Inflammatory bowel disease and pregnancy: patient education, assessment of disease activity and monitoring of drug therapies

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Abstract

Inflammatory bowel disease (IBD) is a chronic relapsing inflammatory condition of the gastrointestinal tract. The disease commonly impacts women during their reproductive years. IBD, particularly when active during pregnancy, is associated with worse maternofoetal outcomes. Pregnancy-related knowledge remains poor in many patients, with concerns regarding drug safety and a lack of understanding of the negative ramifications of active disease in pregnancy.

Safe and effective monitoring of disease activity and drug therapies to control IBD throughout pregnancy are imperative. However, the utility and means of objective disease activity monitoring in pregnancy are unknown. The effect of pregnancy on the pharmacokinetics of immunosuppressant and biologic drugs in pregnancy remains undefined.

This thesis presents a range of clinical research work as part of the prospective *Pregnancy in Crohn's and Colitis: Observations, Levels and Outcomes* (PICCOLO) study. This study aimed to improve the pregnancy-related education and care of women with IBD; characterise the utility of objective disease activity monitoring including gastrointestinal ultrasonography in pregnancy; and examine the pharmacokinetics of thiopurine and biologic medications during pregnancy as well as infant outcomes following *in utero* medication exposure.

I have explored the lived experience of IBD and pregnancy from the patient's perspective using qualitative in-depth interviews. This research unearthed rich data relating to unique maternal fears and uncertainties around IBD medications and enduring a chronic illness throughout the pregnancy journey.

I have demonstrated that a single individualised patient education intervention improves pregnancy-related knowledge among women with IBD. This novel intervention included a simple, accessible educational consultation for women with IBD who were pregnant or wishing to conceive. Pregnancy knowledge and quality of life scores were enhanced following the intervention and patient satisfaction levels were very high.

This work has defined the role of gastrointestinal ultrasonography as a feasible and accurate modality for monitoring IBD in pregnancy. Adequate intestinal views were obtained in most patients to the end of the second trimester. Gastrointestinal ultrasound delivered a high specificity and sensitivity when compared with matched faecal calprotectin concentrations as an objective marker of disease activity.

The research has contributed substantially to the understanding of the pharmacokinetics of thiopurines and biologic medications including infliximab, adalimumab and vedolizumab during pregnancy.

Thiopurine metabolite concentrations were studied longitudinally in patients with IBD across pregnancy and in exposed neonates. Significant shunting of maternal thiopurine metabolites can occur during pregnancy. This work has established that complete clearance of thiopurine metabolites occurs in exposed infants by six weeks of age. Unlike a previous study, this work has shown that there is no association with neonatal anaemia following antenatal exposure to thiopurines. However, I identified the novel findings of thrombocytosis and abnormal liver function tests in exposed infants from six weeks of age, which gradually improved; possible mechanisms behind these infant haematological and biochemical findings are uncertain.

Maternal drug levels of infliximab, adalimumab and vedolizumab in pregnancy were also prospectively assessed. This work has demonstrated that adalimumab levels remain stable and infliximab levels display a small increase in pregnancy. This study has described the first data regarding vedolizumab levels in pregnancy and clearance time in infants exposed to vedolizumab *in utero*. I have identified that maternal vedolizumab levels may show a small decrease in pregnancy, while infant vedolizumab cord blood levels are lower than maternal levels. All infants had undetectable vedolizumab levels by sixteen weeks of age.

I have also presented preliminary data regarding another newer biologic agent, ustekinumab, including maternal levels in pregnancy and placental transfer. Infant cord blood levels of ustekinumab were found to be higher than maternal levels in the small cohort to date.

This series of studies has the potential to change the paradigm of pregnancy-related education, objective disease activity monitoring and optimal use of IBD therapies for pregnant women with IBD globally.

Declaration

This is to certify that this thesis:

i) contains no material that has been accepted for the award of any other degree or diploma in any university or other institution;
ii) comprises only my original work except where indicated in the Preface;
iii) includes due acknowledgement in the text to all other material used; and
iv) is fewer than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices

Emma Kate Flanagan, August 2020

Preface

The *Pregnancy in Crohn's and Colitis: Observations, Levels and Outcomes* (PICCOLO) study was designed and conducted as part of this thesis. This work was carried out under the primary supervision of Associate Professor Sally Bell. This thesis was co-supervised by Professor Alexander Thompson and Dr Emily Wright.

Alyson Ross assisted with data collection, monitoring, study co-ordination and management of the clinical research database.

Others have contributed to the work presented in this thesis as outlined below:

Dr Jacqui Richmond provided supervision and guidance for the qualitative study presented in Chapter 3 and taught me the technique of thematic analysis.

Katerina Kiburg assisted with the statistical analysis and graphical representation undertaken in Chapters 4, 5, 6 and 7.

Associate Professor Jakob Begun and Dr Robert Bryant contributed to the data regarding gastrointestinal ultrasonography in pregnancy for the study included in Chapter 5 of this thesis.

Professor Winita Hardikar provided paediatric expertise for the infant outcomes aspect of the work presented in Chapter 4 in relation to antenatal thiopurine exposure.

Professor Peter Gibson provided expert advice regarding the biologic drug monitoring work included in Chapter 7 of this thesis. The analysis of maternal and infant drug levels was performed through the Monash University Laboratory at Alfred Health.

Recruitment of patients to the PICCOLO study was facilitated with assistance from the IBD Melbourne research group and the Australia and New Zealand IBD Consortium. Writing of this thesis including the research articles was my original work, with feedback and guidance from my supervisors and the collaborating co-authors listed in the submitted publications.

The five major studies in this thesis are presented in article format. The papers in Chapters, 3, 4, 5, 6 and 7.1 have been accepted for publication in peer-reviewed journals. Chapter 7.2 contains unpublished material not submitted for publication.

