposed groups include individuals with chronic inflammatory diseases. These shared characteristics likely reduce, though not completely eliminate, the potential for residual disease misclassification. Nevertheless, any systematic misclassification of disease type, severity, or healthcare utilization patterns could influence our estimates. For instance, if unexposed patients are less frequently diagnosed due to fewer healthcare visits, they may appear healthier than they truly are, which could amplify differences between groups. Even under a conservative assumption that misclassification in TNFi-exposed patients might be inflated by 10-20%, the resultant bias would likely be modest and unlikely to account for the observed association. As such, our findings remain robust and are unlikely to be explained solely by differential case ascertainment. One approach that can be used to try to address the lack of a perfect instrument for ascertainment is to use Bayesian latent class modelling.[133] Another that can be used for time-to-event data[134], unlike simple bias analysis[135], is probabilistic bias analysis.[136] These could be an approach for future research.

7.3.2 TNFi exposure misclassification

Exposure to TNFi was defined based on filled prescriptions, except for infliximab and golimumab, which were also identified by infusion procedure codes. For patients classified as exposed based on filled prescriptions, I could not assess treatment adherence, as there was no information on whether patients took the drugs as prescribed. However, most women who filled a prescription for TNFi likely took ≥1 dose because, within MarketScan commercial databases, the vast majority of subjects have out-of-pocket costs associated with filling prescriptions.[137] The only drugs I could be certain about their adherence were those requiring infusion at hospitals or clinics (such as infliximab and intravenously-administered golimumab), that is, those exposures would be highly likely to be correctly identified versus potentially misclassifying other TNFi exposures (i.e. self-injected therapies may not have been received even if the prescription was filled). This could represent a form of differential misclassification of exposure in my analyses comparing different types of TNFi.

For example, among offspring exposed to TNFi, infliximab exposure may be classified with greater accuracy due to its infusion-based procedure during this study period compared to subcutaneous-only agents such as etanercept, certolizumab, and adalimumab (as a side note, it is

important to note that while infliximab has been primarily administered via infusion, a subcutaneous version was recently approved in October 2023[138]). This differential classification accuracy could contribute to systematic differences in exposure misclassification. Specifically, if high placental transfer TNFi are more likely to be accurately classified as exposed compared to low placental transfer TNFi, any infection risks associated with TNFi exposure could be disproportionately attributed to high placental transfer TNFi. As a result, observed differences in infection risks between high and low placental transfer TNFi could reflect both true biological effects (greater transplacental passage) and the impact of differential exposure classification. As nearly one-third (30%) of pregnancies were exposed to infliximab, the overall estimates of infection risk for TNFi-exposed pregnancies and offspring could have been disproportionally influenced by this group. This could result in a bias away from the null in the overall analysis, as infliximab-exposed pregnancies and offspring are more accurately classified as exposed than low transfer drugs.

As a sensitivity analysis, I required ≥2 filled prescriptions to increase adherence and reduce the risk of exposure misclassification. However, only 539 mothers on TNFi received less than 2 filled prescriptions during the gestational period (potentially excluding those who received prescriptions prior to the onset of gestation and one additional prescription during pregnancy), so the risk of exposure misclassification using only >1 was minimal.

MarketScan (like most administrative databases) does not provide specific information on the onset of gestation, thus affecting my ability to identify the timing of TNFi exposure during pregnancy. Therefore, I estimated the gestational period by applying validated algorithms to term and preterm deliveries separately to determine the onset of gestation and thus when exposure occurred. Some, presumably small, error in estimating the time of conception may remain. However, it is use of TNFi during late pregnancy that may lead to excessive immunosuppression in the offspring. Thus, the timing of exposure in the second and third trimester is more important. To alleviate this concern, I performed a sensitivity analysis where I excluded those who only received one prescription in the first trimester and only included those exposed to TNFi within 6 months of delivery. The results did not change drastically (data not shown).

7.3.3 Serious infections outcome misclassification

Misclassification of the main outcome of interest (serious infections) may be introduced into administrative hospitalization data by medical billing clerks who incorrectly assign ICD classification diagnosis codes upon discharge. In these instances, the misclassification could have been differential between exposure groups if infections are more likely to be detected among the TNFi-exposed group. This may be important if we were interested in milder infections, but seems unlikely in our case since we are relying on admission for serious infections, which is a very objective and relatively uncommon outcome.

There are multiple methods that can be used to investigate measurement error in a binary outcome. These were not performed in this thesis but include using probabilistic sensitivity analyses[136] (quantitative bias analysis; table method) with a range of possible sensitivities and specificities, predictive value weighting, or MC-SIMEX[139] (MisClassification SIMulation EXtrapolation).

7.3.4 Possible residual confounding

In any observational study, we need to consider the possibility of residual confounding from unmeasured variables; in administrative health data (including MarketScan) that may include socioeconomic status (SES), body mass index (BMI), or smoking. SES could confound the association between TNFi and infections if individuals with lower SES have poorer access to healthcare, higher baseline infection risk, or delayed diagnoses and treatment of infections. Lower SES individuals have been shown to have poorer health and higher rates of adverse birth outcomes; therefore, they may experience greater risks due to TNFi use during pregnancy as a result of these pre-existing disparities.[140] As well, studies have shown a negative relationship between treatment access and disease activity in non-pregnant patients.[141] Alternatively, higher SES may be associated with greater healthcare-seeking behaviour, potentially leading to detection bias. BMI has been shown to be positively correlated with chronic inflammation[142] and infections[143]. Therefore, TNFi-exposed women with higher BMI may appear to have a strong association with infection due to this unmeasured confounder. A bias away from the null would also occur due to unmeasured smoking, as smoking is a risk factor for both chronic inflammation[144] and infections.[145]

Also, since MarketScan does not explicitly record chronic inflammatory disease activity measures, residual confounding by disease severity might be of concern. For example, IBD patients exposed to infliximab often have more severe disease than IBD patients who do not need biologics. Since disease activity itself may be associated with severe infections, there could be confounding of the relationship between infliximab and these adverse outcomes, by disease severity. In the absence of direct measures of disease severity, I adjusted for surrogate markers, including the use of other immunomodulators and corticosteroids, and the number of specialist visits, which are likely to be associated with high disease activity. However, there may still be residual confounding related to genetic susceptibility to infections (such as innate complement deficiency, seen in some but not all autoimmune diseases).[146] I also controlled for prior hospitalized infection, as physicians may choose not to prescribe TNFi in people with a past history of severe infections.

Future research could incorporate sensitivity analyses to estimate bias-adjusted measures and further explore how unmeasured confounding can influence the relationship between TNFi-exposure and serious infections. Such methods may include using user-supplied parameters to estimate a bias factor, as proposed by VanderWeele and Arah[147], calculation of an E-value by VanderWeele and Ding[148], or the use of instrumental variable approaches.[149,150] However, all of these sensitivity analyses rely on assumptions and parameters, such as the probability of the unmeasured confounder given TNFi exposure, P(U|X=1), and the probability of the unmeasured confounder, given no TNFi exposure, P(U|X=0). Since reliable estimates for the association between serious infections and potential confounders are not readily available, additional assumptions would be necessary before applying these methods. Therefore, further research would be needed to assess the effect of bias due to unmeasured confounding.

7.3.4.1 Mode of delivery

Mode of delivery is an important variable to consider when evaluating the risk of infections during the postpartum period, as studies have shown that caesarean sections have an increased risk of infection compared to vaginal deliveries (up to a five-fold increase).[151-154] In our cohort, we could not assess its specific impact in this analysis as we had captured deliveries as a single category, preventing us from distinguishing between delivery types and their potential influence

on infection risk. Future analyses will address this limitation by extracting individual delivery codes from MarketScan.

It is possible that mode of delivery could act as a surrogate for disease severity, particularly in conditions like IBD, where sicker individuals may be more likely to require caesarean deliveries. As a result, failing to adjust for mode of delivery may have introduced bias away from the null as TNFi-exposed mothers are often sicker due to more severe disease and may be more likely to undergo caesarean sections. The observed 20% increase in postpartum infection risk is therefore reassuring, as any unmeasured confounding by delivery type would likely have inflated this association, suggesting that the true effect estimate is likely lower than 20%.