These studies were funded by a research grant awarded from The Gutsy Group as well as support from the St Vincent's Hospital Research Endowment Fund. I received an Australian Government Postgraduate Research scholarship. Administrative support was provided through the Department of Gastroenterology, St Vincent's Hospital Melbourne.

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I would like to acknowledge the funding support for the PICCOLO study from the Gutsy Group and the St Vincent's Hospital Research Endowment Fund as well the Australian Government Postgraduate Research Scholarship I received.

Thank you to the extended PICCOLO study group and the project collaborators who referred patients to the study and provided generous expertise and helpful feedback. I am grateful also to the PICCOLO study patients for giving of their time and energy to participate in this research. I would like to thank my friends, colleagues and fellow PhD candidates for your encouragement and comradery.

I am extremely thankful for the love and support of my family including my parents, siblings, grandparents, mother and father-in-law and extended family. Thank you to my sister Stephanie for her assistance in the proofreading of this thesis. To Mum and Dad, thank you for your unwavering commitment to my studies. In particular, heartfelt thanks

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Finally, to my husband Steve, I am immensely grateful for all your love, understanding and remarkable optimism. You have made the completion of this thesis possible and I cannot thank you enough. To our son Harry, thank you for your laughter and curiosity. I have learnt so much already from being your mother.

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Flanagan E, Wright EK, Hardikar W, Sparrow MP, Connell WR, Kamm MA, De Cruz P, Brown SJ, Thompson AJ, Greenway A, Westley I, Barclay M, Ross AL, Kiburg KV, Bell SJ. Maternal Thiopurine Metabolism During Pregnancy in Inflammatory Bowel Disease and Clearance of Thiopurine Metabolites and Outcomes in Exposed Neonates. Aliment Pharmacol Ther 2021. DOI: 10.1111/apt.16294

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Flanagan E, Richmond J, Bell SJ. Exploring the pregnancy-related concerns of women with inflammatory bowel disease. J Gastroenterol Hepatol. 2018;33.

Australian Gastroenterology Week (AGW) 2018 Oral presentation
Flanagan E, Gibson PR, Begun J, Ghaly S, Garg M, Rosella O, Rosella G, Bell SJ. Vedolizumab drug levels during pregnancy and in neonates following intrauterine exposure. J Gastroenterol Hepatol. 2018;33.

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Flanagan E, Ross AL, Hamilton AL, Bell SJ. Thiopurine Metabolite Levels in Pregnant IBD Patients and Infants Following Intrauterine Exposure. J Crohn's Colitis. 2019;13 (Suppl. 1).

European Crohn's and Colitis Congress (ECCO) 2019
Flanagan E, Gibson PR, Ross A, Rosella O, Bell SJ. Stability of serum concentrations of infliximab and adalimumab across pregnancy in IBD. J Crohn's Colitis. 2019;13 (Suppl. 1).

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Flanagan E, Ross AL, Hamilton AL, Bell SJ. Thiopurine Metabolite Levels in Pregnant IBD Patients and Infants Following Intrauterine Exposure. Gastroenterology. 2019;156(6).

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Bell SJ, **Flanagan E**. Updates in the management of inflammatory bowel disease during pregnancy. Medical Journal of Australia. 2019;210(6):276-80. (Appendix V).

Pregnancy, Fertility and Inflammatory Bowel Disease - Gastroenterologist Fact Sheet, Gastroenterological Society of Australia, 2018. (Appendix VI).
https://www.gesa.org.au/public/13/files/Professional/IBD_Pregnancy_Fertility_Gastroenterologist_Factsheet.pdf

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List of Third-party Copyright Material Included in this Thesis

Citation information for Third-party copyright material	Location of item in thesis	Permission granted
Abraham C, Cho JH. Mechanisms of disease. N Engl J Med. 2009;361:2066-78 [33]	Figure 1.1 Page 12	Y, *Copyright Massachusetts Medical Society*
Abraham C, Cho JH. Mechanisms of disease. N Engl J Med. 2009;361:2066-78 [33]	Figure 1.2 Page 38	Y, *Copyright Massachusetts Medical Society*
Gonzalez-Lama Y and Gisbert J, Monitoring thiopurine metabolites in inflammatory bowel disease, Frontline Gastroenterology 2016;7(4):301-7 [237]	Figure 1.4 Page 50	Y, Rightslink *Copyright BMJ Publishing Group Ltd*

1 Introduction, Background and Research Design

1.1 General introduction

Inflammatory bowel disease (IBD) is a chronic, debilitating inflammatory condition of the gastrointestinal tract. IBD incidence is increasing around the world and the peak onset occurs between 15 and 30 years of age, impacting the reproductive years[1-3].

While the precise aetiology of IBD is unknown, it is widely considered that dynamic interactions between the intestinal and systemic immune systems and the gut microbiota contribute to the development of IBD[4]. Pregnancy induces complex changes to both the maternal immune system and the gut microbiota and may thus influence the course of IBD. There is a bidirectional interplay between IBD and pregnancy, in that IBD may also impact pregnancy; IBD itself can be associated with worse maternofoetal outcomes[5].

Historically, pregnancy was considered a state of immune suppression in order to tolerate the foetus, and hence was thought to ameliorate inflammatory diseases such as IBD. However, more recent understanding suggests that pregnancy entails a unique modulation rather than suppression of the immune system[6]. It is understood that a healthy pregnancy requires adaptations of the maternal immune system during the various stage of pregnancy, and this includes pro-inflammatory processes[7].

Likewise, it is now recognised that IBD can flare during pregnancy, increasing the risk for adverse pregnancy events. Active disease around the time of conception has been associated with an increased likelihood of persistent or recurrent active disease in pregnancy[8, 9]. IBD, particularly when active during pregnancy, increases the risk of events such as pre-term birth and low birthweight babies[5], which can be associated with long-term infant health complications.