7.3.5 Generalizability

The MarketScan commercial claims database captures a commercially insured US population, which may limit the generalizability of findings to Americans without insurance (likely including those of lower SES, such as those who are disabled or otherwise unemployed). This issue affects my study's external validity rather than internal validity, meaning the results are still valid within the MarketScan population but may not fully represent the broader US population. According to the Kaiser Family Foundation, in 2022, 48.7% of the total US population had employer-provided health insurance.[155] Notably, Medicaid covered 41% of US births but only 21% of women of reproductive age (ages 15-49).[156]

MarketScan primarily reflects the US middle class with good healthcare access, which may resemble the middle class in countries like Canada. To enhance generalizability, future research could consider incorporating datasets that capture underrepresented populations, such as those on public insurance or in lower-income brackets. Repeating this analysis with US Medicaid data (which includes those without other health insurance, who are affected by poverty and/or certain disabilities) may provide valuable insights, especially in exploring whether the same patterns of infection risk are observed and whether race/ethnicity (which is available in Medicaid data but not MarketScan commercial claims data) plays any role as an effect modifier or confounder.

As well, in our drug use descriptive study (manuscript #3), we excluded pregnancies resulting in stillbirths, despite these cases involving delivery. This exclusion may limit the generalizability of our findings, as it prevents us from capturing the full spectrum of pregnancy outcomes associated with TNFi exposure in women with chronic inflammatory diseases. However,

stillbirths remain relatively uncommon in our cohort, occurring in 1.3% of pregnancies (946/70,529), with 40 cases (4.2%) among the TNFi-exposed group.

Finally, in our maternal serious infections study (manuscript #2), we included only pregnancy events (e.g. spontaneous abortion) that required hospitalization. This approach reduced the risk of misclassification, thereby increasing the specificity of pregnancy identification. However, by excluding outpatient data, we may have underrepresented pregnancies that did not require hospitalization, including routine and low-risk cases. A study using national birth certificate data found that over the years, out-of-hospital births were slightly increasing; yet, in 2017, only 1 in every 62 births (1.61%) in the US was an out-of-hospital birth.[157] This bias toward higher-risk pregnancy events limits somehow the extent to which the study's findings can be applied to the broader population of pregnant women, potentially impacting the generalizability of outcomes to settings where outpatient management is common, such as cases of miscarriage.

7.3.6 Potential limitations due to study designs

7.3.6.1 Rotavirus vaccine effectiveness

The study design for our rotavirus study in manuscript #5 was not intended to assess vaccine effectiveness in infants related to *in utero* TNFi exposure. Instead, it focused on identifying potential safety signals, specifically the risk of diarrhea-associated healthcare events among TNFi-exposed offspring. We initially examined the first 6 months of life following rotavirus vaccine administration to evaluate immediate adverse effects. As no increased risk was observed during this period and given that rotavirus is most severe in infants between 3 and 24 months of age, we extended follow-up to 24 months to capture additional events and assess whether any potential risks might emerge over a longer timeframe. However, as our analysis only included infants who received the first dose and did not look at subsequent doses, we could only look for signals of increased risk of diarrhea-associated healthcare events and not vaccine effectiveness. In order to assess vaccine effectiveness, we would have needed to look at those who received the full vaccine series, either 2 or 3 doses depending on the type of vaccine. This could be the grounds for future research events.

7.3.6.2 Selection bias

A limitation of our analyses is the potential for selection bias arising from classifying TNFi exposure by trimester. Specifically, pregnancies categorized as exposed to TNFi in the third trimester inherently require the pregnancy to have reached the third trimester. This means that extreme preterm births (those occurring before 28 weeks) cannot occur in the third-trimester TNFi-exposed group, as these pregnancies do not reach that stage. In contrast, pregnancies with TNFi exposure limited to the first and/or second trimesters may include a higher proportion of extreme preterm births, which are associated with an elevated risk of serious infections in offspring.[158] In our study, we observed that among the 139 children born before the third trimester, only 16 were exposed to TNFi in the first and/or second trimester, representing 0.4% of the TNFi-exposed group (16/3,711). In comparison, 123 children were in the TNFi-unexposed group, representing 0.2% of the unexposed group (123/53,155). This imbalance in the distribution of extreme preterm births could lead to an overestimation of infection risk in the first and/or second trimester TNFi-exposed group, as their outcomes may disproportionately reflect the higher baseline risk associated with extreme prematurity.

To address this potential selection bias, we conducted a sensitivity analysis restricting the sample to pregnancies that reached the third trimester. The results of this analysis were consistent with those of the primary analysis, indicating that the observed associations were not driven by differences in gestational age distribution between exposure groups. While this strengthens the validity of our findings, the possibility of residual bias cannot be entirely excluded.

7.3.6.3 Prevalent user bias

Women with prior TNFi use and those with infections in the 3-months before conception were included in our assessment of infections during pregnancy and postpartum. This may introduce prevalent user bias, as individuals continuing TNFi from pre-conception may differ systematically from those initiating TNFi during pregnancy in terms of disease severity, baseline infection risk, or healthcare-seeking behaviour. In our cohort, 11% of women initiated TNFi use during pregnancy, suggesting a subset of new users was captured. While this helps mitigate concerns about exclusively assessing long-term TNFi users, differences between initiators and continuers remain a potential limitation. Future studies could separately analyze TNFi initiators and continuers to help further clarify these distinctions.

7.3.6.4 Information and detection bias

A key inclusion criterion for this study was continuous enrollment in MarketScan for ≥12 months before the end of pregnancy. However, disease classification algorithms required varying lookback periods, with some needing one to two years of coverage before gestation, while others assessed diagnoses over a lifetime window. As a result, the duration of pre-conception insurance coverage varied, thus some women have multiple years of data available and others as few as three months. This discrepancy may introduce information bias, as shorter enrollment periods could lead to misclassification of disease status, particularly for conditions requiring longer lookback windows. These limitations may impact the sensitivity and specificity of the algorithms used. Future studies could vary the length of lookback to explore its effect on disease ascertainment.

7.4 Future Directions

This work has implications beyond TNFi. The methodologies employed, such as the time-varying exposure models and large-scale administrative data analysis, offer a robust framework for future studies on other biologic and immunosuppressive agents used during pregnancy. This thesis sets a foundation for expanding research into the safety profiles of various other medications, particularly non-TNFi biologics, used to manage chronic inflammatory diseases in pregnant women. This will facilitate comparisons of risks across drug classes, allowing for a more comprehensive understanding of the risks and benefits associated with biologic therapies during pregnancy.

The framework established in this thesis can be adapted to investigate newer therapies, such as non-TNFi biologics including IL-17 inhibitors, as well as synthetic targeted DMARDs like JAK inhibitors, or other immunosuppressive approaches, including even cellular therapies, that are becoming more common in the treatment of chronic inflammatory conditions and/or the focus of intense research. Expanding this research beyond TNFi will be essential in understanding the broader safety implications of these drugs not only for pregnant women but also for their offspring.

Additionally, as many of these drugs are relatively new, some introduced as early as 1998, with others coming to market later in 2008, 2009, and 2013, we now have at least 10 years of follow-up data on exposed offspring. Exploring the long-term health outcomes of children exposed to TNFi *in utero* could provide valuable insights into immune development, neurological outcomes, and other potential health risks in offspring. These outcomes may include immune

system development, neurological health (e.g. cognitive and behavioural factors), and other potential risks such as hematological malignancies, chronic infections, or the onset of autoimmune conditions in offspring in the longer term. Such longitudinal research would help inform both clinical guidelines and policy decisions regarding the safety of continued biologic therapy during pregnancy.

Finally, as mentioned above, future studies should consider using Medicaid or other datasets to examine the effects of TNFi in more socio-economically diverse populations, addressing the issue of generalizability. Using Medicaid data would also allow examination of race/ethnicity as a potential effect modifier or confounder, since this variable is available in Medicaid data but not in MarketScan commercial claims data. Expanding the research to include international datasets could provide a more diverse picture of TNFi use in pregnancy across different healthcare systems. This would help assess how varying treatment practices and healthcare policies influence maternal and pediatric outcomes globally.