Therapies in IBD have largely focused on targeting the exaggerated inflammatory and immune responses associated with the disease. Therefore, treatments have predominantly relied upon immunosuppressant and biologic drugs, the use of which has increased over time, including throughout pregnancy[10-12]. Patients, however, are often concerned about the safety of these medications in pregnancy. Previous studies have shown pregnancy-related knowledge is poor in a significant percentage of

patients, with concerns regarding drug safety and a lack of understanding of the impact of active disease[13, 14]. Medication safety concerns are associated with poor compliance and hence increased potential for disease flares during pregnancy. The influence of these concerns on maternal mental health has not been studied.

Recently there has been considerable interest in monitoring IBD activity more objectively and 'treating to target', with therapeutic endpoints beyond the control of symptoms to improve patient outcomes[15]. These targets include biochemical and endoscopic remission, therapeutic drug levels, as well as the emerging target of quality of life. Evaluation of treatment outcomes often requires repeated assessment, and therefore non-invasive means of monitoring such as faecal calprotectin, intestinal ultrasound and optimising drug therapies through measurement of drug levels have become important tools. However, the effect of pregnancy on these tools and practices is unclear.

This literature review will outline IBD pathogenesis, assessment, disease course and management and will further explore these issues in relation to pregnancy. This aims to provide sufficient background and context to understand the impact of pregnancy in the setting of this lifelong inflammatory condition. Subsequently, this first chapter presents a more specific literature review of the major topics of this thesis, including (1) Exploration of Pregnancy-Related Concerns Amongst Women with IBD, (2) Education of Women with IBD in Relation to Pregnancy, (3) Assessment of Disease Activity in Pregnancy, (4) Thiopurine Metabolites in Pregnancy and in Exposed Neonates, and (5) Therapeutic Drug Monitoring of Biologic Agents in Pregnancy, concluding with an outline of the research involved in this thesis.

Studies in the literature regarding IBD and pregnancy are commonly retrospective or relatively small, and much detail in the field remains only partially discovered and understood. This makes for fascinating research potential.

1.2 Introduction to IBD

There are two major forms of IBD, namely ulcerative colitis (UC) and Crohn's disease. However, a small proportion of patients, up to 10-15%, cannot be clearly assigned to either and are diagnosed as IBD-unclassified[16,17]. While IBD predominantly affects the gut, extra-intestinal manifestations can also occur in up to 50% of patients[16,18]. These may include arthropathies, cutaneous and ophthalmic manifestations as well as

primary sclerosing cholangitis[18]. There is a diverse spectrum of disease severity, ranging from patients with limited disease and mild symptoms to those requiring surgery.

Clinical, radiologic, endoscopic, and histologic criteria are utilised in the diagnosis of IBD[16]. UC and Crohn's disease have distinct as well as overlapping diagnostic features. UC is characterised by uniform, continuous inflammation extending proximally from the rectum to involve part or all of the colon[19]. In UC, inflammation is confined to the superficial layers of the colon including the mucosa and sub-mucosa. Population studies have shown that at the time of diagnosis disease extent in UC is relatively evenly distributed. Approximately 20-30% of patients have limited proctitis, while around 30-50% have left-sided colitis and up to 20-40% present with pan-colitis, which extends beyond the left colon[20-22].

Conversely, Crohn's disease is characterised by chronic inflammation that can affect any site in the gastrointestinal tract from the mouth to the anus. It involves segmental inflammation known as 'skip lesions' and in these affected areas inflammation may be trans-mural in nature[19]. Crohn's disease is most commonly located in the terminal ileum[23]. At presentation, approximately 40-45% of patients have disease affecting both the terminal ileum and the colon, while approximately 20-30% have terminal ileitis and 25-40% have only colonic disease [20, 21]. Traditionally diagnosed infrequently, recent data have found up to around 20% of patients can have upper gastrointestinal involvement such as the mouth, oesophagus, stomach or proximal small bowel[24, 25].

Due to the transmural nature of the intestinal inflammation, patients with Crohn's disease can develop complications of stenosis and penetrating disease, which includes abscesses and fistulae. Moreover, patients with both UC and colonic Crohn's disease have an increased risk of developing colorectal cancer in the setting of longstanding disease.

1.2.1 Aetiology and Pathogenesis of IBD

1.2.1.1 Introduction

Despite a myriad of scientific and epidemiological studies in the literature, the aetiology of IBD remains elusive. It is a multi-factorial disorder and there is thought to be a dysregulated immune response to the intestinal microbiota, in the setting of environmental factors as well as genetic susceptibility[4]. The highest incidence and

prevalence of IBD are in Western countries, however the incidence is increasing in newly industrialised countries including in the Asia Pacific region[20, 26, 27]. Epidemiological studies therefore suggest a significant role for environmental factors in the increasing burden of disease, including diet and an urbanised environment, which influence the gut microbiota[28-30].

1.2.1.2 Immune dysregulation in IBD

The intestinal immune system contains various barriers, which prevent microorganisms from accessing the systemic circulation and help maintain intestinal homeostasis (Figure 1.1) [31-33]. These barriers include the mucus layer, the intestinal epithelial cells and the intestinal immune cells. Defects or dysfunction in these barriers and responses have been implicated in the pathogenesis of Crohn's disease and UC[31, 34, 35].

The systemic immune system of the human body is an intricate, multi-layered defence mechanism towards pathogenic organisms. It features a wealth of different cell types, which are typically divided into innate and adaptive immune responses[36]. The innate immune system serves as the first line of host defence, incorporating cells that are present in body tissues and act rapidly as guards[7]. Functions of innate immunity include non-specific phagocytosis and presentation of pathogens on the surface of dendritic cells and macrophages in order to activate cells of the adaptive immune system. Meanwhile, the adaptive immune system, which forms the second line of defence, is extremely specific and is able to form immunological memory[33]. Upon activation of their specialised antigen receptors, T and B cells undergo clonal amplification as part of adaptive immunity.

An important subset of the immune cells that are involved in the pathogenesis of IBD include the adaptive immune system T helper cells; Th1, Th2, and Th17, and regulatory T cells, which each produce different cytokines and provide different functions[7]. Simplistically, IBD has been described as an imbalance between pro-inflammatory T cells and regulatory T cells. Crohn's disease is traditionally considered a Th1/Th17 dominant disease and UC a Th2/Th17 driven disease due to the distinct cytokine expression patterns observed[7, 37]. Th17 cells are largely responsible for interleukin-17 (IL-17) production, which is an important pro-inflammatory cytokine that is increased in IBD[38]. Tumour-necrosis-factor alpha (TNF-alpha) is produced by Th1 cells amongst other cells, and is involved in a number of in pro-inflammatory pathways that have been demonstrated to play an important role in the pathogenesis of IBD[38].

Interleukin-12 (IL-12) and Interleukin-23 (IL-23) cytokines are involved in the proliferation of Th1 and Th17 cells and are also upregulated in IBD[4, 39].

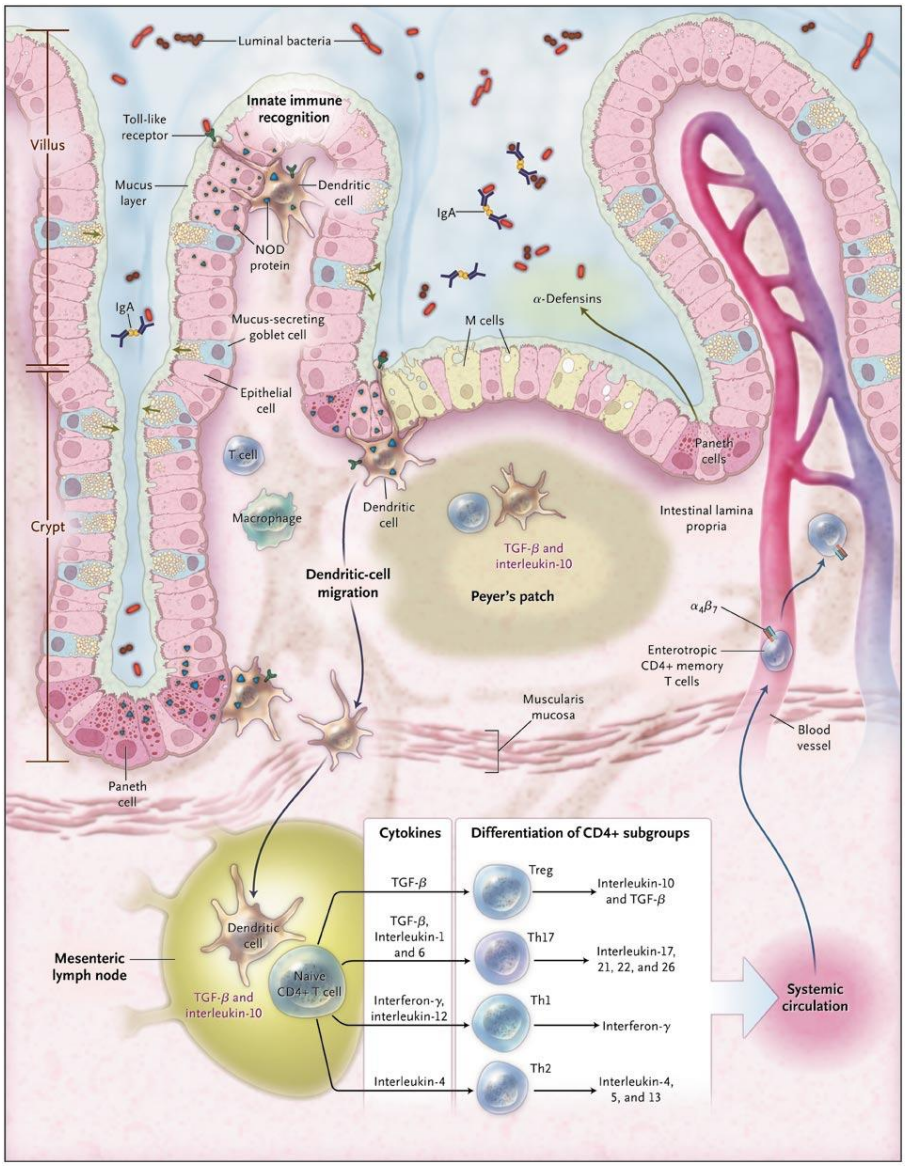

Figure 1.1: The Intestinal Immune System

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1.2.1.3 Genetic factors

Genetic mutations in IBD can cause dysfunction in the intestinal immune system responses. Multiple genetic susceptibility loci have been identified in genome wide association studies. The first and most studied of these is the nucleotide-binding oligomerization domain 2(NOD2)/caspase activation recruitment domain 15 (CARD15) gene on chromosome 16, identified as a risk factor for Crohn's disease[40, 41]. NOD2 is an intracellular protein expressed in intestinal epithelial cells and in particular in Paneth

cells at the base of intestinal crypts[42]. Pro-inflammatory cytokines such as TNF-alpha upregulate CARD15/NOD2 gene expression[43]. NOD2/CARD15 is involved in sensing muramyl dipeptide (MDP), which is a key component of bacterial cell walls[44]. Inherited mutations in NOD2 cause defects in MDP sensing, and hence an impaired immune response to bacteria resulting in uncontrolled intestinal inflammation[40, 42, 44]. Cleynen et al recently showed that the NOD2 mutation was associated with a younger age at diagnosis and ileal disease location, both risk factors for surgery in patients with Crohn's disease[45].