7.5 Conclusions

In this thesis, I explored the implications of TNFi use during pregnancy in women with chronic inflammatory diseases. The findings from each manuscript collectively contribute to a more nuanced understanding of the safety profiles and patterns of TNFi use, thereby influencing clinical guidelines and healthcare policy regarding the management of these patients during pregnancy and the subsequent risks to their exposed offspring.

Assessing the implications of TNFi use during pregnancy for women with chronic inflammatory diseases is crucial for informing clinical guidelines and healthcare policy. I demonstrated how insights from epidemiology can enhance our understanding of TNFi use and safety profiles in these populations. By employing robust statistical methods and comprehensive analyses, I identified key factors influencing the risk of serious infections associated with TNFi exposure, particularly concerning the timing of exposure during pregnancy.

While limitations in data sources and potential confounding factors prevent definitive causal conclusions, this thesis serves as a valuable resource for informing future research and enhancing the understanding of medication safety in pregnant women with chronic inflammatory diseases. Overall, these findings highlight the need for updated clinical guidelines that balance the health of mothers and their children.

CHAPTER 8 - REFERENCES

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CHAPTER 9 APPENDIX

9.1 Appendix A – International Classification of Diseases (ICD) Codes

Table 9.1.1 Definitions used within MarketScan databases, based on diagnostic and procedure codes

Definitions	ICD-9	ICD-10	Diagnosis-Related Group (DRG) codes	CPT Procedure codes
Vaginal delivery	650, V27.0, V27.2, 72.0-72.9, 73.22, 73.59, 73.6	O60.1-3, O68, O69, O70, O80, O81, O83	v28-v35: 767, 768, 774, 775 v36-v39: 796-798, 805-807	59400, 59409, 59410, 59610, 59612, 59614
Caesarean section delivery	669.7, 74.0-74.2, 74.4, 74.4, 74.99	Z38.01, O82	v28-v35: 765, 766 v36-v39: 783-788	59510, 59514, 59515, 59618, 59620, 59622
Stillbirth	V27.1, 632, 656.4, 768.0, 768.1, 779.9	O02.1, O36.4, Z37.1, Z37.4, Z37.7		
Ectopic pregnancy	633.x	O00, O08 (ectopic & molar)	DRGv28-35: 777 Deleted after v35	
Molar pregnancy	630	O01, O08 (ectopic & molar)		
Spontaneous abortion	634.x	O03		
Legally induced abortion	635, 69.01, 69.51, 69.6, 74.91, 75.0, V25.3	O04, O07	DRGv28-39: 770, 779	59840, 59841, 59850-59852, 59855, 59857
Other	631, 632, 638.x, 639.x,			
Premature rupture of membranes	658.1, 658.2	O42.1, O42.9		
Prolonged labour	662.01, 662.11,	O63.0, O63.1, O63.9		
Multiple gestation	651.x, V27.2-V27.7, V91.x	O30, O84, Z37.2-Z37.7, Z38.3-Z38.8		
Inflammatory bowel diseases (Crohn's disease & Ulcerative colitis)	555.xx, 556.xx	K50.x, K51.x		
Psoriasis or Psoriatic Arthritis	696.0, 696.1	L40.0-L40.4, L40.5x, L40.8, L40.9, M07.0-M07.3, M09.0		
Rheumatoid Arthritis	714	M05, M06		
Ankylosing Spondylitis	720.0	M45, M08.1		
Preterm delivery	644.0x-644.1x, 644.2x (765.0, 765.1 in offspring)	O60	DRGv28-35: 791, 792 DRGv36-39: 791, 792	
Maternal asthma	493	J45		

Maternal chronic kidney disease	585, 403, 404	N18, I12, I13		
Maternal hypertension	401.0, 401.1, 401.9, 402.0–405.9, 642.0, 642.1, 642.2	I10-I15, O131-O133, O169		
Pre-gestational diabetes	250-250.93, 648.00-648.04	O24.0-24.3, E10-E14		
Gestational diabetes	648.8	O24.4, O24.9		
COVID-19 Infection		U07.1		
Rotavirus vaccination: RV1				90680
Rotavirus vaccination: RV5				90681
Diarrhea-associated health care events	008.6-008.8, 001.0-005.9, 008.0-008.5, 006.0-007.9, 009.0-009.3, 558.9, 787.91	A00-A09		
Rotavirus disease	008.61	A08.0		

Table 9.1.2 Serious infection ICD-9 and ICD-10 codes used within IBM MarketScan databases

	ICD-9	ICD-10
Infectious and parasitic disease	001–139.9	A00-B99
Further separated into organ involvement		
Abdominal		A00.9, A01.1, A02.0, A03.8, A04.3, A04.5, A04.7, A04.8, A04.9, A05.9, A08.0, A08.1, A08.2, A08.3, A08.4, A08.5, A09, A09.9, B67.0, K35.0, K35.0A, K35.1, K35.1A, K35.9, K57.2B, K57.3, K57.3A, K57.3B, K57.3F, K57.9A, K65.0,K65.0A, K65.0G, K65.0J, K65.8, K65.8I, K65.9, K75.0, K80.3, K80.4, K81.0, K81.9, K83.0
Cardiovascular	421	I30.0, I30.1, I30.8, I30.9, I33.0, I33.9, I38.9, I39.8
Central nervous system	320, 323, 324	A39.0, A39.2A, A86.9, A87.0, A87.9, B00.3, B00.4, B02.0, B02.2, B02.2A, B02.2B, B91.9, G00.1, G00.8, G00.9, G00.9A, G01.9, G04.0, G04.2, G06.0, G06.0F, G06.2, G07.9
Respiratory system	460-466, 473, 480-487, 510	Pneumonia: A31.0A, A48.1, B37.1, J12.0, J13.9, J14.9, J15, J15.0, J15.1, J15.2, J15.4, J15.5, J15.7, J15.8, J15.9, J17.0, J17.8C, J18, J18.0, J18.1, J18.8, J18.9, J20.9, J20.9A, J21.9, J22.9, J69.0, J69.8, J69.8A Other: A15.0, A15.1, A15.2, A15.9, B90.9, J40.9, J44.0, J85.1, J85.2, J86.0, J86.9
Other sites of infection	790.7	B00.2A, B02.3G, B37.3A, B37.4, B37.8C, E06.0, E06.1, H65.1, H66.0, H66.9, J00.9B, J01.0, J01.1, J01.2, J01.8, J01.9, J02.0, J02.9, J02.9B, J03.0, J03.9, J03.9A, J04.0, J05.1, J06.9, J36.9, J39.0C, K04.0A, K05.3A, K10.2C, K11.2C, K12.1, K62.8L, N41.2, N45.0B, N45.9, N45.9A, N76.4A, O86.8
Skin, muscles, and bones	681-686, 711.0, 730	A46.9, B00.1A,B00.1B, B37.2, K61.0, K61.0A, K61.1, K61.2, L02.2, L02.2T, L02.4, L02.4F, L02.4K, L02.9, L02.9A, L03.1, L03.1E, L03.3, L08.8, L08.9, M00.0, M00.2, M00.2A, M00.8, M00.9, M46.3, M46.4, M46.5, M46.5A, M46.9, M71.1, M86.1, M86.8, M86.9
Unknown		A40.1, A40.3, A40.8, A40.9, A41.0, A41.1, A41.1A, A41.2, A41.3, A41.4, A41.5, A41.8, A41.9, A49.9A, B37.7, A32.9, A41.9A, A42.9, A44.9, A48.2, A49.0, A49.1, A49.3, A49.8, A49.9, A68.9, A70.9, A81.2, B00.8, B02.9, B34.0, B34.9, B36.9, B37.0, B37.8, B80.9, B89.9, B95.5, B95.6, B95.6A, B96.4, B96.5, B96.8, B99.9, R50, R50.0, R50.8, R50.9, T81.4D, T84.6, T89.9
Urinary tract	590	A41.9B, N10.9, N12.9, N13.6, N30.0, N30.8, N30.9, N39.0, N39.0B
Viral/Systemic		A51.5, A79.9, B00.1, B05.9, B20.4, B20.6, B20.8, B23.0, B23.2, B24.9, B25.8, B25.9, B27.0, B27.9, B50.9, B52.9, B54.9, B55.0, B58.9, J09.1, J09.9, J10.0, J10.8, J11, J11.0, J11.1, J11.8