Various other mutations associated with IBD have since been identified, for example featuring Nod-like receptors (NLRs) and Toll-like receptors (TLRs) in the mucosal innate immune system[40], as well involving adaptive immune responses including the IL-23 and Th17 cell pathway[4]. However, the currently identified susceptibility genes only account for around 20% of the genetic contribution to disease risk[46] and the number of known gene mutations exceeds the clinical prevalence of the disease. This highlights the significance of microbial and environmental factors in triggering the onset of IBD and disease progression.

In population-based studies, it has been observed that the genetic risk for IBD is greater in Crohn's disease than UC and is higher when multiple family members are affected[47]. In a recent large Danish population study, with maternal Crohn's disease the incidence rate ratio for Crohn's disease in the offspring was 6.4 and the absolute risk was 2.7%[48, 49]. For maternal UC, the incidence rate ratio was 3.7 for UC in the offspring and the absolute risk was 1.6%[48, 49]. When both parents have the disease, the risk of an offspring developing IBD increases to around 30%[50-52]. Interestingly, the phenotype of IBD inherited may vary[53], and in monozygotic twin studies, there was concordance in 20–56% of Crohn's disease and 6–19% of UC cases[47], indicating genetic profile is not the only determinant of disease.

1.2.1.4 The Gastrointestinal Microbiota

Along with individual genetic susceptibility, the intestinal microbiota is considered fundamental to the development of IBD. The microbiota in the gut exhibits a low diversity at birth and develops into a highly complex and individually distinct microbial profile by around 12 months of age[54-56]. The first three years of life are the most critical for the establishment of the intestinal microbiota[55]. Multiple factors have been shown to alter the microbiota, including mode of delivery, pre-term birth, age, diet including

breastmilk, medications including antibiotics, smoking, genetics and geographic location[30, 54, 55, 57, 58].

Gut dysbiosis has been shown to be associated with IBD. Studies have demonstrated an increase in the relative abundance of certain bacteria such as Enterobacteriaceae in association with IBD[59]. Additionally, it has been found that the diversity of the microbiota is reduced in patients with IBD. Data have shown a decrease in normal anaerobic bacteria such as Bacteroides species in patients with IBD[60]. In this context, it has been recognised that the gut microbiota can modulate the mucosal immune response [54]. For example, Bacteroides species may induce the expansion of regulatory T cells to moderate intestinal inflammation[61].

The gut microbiota also has the capacity to ferment dietary fibre, which results in the production of short-chain fatty acids (SCFAs)[54]. SCFAs are the primary energy source for colonic epithelial cells[62] and can also induce the expansion of colonic regulatory T cells[61]. A diet low in fibre has been associated with a low concentration of SCFAs as well as with the development of IBD[63].

Diet is one of the most important factors influencing the gut microbiota[64]. The Western diet has been associated with reduced diversity of gut microbiota and predisposition to IBD[54]. A recent systemic review has shown there is also an association between an increased risk of IBD with increased consumption of meat and fats, typically consumed as part of a Western diet[65].

1.2.1.5 Conclusion

The precise aetiology of IBD remains unknown. Family history is a significant risk factor for the development of IBD. However, epidemiological evidence suggests that lifestyle and environmental factors are key contributors to the increasing incidence of the disease. These insights are important in the setting of pregnancy, when factors such as breastfeeding and avoidance of antibiotics where possible can be promoted in order to optimise the microbiota and intestinal immune system of mother and infant. The effects of pregnancy on the immune system and gut microbiota will be discussed in Sections 1.2.7.2-3.

1.2.2 Overview of Disease course in IBD

1.2.2.1 Introduction

It is important to note that IBD is a lifelong, disabling condition that is associated with relapsing and at times continuous symptoms. It is a dynamic disease and its phenotype can change over time. IBD brings significant morbidity, including the potential for hospitalisation and surgery and risk of cancer. More recent therapeutic strategies have aimed to minimise these disease complications and improve the overall disease course.

1.2.2.2 Progression of Disease Phenotype in IBD

In UC, the disease location can both regress as well as extend more proximally. Most studies evaluating the natural history of UC have focused on disease progression and the data are scarce in relation to regression of disease[66]. A study of the Swiss IBD Cohort has shown that 16% of patients with UC experienced disease regression over a median nine-year follow up, but no known factors associated with disease regression have been identified[66]. A recent meta-analysis demonstrated that in approximately a quarter of patients with proctitis and/or left sided disease, within ten years the disease extent can progress to pan-colitis, which is associated with higher rates of colectomy and colorectal cancer[67]. Identified risk factors for disease progression included younger age at diagnosis (under 18 years), and other studies have also reported higher rates of disease extension in paediatric populations[67].

Change in the disease phenotype is significant in the natural history of Crohn's disease. The location of disease remains the same in the majority of patients, with only around 15% developing extension of their disease location[68]. However, the behaviour of disease can progress from an inflammatory phenotype to more complex stricturing and penetrating disease forms, which are less likely to respond to medical therapy and are in turn associated with increased need for hospitalisation and surgery[69]. Phenotype progression is more frequent in patients with small bowel disease[10, 70].

In a well-known population-based study from the Olmsted County assessing disease behaviour in patients diagnosed with Crohn's disease between 1970 and 2004, 5% had stricturing disease and 14% penetrating disease at diagnosis [71]. In this study, from the pre-biologic era, the cumulative risk of progressing to stricturing or penetrating disease was 33% at 5 years, 39% at 10 years and 50% at 20 years [71]. However, more recent data from the large 'Epi-IBD' European multicentre population-based inception cohort has shown that 14% of patients diagnosed with non-stricturing, non-penetrating

Crohn's disease in 2010 progressed to either stricturing and/or penetrating disease at five years[72]. Other recent population-based studies in the biologic era have also found that approximately 20% of patients experience progression of their disease behaviour within five to seven years of diagnosis[10, 69].

About 25% of patients with Crohn's disease develop perianal or rectovaginal fistulas [73, 74]. Perianal fistulising disease is seen frequently in the setting of colonic Crohn's disease that involves the rectum [74]. Fistulising perianal Crohn's disease is particularly difficult to treat and leads to need for recurrent surgery and significantly impaired quality of life.

1.2.2.3 Hospitalisation in IBD

Management of IBD largely takes place in the outpatient setting, however hospitalisation is still required in severe disease. The annual likelihood of requiring hospital admission for Crohn's disease is highest in the first year after diagnosis and is around 20% in recent population studies, with the rate of hospitalisation tending to decline thereafter [72]. In population-based cohorts of UC patients, approximately 20% of patients will require admission within the first five years [75]. Approximately 20-25% of patients with UC with require hospitalisation during their lifetime for acute severe UC, which is a medical emergency and carries a mortality risk of around 1% [76].

1.2.2.4 Surgery in IBD

Older population-based studies reported an estimated rate of surgery for patients with Crohn's disease of 50% within ten years, with around 50% of these patients having post-operative disease recurrence at ten years[77]. A recent systematic review and meta-analysis including 30 population-based studies has shown the pooled risk of surgery in Crohn's disease diagnosed after 1990 was 14.3% (95% confidence interval [CI], 11.0%–18.6%) after one year and 38.7% (95% CI, 31.0%–48.3%) at ten years[78]. In UC, the risk of surgery was 4.1% (95% CI, 2.9%–5.7%) at one year and 13.7% (9.3%–20.3%) after ten years[78], with the main indication for colectomy in UC being severe or refractory disease, while at ten years after the diagnosis colectomy is increasingly performed for dysplasia or colorectal cancer[78].

1.2.2.5 Colorectal cancer in IBD

Patients with UC and colonic Crohn's disease are known to have an increased risk of developing colorectal cancer. There have been many population-based and referral

centre studies aiming to quantify this risk, however, there has been heterogeneity in design and study population, for example including varying disease duration and extent, resulting in varying estimates of cancer risk[79].

The incidence of colorectal cancer in IBD appears to be decreasing in recent decades, attributed to improved strategies for controlling inflammation and colonoscopic surveillance technologies. However, several recent studies including a meta-analysis have shown the risk remains almost two-times greater than the background population[80]. The meta-analysis, which corrected for isolated small bowel Crohn's disease, showed the pooled standardised incidence ratio of colorectal cancer in patients with IBD was 1.7 (95% CI, 1.2–2.2) in population studies[80]. This analysis calculated a cumulative risk of colorectal cancer of approximately 1%, 2%, and 5% after 10, 20, and >20 years of disease duration, respectively[80]. Consistent with previous literature, this study reported a higher risk of colorectal cancer in those with extensive colonic disease and longer disease duration.

1.2.2.6 Conclusion

Despite more aggressive and potent treatment options and strategies, there remains a significant, incurable burden of disease and potential for significant impact on a patient's life. The influence of pregnancy on the disease course will be discussed in a subsequent Section 1.2.7.4.

1.2.3 Clinical Manifestations of IBD

The patient experience of the disease is often dictated by the clinical symptoms suffered. Clinical manifestations of active luminal IBD can vary but often correlate with the anatomical region of bowel affected and the phenotype of disease present. Typical symptoms of colonic inflammation include increased bowel frequency with diarrhoea, rectal bleeding, urgency to evacuate the bowels and crampy abdominal pain[16, 81]. In more extensive or severe disease, patients can have more systemic symptoms such as fever and weight loss or, rarely, may present with severe abdominal pain and distention associated with acute colonic dilatation (toxic megacolon) in acute severe UC, with the concomitant risk of spontaneous colonic perforation and peritonitis.

In contrast, small bowel inflammation can present with signs of impaired absorption and even intestinal obstruction, including post-prandial abdominal pain and distension, nausea and vomiting, weight loss and nutritional deficiencies[16, 81]. Chronic inflammation in any affected segment that has progressed to stricturing disease causes intestinal

obstructive symptoms; this is most commonly linked to Crohn's disease involving the terminal ileum. Furthermore, with the development of penetrating Crohn's disease complications, patients may present with severe localised pain and tenderness, fevers and sepsis related to abscess formation. Fistulising disease can also result in symptoms related to the location of the fistula, for example passage of air or faecal matter from the vagina in cases of enterovaginal fistula or drainage from the skin with enterocutaneous fistulae.

1.2.4 Disease Classification and Disease Activity Assessment Tools

In an attempt to quantify and describe the broad variation in disease distribution and progression, various IBD disease classification systems have been developed over the years. The Montreal disease classification was established by a Working Party of investigators in 2003 as an update to the previous Vienna classification[82]. It is now widely used to classify the current phenotype and hence severity and potential prognosis of a patient's IBD. The Montreal classification for patients with Crohn's disease includes the age at diagnosis, the disease location (ileal, ileocolonic, colonic or isolated upper gastrointestinal disease) and the behaviour of the inflammation present (inflammatory, stricturing or penetrating), as well as the presence of fistulising perianal disease[82]. Perianal fistulae are not always associated with an internal penetrating Crohn's disease phenotype, which is reflected in the separate disease modifier for perianal fistulising disease. For patients with UC, it classifies patients based on disease extent from limited proctitis, to left-sided distal disease or extensive pan-colitis[82].