9.2 Appendix B – Reprint of Published Manuscripts

9.2.1 Manuscript #1

Scandinavian Journal of Rheumatology

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Tumour necrosis factor inhibitors and serious infections in reproductive-age women and their offspring: a narrative review

LK Flatman, I Malhamé, I Colmegna, A Bérard, S Bernatsky & É Vinet

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Tumour necrosis factor inhibitors and serious infections in reproductive-age women and their offspring: a narrative review

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Tumour necrosis factor inhibitors (TNFi) are commonly used to treat patients with chronic inflammatory diseases, and function by inhibiting the pro-inflammatory cytokine tumour necrosis factor-α (TNF-α). Although beneficial in reducing disease activity, they are associated with an increased risk of serious infections. Data on the risk of serious infections associated with TNFi use during the reproductive years, particularly in pregnancy, are limited. For pregnant women, there is an additional risk of immunosuppression in the offspring as TNFi can be actively transported across the placenta, which increases in the second and third trimesters. Several studies have explored the risk of serious infections with TNFi exposure in non-pregnant and pregnant patients and offspring exposed in utero, indicating an increased risk in non-pregnant patients and a potentially increased risk in pregnant patients. The studies on TNFi-exposed offspring showed conflicting results between in utero TNFi exposure and serious infections during the offspring's first year. Further research is needed to understand differential risks based on TNFi subtypes. Guidelines conditionally recommend the rotavirus vaccine before 6 months of age for offspring exposed to TNFi in utero, but more data are needed to support these recommendations because of limited evidence. This narrative review provides an overview of the risk in non-pregnant patients and summarizes evidence on how pregnancy can increase vulnerability to certain infections and how TNFi may influence this susceptibility. This review focuses on the evidence regarding the risk of serious infections in pregnant patients exposed to TNFi and the risk of infections in their offspring.

Tumour necrosis factor inhibitors (TNFi) are powerful immunomodulating drugs widely used in chronic inflammatory diseases, including during pregnancy (1). While TNFi have been associated with increased infections in non-pregnant patients, data on pregnant women are lacking. Given that pregnant women are already at a higher risk of infections in pregnancy and postpartum as a result of several immune system changes, this narrative review primarily aims to explore the association between TNFi use during pregnancy and the risk of severe infections for both pregnant patients and their offspring. This review also provides an overview of the risk in non-pregnant patients and briefly summarizes evidence on how pregnancy can increase vulnerability to certain infections and how TNFi may influence this susceptibility. Relevant manuscripts were identified for this narrative review by searching through PubMed for original articles (including clinical trials, observational studies, and meta-analyses) combining search terms related to serious infections, TNFi use in pregnant and non-pregnant subjects, as well as exposed offspring. The reference lists of identified papers were also searched for additional articles. From this selection, the most relevant studies were summarized to describe the current literature and identify knowledge gaps pertaining to

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serious infections and TNFi use during the reproductive years.

Tumour necrosis factor-α and the immune system

TNF-α, a pro-inflammatory cytokine, is produced by multiple cells and, through several critical cell functions (e.g. cell survival, differentiation, proliferation, and apoptosis), is involved in immunity and inflammation (2). TNF-α and the TNF receptor signalling pathway play a role in the defence against infections (3). In response to bacteria, specifically the lipopolysaccharides on the cell surface of bacteria and other bacterial products, large amounts of cytokines and soluble TNF-α are released by macrophages to initiate inflammation, activating phagocytosis, leucocyte recruitment, and eradication of the bacteria (4). A similar mechanism protects against parasites (3). TNF-α also has antiviral activity that can induce resistance in uninfected cells or selectively kill virus-infected cells directly or by producing interferons (3).

Role of TNF-α in chronic inflammatory diseases

TNF-α is also pathogenic in chronic inflammatory diseases. In diseases such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), psoriasis (PsO), psoriatic arthritis (PsA), and ankylosing spondylitis (AS), there are excessive amounts of TNF-α and disease activity correlates with high TNF-α serum levels (5). These immune-mediated inflammatory diseases are prevalent in the USA (US) and Europe at 5–7% (6) and are treated with non-steroidal anti-inflammatory drugs, glucocorticoids, and disease-modifying anti-rheumatic drugs (DMARDs), comprised of conventional DMARDs (csDMARDs; e.g. hydroxychloroquine, methotrexate, sulfasalazine), biological DMARDs (bDMARDs; e.g. TNFi, interleukin-6 receptor inhibitors, anti-integrin agents, interleukin-12/23 antagonists), and targeted synthetic DMARDs (e.g. Janus kinase inhibitors) (7, 8). bDMARDs are most commonly prescribed to patients with active disease who have failed on csDMARDs.

Five TNFi have been approved for use in the USA, starting in 1998 with infliximab (9). Since then, etanercept (10), adalimumab (11), certolizumab (12), and golimumab (13, 14) have been approved. TNFi biosimilars were also approved in 2013 as cost-effective alternatives with similar properties and mechanisms of action as the originators (15, 16). TNFi are administered via subcutaneous injection or intravenous infusion. Most TNFi are monoclonal immunoglobulins G (IgG) with a fragment crystallizable (Fc) region (adalimumab, infliximab, golimumab), while etanercept is a fusion protein comprising a TNF receptor and the IgG Fc region, and certolizumab is a pegylated Fab fragment of an anti-TNF monoclonal antibody without an Fc region (15, 17).

The mechanisms of action for the five TNFi differ slightly (18). Adalimumab and infliximab prevent the interaction of TNF-α with the two cell-surface TNF receptors by binding to soluble TNF-α and possibly membrane-bound TNF-α to reduce macrophage and T-cell function. Golimumab has a high affinity for both forms of TNF-α and inhibits it from binding to its receptors, stopping TNF-initiated signalling cascades. Etanercept blocks TNF-α activity and lymphotoxin-α, and certolizumab neutralizes both forms of TNF-α.

TNFi exposure may lead to serious infections

TNFi use in chronic inflammatory diseases may result in serious infections (Table 1). Highlighting two meta-analyses, one published in 2021, which included 18 observational studies and randomized controlled trials with 37 693 patients with RA, PsA, and AS, showed that TNFi use is associated with an increased risk of serious infections [odds ratio (OR) 1.72; 95% confidence interval (CI) 1.56, 1.90] (19). However, this meta-analysis combined studies with different TNFi exposures (e.g. adalimumab only vs infliximab or etanercept; TNFi + DMARDs) and different follow-up periods (between 70 days and 2 years), and only looked at TNFi use in the context of RA, PsA, and AS. Most studies were neither specifically designed nor powered to evaluate serious infections associated with TNFi. Finally, another meta-analysis of 44 RCTs in patients with IBD found that when they focused on the 14 studies with a low risk of bias, the use of biologics (TNFi, natalizumab, vedolizumab) significantly reduced the risk of serious infections compared to placebo groups (OR 0.56; 95% CI 0.35, 0.90) (20). Vedolizumab is an anti-integrin monoclonal antibody with a local effect on the gut, and not a systemic immunosuppressant, thus potentially having a lower risk of serious infections than TNFi (21). As a result of the pooling of studies concerning TNFi and vedolizumab, the measure of effect for biologics and serious infections may be diluted. The majority of these studies suggest that there may be an increased risk of infection associated with TNFi use in non-pregnant patients with chronic inflammatory diseases. This risk may be further elevated during pregnancy.

Table 1. Characteristics of systematic reviews and meta-analyses (n = 3 studies) and observational studies (n = 6 studies) included in this review on serious infection outcomes in non-pregnant patients taking tumour necrosis factor inhibitors (TNFi).