Similarly, in order to quantify and compare the various clinical presentations of IBD between time-points and patients, standardised disease activity indices have been developed predominantly for use in research trials. The use of purely clinical scores in routine practice is limited by poor correlation between these scores and objective markers of inflammation such as endoscopic findings. While none of the scores have been validated in a pregnant IBD population, clinical disease activity indices provide a basis for systematic evaluation and comparison of symptoms.

For Crohn's disease patients, the Harvey Bradshaw Index (HBI) is a commonly used clinical assessment tool (Table 1.1). The HBI measures the overall feeling of wellbeing, degree of abdominal pain, number of liquid stools, presence of an abdominal mass as well as extra-intestinal manifestations or complications of disease[83]. HBI scores of four or less are classified as clinical remission[83]. The HBI is shorter and simpler than the standard but more cumbersome Crohn's Disease Activity Index (CDAI), which

incorporates laboratory as well as clinical indices including physical examination findings and a 7-day symptom diary. The CDAI is widely used in clinical trials, with clinical remission defined as a score less than 150[84].The HBI correlates well with the traditional CDAI[85], although both clinical indices correlate poorly with endoscopic bowel inflammation[86, 87]. Given this limitation, along with growing recognition of the importance of patient reported outcomes combined with mucosal healing, it has been proposed that clinical trials include endoscopic endpoints along with purely patient reported outcome measures. A retrospective analysis by Khanna et al found that a combination of two patient reported outcomes for disease activity including stool frequency and abdominal pain (PRO2), showed similar treatment effect estimates to the total CDAI[88], and a composite endpoints approach along with mucosal healing has been recommended[15].

Meanwhile, in UC, the Mayo Clinic score is widely used in clinical trials and is a composite score including clinical features (stool frequency and degree of rectal bleeding), endoscopic findings and Physician Global Assessment[89, 90]. Each of these four categories is scored between 0 and 3, with a total score of 0-12[90]. Remission has been defined as a total Mayo score less than or equal to 2, with no sub score higher than 1. The Partial Mayo score can also be calculated without the endoscopic component and has shown strong correlation to the Total Mayo Score[91]. The Simple Clinical Colitis Activity Index, however, is a purely clinical index (Table 1.2). The SCCAI rates the clinical symptoms of patients with UC, again according to overall wellbeing and presence of extra-intestinal manifestations, in addition to bowel frequency, urgency and amount of rectal bleeding[92]. The SCCAI score has been shown to be a valid, reliable non-invasive instrument with a score of two or less consistent with clinical remission[89, 93]. A recent systematic review showed good correlation between non-invasive disease activity indices and presence of endoscopic activity in patients with UC[94]. This review also reported that normalisation of two key patient reported outcomes, stool frequency and rectal bleeding (PRO2), correlated well with endoscopic remission in UC[94].

Commonly used across both UC as well Crohn's disease is the Physician Global Assessment (PGA), which categorises disease activity as inactive (remission), mild, moderate or severe. The PGA is subjective and there can be inter-observer variation in practitioner assessment[89], however this limitation also exists with clinical and endoscopic scoring systems. The benefits of the Physician Global Assessment are that

it can incorporate all available information and it is reflective of clinical practice generally.

Table 1.1 Harvey Bradshaw Index [83]

Criteria		**Score**
General wellbeing	*Very well* *Slightly below par* *Poor* *Very poor* *Terrible*	0 1 2 3 4
Abdominal pain	*None* *Mild* *Moderate* *Severe*	0 1 2 3
Number of liquid or soft stools per day		
Abdominal mass	*None* *Dubious* *Definite* *Definite and tender*	0 1 2 3 4
Extra colonic manifestations (1 per manifestation)	*None* *Arthralgia* *Uveitis* *Erythema nodosum* *Aphthous ulcers* *Pyoderma gangrenosum* *Anal fissure* *New fistula Abscess*	1 1 1 1 1 1 1 1

Table 1.2 Simple Clinical Colitis Activity Index [92]

Criteria		**Score**
Bowel Frequency/Day	*1-3* *4-6* *7-9* *>9*	0 1 2 3
Bowel Frequency/Night	*0* *1-3* *4-6*	0 1 2
Urgency of defecation	*None* *Hurry* *Immediately* *Incontinence*	0 1 2 3
Blood in stool	*None* *Trace* *Occasionally frank* *Usually frank*	0 1 2 3

General wellbeing	*Very well* *Slightly below par* *Poor* *Very poor* *Terrible*	0 1 2 3 4
Extra colonic manifestations (1 per manifestation)	*Arthritis* *Pyoderma gangrenosum* *Uveitis* *Erythema nodosum*	1 1 1 1 1

1.2.5 Objective Assessment of disease activity

1.2.5.1 Introduction

Given the limitations of clinical disease activity scoring systems, which can be subjective, more attention is now paid to tight disease monitoring using objective assessments of inflammation in IBD. The ideal marker for disease activity should be easy to perform, cheap, non-invasive, reproducible, able to predict the disease course and monitor the effects of treatment[95]. A single marker with these characteristics does not currently exist; therefore, a combination of available modalities is employed to evaluate the disease. Serum and faecal biomarkers of disease activity are used to objectively yet non-invasively assess and monitor disease activity, most commonly in the form of C-reactive protein (CRP) and faecal calprotectin, while gastrointestinal ultrasonography is also being increasingly used in this setting.