Authors (ref.)	Design	Disease	Exposure	Comparison	Outcome	Size of the exposed population	Size of the unexposed population	Results
Bonovas et al (20)	Systematic review and meta-analysis (44 RCTs)	IBD	Biologics (ADA, CTZ, GOL, IFX, natalizumab, vedolizumab)	Placebo	Infections associated with hospital admission	8627	5405	OR 0.56; 95% CI 0.35, 0.90
Li et al (19)	Meta-analysis of 18 observational studies and RCTs	RA, PsA, AS	ADA, CTZ, ETN, GOL, IFX	Without TNFi (controlled or placebo)	Infections requiring antimicrobial treatment and/or hospitalization	26 431	11 262	OR 1.72; 95% CI 1.56, 1.90
Minozzi et al (22)	Systematic review and meta-analysis of 58 RCTs	RA, PsA, AS	ADA, CTZ, ETN, GOL, IFX	Placebo or no treatment, or multi-interventional therapies	Infections requiring antimicrobial therapy and/or hospitalization	13 430	7366	OR 1.41, 95% CI 1.16, 1.73
Bernatsky et al (23)	Nested case–control; administrative database	RA	IFX, ETN	Controls who have not yet experienced the outcome	Infections requiring hospitalization	261		IRR 1.93; 95% CI 0.70, 5.34
Cecconi et al (24)	Prospective cohort; Brazilian registry study	RA, AS, PsA	IFX, ADA, GOL, ETN, CTZ	csDMARDs	Serious adverse event: a condition that causes death or is life-threatening, implies inpatient hospitalization or prolongation of an existing one, and involves persistent or significant disability or a congenital abnormality	1698	572	IRR 2.96; 95% CI 2.01, 4.36
Curtis et al (25)	Retrospective cohort; large US healthcare organization	RA	ETN, IFX, ADA	Methotrexate	Hospitalization with a bacterial infection	2393	2933	HR 1.9; 95% CI 1.3, 2.8
Dixon et al (26)	Prospective cohort; British biologics registry	RA	ETN, IFX, ADA	Traditional DMARDs	Infections that led to hospitalization or death or required intravenous antibiotic treatment	7664	1354	IRR 1.03; 95% CI 0.68, 1.57
Galloway et al (27)	Prospective cohort; British rheumatology biologics registry	RA	ETN, IFX, ADA	Traditional DMARDs	Serious skin and soft tissue infections, defined as resulting in hospitalization, requiring intravenous antibiotics, or causing death	11 881	3673	HR 1.3; 95% CI 0.8, 2.2
Listing et al (28)	Prospective cohort; biologics registry	RA	ETN, IFX	csDMARDs	Serious adverse event: a condition that causes death or is life-threatening, implies inpatient hospitalization or prolongation of an existing one, and involves persistent or significant disability or a congenital abnormality	ETN: 512 IFX: 346	601	ETN: RR 2.16; 95% CI 0.9, 5.4 IFX: RR 2.13; 95% CI 0.8, 5.5

ADA, adalimumab; AS, ankylosing spondylitis; CI, confidence interval; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; CTZ, certolizumab pegol; DMARD, disease-modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; HR, hazard ratio; IFX, infliximab; IRR, incidence rate ratio; OR, odds ratio; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RCT, randomized controlled trial; RR, risk ratio.

Infections during pregnancy

Pregnant women are disproportionally affected by infections owing to an increase in susceptibility and/or severity associated with specific organisms, such as the bacteria *Listeria*, the parasite *Plasmodium falciparum* (malaria), and certain viruses, including influenza, hepatitis E, herpes simplex, and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (29, 30). These observed increases in susceptibility and/or severity may be due to the shift in T-lymphocyte helper (Th) subsets from Th1 to Th2 immunity during pregnancy (29). Th2 cells suppress the cytotoxic T-lymphocyte response, decreasing cell-mediated immunity, which could explain part of the increased severity of certain infections in pregnancy (29). A study in the general population found that 3% of pregnant women were hospitalized for an infection during pregnancy (31). During the postpartum period, 6–20% of women experienced an infection, with the variability in risk explained by the type of delivery (i.e. vaginal vs caesarean delivery) (32–36). The most common postpartum infections were mastitis, urinary tract infections, endometritis, and surgical site infections (32–34).

In patients with chronic inflammatory diseases, disease activity varies over time, often with periods of remission or low disease activity. However, disease flares are frequent (37). Specifically, flares during pregnancy are not uncommon and may be associated with adverse pregnancy outcomes. A study by Gerardi et al found that the risk of flares during pregnancy in women with RA was associated with discontinuing bDMARDs early in pregnancy (OR 2.86; 95% CI 1.11, 8.32) (38). They found links between pregnancy flares and preterm delivery (OR 4.63; 95% CI 1.03, 20.83) (38). Based on the available literature, guidelines have recommended continuing TNFi during pregnancy (1, 39–41). Studies have shown no increased risk of pregnancy complications, such as miscarriages, foetal deaths, congenital malformations, low birth weight, and/or preterm births (40–42). As a result, TNFi are prescribed in up to 20% of pregnant women with chronic inflammatory diseases, representing a three-fold increase over the past 10 years (43).

Risk of serious infections associated with TNFi use in pregnancy

Pregnant women are commonly excluded from clinical trials (44). They are often underrepresented in observational studies as a result of possible challenges surrounding the recruitment and retention of pregnant women. The largest studies on serious infections in pregnant women with chronic inflammatory diseases are observational and population based (Table 2). An observational cohort study using US administrative data identified 776 women with RA, AS, PsA, or IBD receiving TNFi during pregnancy (45). Pregnant women using TNFi in combination with steroids or non-biologics had a higher risk of serious infections requiring hospitalization (such as bacterial or opportunistic infections) compared with pregnant women on non-biologics, but the 95% CI was wide [hazard ratio (HR) 1.36; 95% CI 0.47, 3.93] (45). A similar study using a French national health system database focusing on 1457 pregnant women with IBD found that exposure to TNFi (infliximab, adalimumab, golimumab, or certolizumab) during pregnancy was associated with in-hospital infections (OR 1.25; 95% CI 1.04, 1.50), and when looking at third-trimester exposure (> 24 weeks), the association was similar (OR 1.31; 95% CI 1.09, 1.59) (46). These two studies restricted the analyses to only the gestational period, excluding postpartum infections resulting from hospitalization for childbirth. They also classified TNFi as a fixed exposure, potentially introducing immortal-time bias, as the unexposed time when the patient is not taking the medication may be misclassified as exposed (47). Therefore, if a serious infection occurs when the woman is not currently taking TNFi but was previously doing so during the study period, the outcome will be misclassified as an exposed outcome and associated with the exposure instead of being classified as unexposed (48). Similarly, a multicentre cohort study in Europe looking at gestational infections in women with IBD found that the proportion of infections in patients taking TNFi during gestation (n = 388) was higher than in those not on TNFi (n = 453) (4.1% vs 0.9%; p = 0.002), but did not look at the postpartum period (49).

More evidence among pregnant women taking TNFi is needed regarding the risk of serious infections during pregnancy and postpartum. Analysing infectious events related to hospitalization for delivery is important. Women with chronic inflammatory diseases have a two-fold higher rate of caesarean delivery (approximately 40% of affected women), and infection complicates up to 10% of caesarean deliveries among healthy women (36, 50). However, most studies only look at infections occurring during gestation. A Canadian population-based cohort study of 6218 women with autoimmune diseases focusing on the postpartum period could not find an association between biologics (TNFi, abatacept, alefacept, anakinra, belimumab, natalizumab, rituximab, tocilizumab, and ustekinumab; n = 90) and an increased risk of serious maternal postpartum infections (OR 0.79; 95% CI 0.24, 2.54) (51). However, the exposure and outcome were rare, resulting in potentially unstable estimates. Ultimately, assessing infection risk in women exposed to TNFi throughout pregnancy and postpartum will improve our understanding of these medications and inform guidelines to optimize pregnancy management for patients and their offspring.

Table 2. Characteristics of studies included in this review (n = 4 studies) on serious infection outcomes in women taking tumour necrosis factor inhibitors (TNFi) during pregnancy.

Authors (ref.)	Design	Disease	Exposure	Comparison	Outcome	Size of the exposed population	Size of the unexposed population	Results
Chaparro et al (49)	Retrospective cohort	IBD	IFX, ADA, CTZ	Unexposed	Infection during pregnancy	388	453	4.1% (TNFi) vs 0.9% (unexposed); p = 0.002
Desai et al (45)	Retrospective cohort	RA, AS, PsA, IBD	ADA, CTZ, ETN, GOL, IFX	Non-biologics	Composite of bacterial infection or opportunistic infection identified using discharge diagnosis codes from hospital admission records	776	816	HR 1.36; 95% CI 0.47, 3.93
Luu et al (46)	Retrospective cohort	IBD	IFX, ADA, GOL, CTZ	Unexposed	Infections requiring hospitalization	1457	9818	OR 1.25; 95% CI 1.04, 1.50 3rd trimester: OR 1.31; 95% CI 1.09, 1.59
Tsao et al (51)	Retrospective cohort	RA, IBD, PsO, PsA, AS, juvenile idiopathic arthritis, and systemic autoimmune rheumatic diseases	Abatacept, ADA, alefacept, anakinra, belimumab, CTZ, ETN, GOL, IFX, natalizumab, rituximab, tocilizumab, ustekinumab	Disease-matched women with no biologics	Serious infections requiring hospitalization during the postpartum period	90	6128	OR 0.79; 95% CI 0.24, 2.54

ADA, adalimumab; AS, ankylosing spondylitis; CI, confidence interval; CTZ, certolizumab pegol; ETN, etanercept; GOL, golimumab; HR, hazard ratio; IBD, inflammatory bowel disease; IFX, infliximab; OR, odds ratio; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis.

Placental transport of TNFi during pregnancy

During pregnancy, the transplacental passage of maternal circulating IgG proteins takes place. During the first trimester, the transfer occurs mainly via simple diffusion across the placenta, while active transfer begins around gestational week 16 and increases throughout pregnancy, mediated by neonatal Fc receptors (52). Between 17 and 20 weeks, the foetal to maternal level of IgG is 10% of the maternal concentration, while at term, it is 130% of maternal levels (53). All TNFi except for certolizumab contain an Fc region; therefore, most TNFi are actively transported across the placenta via the foetal Fc receptors, enter the foetus's bloodstream, and may reach higher blood levels in the foetus than in the mother owing to active placental transfer and the biological half-life being longer in newborns than in adults (54). Infliximab, adalimumab, and golimumab have the highest transplacental transfer (reaching cord blood levels of, respectively, 160%, 150%, and 121% of maternal blood levels), while etanercept and certolizumab display the lowest passage (cord blood levels of, respectively, 4% and < 0.25% of maternal blood levels) (15, 17, 55–58). As foetuses can be exposed to therapeutic (and potentially supratherapeutic) TNFi doses, TNFi could theoretically cause immunosuppression in the offspring (59).

Furthermore, owing to differences in placental transfer ability as a result of the differing TNFi structures, evaluating the potential risks of each subtype is critical for delivering appropriate care to mother and child. Similarly, because of the fear of excessive immunosuppression in the offspring, many experts recommend cessation of TNFi (primarily infliximab, adalimumab, and golimumab) during late pregnancy (late second or early third trimester) (1, 39, 41). Specifically, the American College of Rheumatology (ACR) conditionally recommends (with low evidence) continuing infliximab, etanercept, adalimumab, and golimumab prior to and during pregnancy (41). The European Alliance of Associations for Rheumatology (EULAR) suggests the continuation of infliximab and adalimumab up to gestational week 20, and up to gestational week 30–32 for etanercept, unless these drugs are indicated, in which case they can be used throughout pregnancy (1). Owing to limited evidence, EULAR recommends considering alternative medications instead of continuing golimumab throughout pregnancy (1). The American Gastroenterological Association (AGA) suggests continuing scheduled dosing throughout all three trimesters for adalimumab, golimumab, and infliximab, but, if possible, recommends planning the final dose according to the drug half-life to minimize placental transfer near the time of delivery (39). As a result of the low placental transfer ability of certolizumab, all three guidelines (ACR, EULAR, and AGA) strongly recommend continuing certolizumab prior to and throughout pregnancy (1, 39, 41).

Risk of serious infections in TNFi-exposed offspring

In offspring exposed in utero to known immunosuppressants (e.g. TNFi), the risk of serious infections may differ from that in unexposed children. In the general population, the risk of infections requiring hospitalization during the first year of life is around 2% (60, 61). The studies below demonstrate conflicting evidence regarding the association between TNFi-exposed offspring and the risk of serious infections (Table 3).

Exposure to biologic drugs, not restricted to TNFi

Three studies and one meta-analysis evaluated the association between biologic exposure in offspring and the risk of serious infections; however, these studies did not focus solely on TNFi as they also included anti-integrins and anti-interleukin-12/23 (51, 62–64). A meta-analysis of 10 studies that included infants exposed in utero to biologics used to treat IBD, including TNFi, showed no significant increase in infection-related hospitalization risk during the first year of life in exposed children compared to unexposed children (OR 1.33; 95% CI 0.95, 1.86) (62). The meta-analysis included a study on vedolizumab that found the risk of serious infections to be 0.37 (95% CI 0.09, 1.48) (65). A cohort study (64) also combined TNFi with other biologics, including vedolizumab, possibly affecting the observed effect of biologics and serious infections. The Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) prospective observational study in the USA found no increased risk of infection requiring hospitalization in exposed offspring (n = 848) compared to unexposed offspring (n = 423) when assessing the use of biologics (TNFi, anti-integrin, and anti-interleukin -12/23) (OR 0.92; 95% CI 0.70, 1.20) (64). However, it is worth noting that 5% (n = 41) of the biologic-exposed offspring were exposed to vedolizumab, which could have influenced the results. Another study by Tsao et al in a cohort of Canadian offspring born to mothers with RA, IBD, PsO, PsA, AS, juvenile idiopathic arthritis, and systemic autoimmune rheumatic diseases showed no association between in utero exposure to biologics and serious infections requiring hospitalization (OR 0.56; 95% CI 0.17, 1.81) (51). Chambers et al investigated pregnant women with RA and their offspring in the USA and Canada but found no association between biologic (unspecified)-exposed or unexposed offspring [risk ratio (RR) 0.71; 95% CI 0.30, 1.71] regarding the risk of serious infection (63). This lack of association remained even after analysing only offspring exposed after gestational week 24 (n = 155; RR 1.00; 95% CI 0.40, 2.48) and after gestational week 32 (n = 143; RR 0.90; 95% CI 0.34, 2.39) (63).

Table 3. Characteristics of studies included in this review (n = 16 studies) on serious infection outcomes in offspring exposed in utero to tumour necrosis factor inhibitors (TNFi).

Authors (ref.)	Design	Maternal disease	In utero exposure	Comparison	Outcome	Size of the exposed population	Size of the unexposed population	Results
Barenburg et al (66)	Systematic review and meta-analysis (7 studies)	IBD, RA, PsO	IFX, ADA, GOL, CTZ, ETN	Children born to diseased controls	Infections in newborns	2507	13 059	OR 1.12; 95% CI 1.00, 1.27
Bröms et al (67)	Retrospective cohort	RA, PsO, PsA, AS, IBD	ETN, IFX, ADA, CTZ, GOL	Children of the general population	Hospital admissions for infection in the first year	1027	1 617 886	Any: IRR 1.43; 95% CI 1.23, 1.67 ADA: IRR 1.35; 95% CI 1.00, 1.83 ETN: IRR 1.37; 95% CI 1.05, 1.78), CTZ: IRR 1.50; 95% CI 1.13, 1.98
Chambers et al (63)	Prospective cohort	RA	Biologics (not specified)	Children born to diseased unexposed or healthy cohort (no RA) mothers	Infections requiring hospitalization or those from a specific checklist (up to 1 year of age)	252	463 (diseased), 469 (healthy control)	Diseased unexposed: RR 0.71; 95% CI 0.30, 1.71 Healthy controls: RR 1.09; 95% CI 0.43, 2.72
Chambers et al (75)	Prospective cohort	RA, CD	ADA	Children born to diseased unexposed or healthy cohort (no CID) mothers	Infections requiring hospitalization or those from a specific checklist (up to 1 year of age)	229	111 (diseased), 203 (healthy control)	Diseased unexposed: RR 0.97; 95% CI 0.34, 2.77 Healthy control: RR 1.77; 95% CI 0.62, 5.05
Chaparro et al (49)	Retrospective cohort	IBD	IFX, ADA, CTZ	Unexposed	An infection that led the child to be admitted to the hospital at any time during follow-up	388	453	HR 1.2; 95% CI 0.8, 1.8
De Lima et al (72)	Prospective cohort	IBD	IFX, ADA	Children born to non-IBD mothers not treated with TNFi	Infections requiring hospitalization during first year of life	55	459	p = 0.49

(*Continued*)

Table 3. (Continued).

Authors (ref.)	Design	Maternal disease	In utero exposure	Comparison	Outcome	Size of the exposed population	Size of the unexposed population	Results
Duricova et al (74)	Prospective cohort	IBD	IFX, ADA	Unexposed children of non-IBD mothers (general population offspring)	Infection leading to antibiotic treatment and/or hospitalization	72	69	OR 0.86; 95% CI 0.32, 2.32
Gubatan et al (62)	Systematic review and meta-analysis	IBD	IFX, ADA, GOL, CTZ, natalizumab, vedolizumab, ustekinumab	Infants not exposed to biologics	Infection-related hospitalization	1965	6584	OR 1.33; 95% CI 0.95, 1.86
Kanis et al (73)	Retrospective cohort	IBD	IFX, ADA	Unexposed children	Admission to hospital because of infection during first 5 years of life	163	564	IRR 1.66; 95% CI 0.91, 3.04
Luu et al (46)	Retrospective cohort	IBD	IFX, ADA, GOL, CTZ	Unexposed offspring	Infections requiring hospitalization	797	4836	OR 0.85; 95% CI 0.64, 1.13
Mahadevan et al (64)	Prospective cohort	IBD	IFX, ADA, CTZ, GOL, vedolizumab, natalizumab, ustekinumab	Children born to women with IBD who did not take thiopurines or biologics	Infection requiring hospitalization	848	423	OR 0.92; 95% CI 0.70, 1.20
Meyer et al (70)	Retrospective cohort	IBD	IFX, ADA, GOL, CTZ	Unexposed offspring	Infection requiring hospitalization as the primary diagnosis during the first 5 years of life	3399	18 954	HR 1.10; 95% CI 0.95, 1.27
Nørgård et al (68)	Retrospective cohort	IBD, rheumatological diseases, PsO, connective tissue disease, liver disease	IFX, ADA, ETN, GOL, CTZ	Unexposed children	Infections that were diagnosed in a hospital in children ≤ 1 year of age	493	728 055	HR 1.44; 95% CI 1.19, 1.74
Seirafi et al (71)	Case–control	IBD	IFX, ADA, CTZ	Unexposed offspring born to IBD mothers	Neonatal infection	133	99	p = 0.73
Tsao et al (51)	Retrospective cohort	RA, IBD, PsO, PsA, AS, juvenile idiopathic arthritis, and systemic autoimmune rheumatic diseases	Abatacept, ADA, alefacept, anakinra, belimumab, CTZ, ETN, GOL, IFX, natalizumab, rituximab, tocilizumab, ustekinumab	Offspring born to disease-matched women with no biologics	Serious infections requiring hospitalization anytime during the first year of life	100	8507	OR 0.56; 95% CI 0.17, 1.81
Vinet et al (69)	Retrospective cohort	RA	ADA, CTZ, ETN, GOL, IFX	Randomly selected control children born live and exposed to RA mothers	Hospitalization with infection as the primary reason for admission within the first year of life	380	2476	OR 1.4; 95% CI 0.7, 2.8

ADA, adalimumab; AS, ankylosing spondylitis; CD, Crohn's disease; CI, confidence interval; CID, chronic inflammatory disease; CTZ, certolizumab pegol; ETN, etanercept; GOL, golimumab; HR, hazard ratio; IBD, inflammatory bowel disease; IFX, infliximab; IRR, incidence rate ratio; OR, odds ratio; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; RR, risk ratio; TNFi, tumour necrosis factor inhibitor.

Exposure to TNFi, combining high and low placental transfer subtypes

A meta-analysis, including 39 studies on pregnancy and neonatal outcomes in women with IBD, RA, and PsO, found a small increased risk of infections in newborns in the TNFi-exposed group compared to diseased controls (OR 1.12; 95% CI 1.00, 1.27), when looking at seven studies which focused on the risk of infections in offspring born to mothers with IBD and RA (66). The range of TNFi-exposed offspring among these seven studies was 15 to 1457 (total = 2507). However, this analysis had some limitations, such as not including certain studies, combining different exposure definitions and TNFi subtypes, only including offspring born to mothers with IBD and RA, and comparing outcomes that looked at any infection or infection leading to hospitalization. Future analyses are needed to explore the risk of serious infections in all chronic inflammatory disease groups according to specific TNFi subtypes.

A population-based cohort study involving 1027 children born to mothers with RA, PsO, PsA, AS, and IBD in Denmark, Finland, and Sweden found an increased risk of infant hospital admissions for infection in their first year associated with TNFi use [incidence rate ratio (IRR) 1.43; 95% CI 1.23, 1.67] compared to the general population (67). Specifically, the use of adalimumab (IRR 1.35; 95% CI 1.00, 1.83), etanercept (IRR 1.37; 95% CI 1.05, 1.78), and certolizumab (IRR 1.50; 95% CI 1.13, 1.98) was associated with first-year hospitalization for infection.

Another study, using Danish health registries, revealed an elevated risk of any infections in children born to mothers treated with TNFi in Denmark (n = 493) compared to unexposed children, including children born to healthy women (n = 728 055) (HR 1.44; 95% CI 1.19, 1.74) (68). This elevated risk was observed for urological/gynaecological, respiratory, and other infections (68). Alternatively, an administrative database study did not find an increased risk of hospitalization for infection within the first 12 months of life in American offspring born to mothers with RA exposed to TNFi during pregnancy (n = 380) compared to unexposed RA offspring (n = 2476) (OR 1.4; 95% CI 0.7, 2.8) (69). However, this study may have been underpowered because of its small sample size. Regarding offspring born to mothers with IBD exposed to TNFi, except for etanercept, in utero, two studies did not find associations with an increased risk of infection during their first year of life compared to TNFi-unexposed children born to mothers with IBD (46, 70).

In specific studies focusing on exposure to infliximab, adalimumab, or certolizumab, a multicentre European study of children born to IBD mothers did not find an association between TNFi and infections that required hospital admissions in the first year of life (HR 1.2; 95% CI 0.8, 1.8) (49). Similarly, another study from France and Belgium on IBD offspring found a non-significant difference in the proportions of neonatal infection between the TNFi-exposed group and the control group (p = 0.73) (71).

Exposure to high placental transfer TNFi

In utero exposure to high placental transfer TNFi (infliximab or adalimumab) was assessed in several studies. de Lima et al studied TNFi-exposed children born to mothers with IBD (n = 55) in the Netherlands and compared them with unexposed non-IBD offspring (n = 459), but found no statistically significant difference in infections requiring hospitalization (p = 0.49) (72). Kanis et al also examined 1000 IBD offspring from the Netherlands and found an adjusted IRR of 1.66 (95% CI 0.91, 3.04) for TNFi-exposed offspring compared to unexposed offspring in terms of hospital admission due to infection (73). Finally, a multicentre study from the Czech Republic found no association between TNFi-exposed IBD offspring and infection leading to antibiotic treatment and/or hospitalization compared with the general population (OR 0.86; 95% CI 0.32, 2.32) (74). Chambers et al investigated adalimumab exposure in offspring born to mothers with RA and Crohn's disease in a pregnancy registry in the USA and Canada, finding no significant differences in the risk of serious infections when compared to both diseased unexposed children (RR 0.97; 95% CI 0.34, 2.77) and a healthy group (RR 1.77; 95% CI 0.62, 5.05) (75).

Because of the diverse study designs, including the type of TNFi and whether other biologics were included, the comparison groups, and maternal chronic inflammatory disease diagnoses, direct comparison across studies is challenging. This leads to conflicting results, with some studies demonstrating a slight increase in the risk of serious infections while others could not establish a risk. In addition, the studies may be underpowered to detect a clinically meaningful difference between exposed and unexposed groups. Finally, some studies analysed the risk of serious infections according to individual TNFi; however, no known study, besides those from our group, separated TNFi according to placental transfer ability and compared the risk of infection across subtypes. Therefore, it is crucial to assess the TNFi subtypes separately, as their different transplacental passage abilities may affect the risk of infection during the child's first year of life.

In utero exposure to TNFi can delay rotavirus vaccine in offspring

TNFi can be detected in infants for up to 6 months (54). Thus, adverse events may occur, including those linked with routine childhood immunizations. Live vaccines such as rotavirus, bacillus Calmette–Guérin (BCG), and measles, mumps, and rubella (MMR) use weakened

viruses to create lasting immune responses (59). In patients with suppressed immune systems, such as those exposed in utero to TNFi, live vaccines could lead to the systemic spread of the microorganism or virus with infection. This was described in a case report of a child exposed in utero to TNFi who developed a fatal infection at 4.5 months old after receiving the BCG vaccine at 3 months (59). Previous rheumatology guidelines recommended withholding rotavirus vaccine in offspring exposed in utero to any TNFi until 6 months of age, instead of routine immunization starting at 2 months (1, 39, 41).

Most severe rotavirus disease, which can be fatal, occurs primarily among unvaccinated children aged 3–12 months (76). In North America, the rotavirus vaccine is the only live vaccine administered before 6 months of age as part of the routine immunization schedule. Two oral live attenuated vaccines (with similar efficacy and safety) are available for the prevention of rotavirus disease, the pentavalent (RV5) and the monovalent (RV1) rotavirus vaccines. RV5 is administered at 2, 4, and 6 months of age, while RV1 is administered at 2 and 6 months (77, 78). Rotavirus vaccines effectively prevent rotavirus disease, reducing diarrhoea-related events by > 90% (77, 78). Delaying vaccine administration until 6 months of age may be associated with a greater risk of diarrhoea-associated morbidity. However, there are limited data on rotavirus disease after vaccination or the impact of postponing vaccines in TNFi-exposed offspring. The new 2022 ACR vaccination guidelines conditionally recommend administering the rotavirus vaccine within the first 6 months of life, but are based on three observational studies with a combined 58 TNFi-exposed offspring (79). The small sample sizes of these studies highlight the need for larger ones. Thus, there is an urgent need to provide quality data to confirm the recommendations made by the 2022 guidelines to minimize complications and confusion.

Conclusion

Several studies have investigated the risk of serious infections associated with TNFi exposure (either directly for pregnant or non-pregnant patients or in utero for offspring). Non-pregnant patients have an increased risk of infections associated with the use of TNFi. In pregnant patients, there are limited data during the gestational period and no data postpartum; however, available data suggest a potential increased risk. Concerning offspring exposed to TNFi in utero, multiple studies show small relative increases in risk with a small absolute difference. Knowing whether the risk is differential according to TNFi subtype, and the potential risk of adverse maternal and foetal outcomes associated with switching TNFi subtypes before pregnancy, would be very informative. Moreover, new guidelines conditionally recommend administering the rotavirus vaccine before 6 months of age in offspring exposed to TNFi in utero. This conditional recommendation is based on limited evidence, highlighting the need for more data to support these guidelines.

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BACK CLOSE

9.3 Appendix C – Cinnamon Bread

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Commentary

Cinnamon Bread

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INTRODUCTION

This recipe was originally introduced to me by my late Gramma, to whom I dedicated my doctoral thesis. Born in Manitoba, she learned to cook from her mother, my Baba. Her love for baking was passed down through the generations, from my mother to me. I fondly remember baking with her and learning her recipes. In November 2020, I had the opportunity to teach her cinnamon bread recipe virtually to students and staff in the Department of Epidemiology, Biostatistics and Occupational Health during a baking event. Following the loss of my Gramma during my doctoral studies and through the opportunity to teach this recipe to others in the department, I recognized the importance of including it in my thesis, as it has been a meaningful part of my academic and personal journey.

TOOLS

To conduct this study, the following equipment and materials will be required: one (1) loaf pan, one (1) large mixing bowl, one (1) whisk, one (1) set of measuring cups and spoons, one (1) spoon (ideally wooden) or a spatula for mixing, one (1) tea towel (or something to cover the dough with), one (1) rolling pin, and something to spread the butter on the dough (e.g., spoon, spatula, pastry brush).

INGREDIENTS

To prepare this bread, you will need the following ingredients:

No Knead White Bread (1 loaf)[1]:
- 4 tsp melted margarine (or butter)
  - equivalent to 1 tbsp + 1 tsp
- 1/2 cup hot tap water
- 1/4 cup milk (cold)
- 4 tsp sugar
  - equivalent to 1 tbsp + 1 tsp
- 1/4 beaten egg (beat 1 egg and take 1 tbsp)
- 2 ¼ tsp instant yeast
- 2 cups white flour
- 1/2 tsp salt

Cinnamon Filling:
- 1/8 - 1/4 cup butter (softened)
- 1/8 cup brown sugar
- 1/8 cup white sugar
- 1 tbsp cinnamon

METHODS

The dough was prepared as follows: in a large mixing bowl, hot tap water and milk were combined, ensuring the mixture reached a lukewarm temperature. Sugar and an egg were then added, and yeast was sprinkled over the surface. The mixture was whisked until smooth using a wire whisk.

An initial 3/4 cup of flour was added and mixed until smooth. Subsequently, melted margarine or butter and salt were incorporated, and the mixture was beaten until well combined. The remaining 1 1/4 cups of flour were added, and the mixture was stirred vigorously with a wooden spoon until fully combined. The dough was then worked with hands and kneaded on a floured surface.

The kneaded dough was placed in a greased bowl (coated with olive, vegetable, or any available oil), covered with a tea towel, and allowed to rise for 20-30 minutes or until the dough reached the top of the bowl. Following the rising period, the dough was punched down and rolled out for further use.

The prepared dough was rolled out to an even thickness (Figure 1A). The cinnamon filling was created by brown sugar, white sugar, and cinnamon in a bowl. Softened butter was evenly spread over the surface of the dough (Figure 1B) and the cinnamon filling was sprinkled over (Figure 1C). The dough was rolled tightly into a tube and transferred to a well-greased loaf pan.

The loaf was allowed to rise until it doubled in size. Baking was conducted at 350°F (175°C) for 25–30 minutes or until the crust achieved a golden-brown appearance.

EXPECTED RESULTS

It is anticipated that the bread will rise to a soft and fluffy texture with a slightly golden-brown crust. The inside should resemble a spiral due to the rolling of the dough prior to baking (Figure 2, 3).

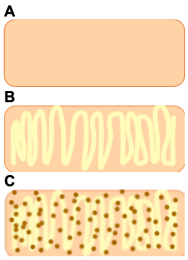

Figure 1. Schematic of the dough and cinnamon filling, illustrating the layering process before rolling into a loaf.

Figure 2. Finished loaf of cinnamon bread with a golden-brown crust and a visible swirl of cinnamon filling.

Figure 3. Closeup of a finished loaf of cinnamon bread.

FUTURE DIRECTIONS

Future research could explore the development of ***dill bread*** as a savoury alternative to cinnamon bread, catering to individuals with a preference for less sweet options. This variation would require the following ingredients: a substantial quantity of fresh dill, one (1) diced yellow onion, a couple of tablespoons of butter, and a dash of salt.

The dill mixture is prepared by combining diced yellow onions, fresh dill, butter, and salt in a frying pan over medium heat. The mixture is cooked until the onions are softened. The bread dough is rolled out, and the prepared dill mixture is evenly spread over the surface (Figure 4). The dough is then rolled into a tube and transferred to a well-greased loaf pan. After allowing the dough to rise until doubled in size, it is baked at 350ºF (175ºC) for 25-30 minutes or until the crust is golden brown (Figure 5).

Figure 4. Dill filling spread evenly over the rolled-out dough before being rolled into a loaf.

LIMITATIONS

A potential limitation of this study is that participants may develop an increased preference for the bread, potentially leading to frequent preparation and consumption. The author assumes no responsibility for any such outcomes or their associated implications.

Figure 5. Finished loaf of dill bread with a golden-brown crust and evenly distributed dill filling.

CONCLUSION

This recipe offers a simple, adaptable approach to homemade bread, with options to suit both sweet and savoury tastes. I hope that sharing my Gramma's bread recipe allows others to enjoy baking it as much as my family has over the years.

ACKNOWLEDGMENT

The author wishes to thank her family and friends for always enjoying the bread!

Conflict of interest: None declared.

REFERENCE

1. This recipe was originally from a cookbook, potentially the Fermipan recipe book. However, after being passed down by generations, the original recipe source has been lost and all that remains is recipe cards. As a result, this is a variation of the original No Knead White Bread that makes 4 loaves.