1.2.5.2 Common Biomarkers in IBD

Blood test parameters commonly used to help assess inflammation in IBD include haemoglobin, serum albumin and acute phase reactants. The presence of anaemia can reflect the inflammatory load while hypoalbuminemia can relate to severe protein loss or malabsorption[16]. CRP is an acute phase reactant protein that is produced by hepatocytes in response to the release of pro-inflammatory cytokines including interleukin-6 (IL-6) and TNF-alpha[96]. Serum concentrations of CRP are widely used to measure the state of inflammation in the body generally, and although non-specific, are useful to evaluate the presence of inflammation in the setting of IBD.

CRP, as a serologic biomarker of inflammation, may not always be elevated when active IBD is present[97]. It is often elevated with severe or extensive disease, although can be normal in distal colonic disease. An elevated CRP has been shown to correlate with endoscopic disease activity in Crohn's disease as well as in UC[98]. In UC, an elevated CRP can be predictive of colectomy but there is only modest correlation

between CRP and mucosal healing[15]. This limitation with CRP has been reflected in a recent systematic review that has shown a high specificity for detecting endoscopic disease activity in IBD, but poor sensitivity, with a pooled specificity and sensitivity of 0.92 (95% CI 0.72–0.96) and 0.49 (95% CI 0.34–0.64), respectively[99], However, it is a non-invasive, repeatable and inexpensive test and is useful for comparison over time in an individual patient as part of disease activity monitoring.

Calprotectin is an inflammatory protein produced by neutrophils in response to colonic inflammation, and it is therefore more sensitive than CRP [100]. Elevated faecal calprotectin levels have consistently been shown to correlate with endoscopic IBD activity and can be predictive of relapse, while a low faecal calprotectin is reflective of mucosal healing[101].

Several studies have previously assessed the most appropriate faecal calprotectin cut-off to determine disease remission, and there have been varying results, especially among different disease locations in Crohn's disease[102]. For example, faecal calprotectin can be lower in small bowel Crohn's disease, especially in fibrotic disease. Additionally, at higher faecal calprotectin cut-off values, the specificity for active inflammation can become higher but the sensitivity lower.

Older studies include a prospective study by Sipponen et al with 77 patients with Crohn's disease, which demonstrated that a calprotectin cut-off of 200 μg/g had a sensitivity of 70% and a specificity 92% for active endoscopic disease[103]. In another prospective study including 87 patients with ileal and/or colonic Crohn's disease, D'Haens et al found that calprotectin levels below 250 μg/g predicted endoscopic remission with a sensitivity of 94% and specificity of 62%[101]. The same study found that in patients with UC (n=39), a calprotectin cut-off level of 250 μg/g provided a sensitivity of 71% and a specificity of 100% for active endoscopic activity.

Meanwhile, prospective data from the Post-Operative Crohn's Endoscopic Recurrence (POCER) study, published by Wright et al, found that faecal calprotectin levels below 100 μg/g predicted endoscopic remission in post-operative ileal Crohn's disease with a sensitivity of 90% and specificity of 57%[104]. In this study, CRP and CDAI did not correlate with endoscopic disease.

There have been multiple other studies in the literature supporting the use of faecal calprotectin as a non-invasive faecal marker to monitor intestinal inflammation in patients with colonic or ileocolonic IBD; although the optimal concentration to define remission remains yet to be precisely defined.

Thus, both CRP and faecal calprotectin are helpful adjunctive measures of inflammation for monitoring of disease activity. Further radiologic and/or endoscopic or radiologic evaluation should be considered when there are elevations in these markers[15].

1.2.5.3 Imaging in IBD

Radiologic investigation in the form of computed tomography (CT), magnetic resonance imaging (MRI) and gastrointestinal ultrasonography (GIUS), is also utilised to objectively assess disease activity in IBD. In small bowel Crohn's disease, it is particularly useful for the assessment of disease extent as well as stricturing and penetrating disease complications such as stenosis, extra-luminal fistulae and abscesses.

GIUS, CT and MRI have all been shown to have similar diagnostic accuracy in assessing luminal IBD activity (greater than 80%)[105-107]. MRI or ultrasound, when accessible, are generally preferred over CT due to the lack of ionising radiation exposure with these modalities. Additionally, MRI and GIUS are useful for differentiating active inflammation from fibrostenotic lesions. Pelvic MRI is also an important tool in the assessment of anorectal fistulae and complications in perianal Crohn's disease[16].

Traditionally, imaging has been applied less frequently in the evaluation of UC, given inflammation is not transmural and the disease can be accessed with colonoscopy. However, although uptake of GIUS in many countries and incorporation of GIUS in clinical trials has been slow, there is now growing interest in the use of GIUS for the assessment of both small bowel and colonic inflammation[108, 109].

GIUS has been found to be accurate for the evaluation of small intestinal inflammation, particularly ileal Crohn's disease, as well as for colonic inflammation, although views of the rectum can be limited[108, 110-112]. Much of the literature pertains to the use of GIUS as a diagnostic tool in Crohn's disease. A systematic review and a meta-analysis have reported a sensitivity and specificity for the diagnosis of Crohn's disease between 84%-

88% and 92-97%, respectively[105, 113]. There is less data regarding the role of GIUS in UC, but its sensitivity and specificity in the diagnosis of endoscopically active UC proximal to the rectum has been found to be 89% and 87%, respectively [112].

1.2.5.4 Endoscopy in IBD

Ileocolonoscopy is a mainstay in the diagnosis and assessment of luminal IBD[16]. Endoscopic UC severity is assessed based on the degree of mucosal findings including erythema, friability, vascularity and erosions, with ulceration and spontaneous bleeding signifying severe disease. Endoscopic features of Crohn's disease can include mild inflammation with aphthous ulcers, as well as characteristic longitudinal ulceration, a cobblestone appearance or severe inflammation with deep ulceration. Stricturing disease can be assessed as narrowing at the time of endoscopy and penetrating disease with fistulae can also be visualised endoscopically. In both UC and Crohn's colitis, the presence of deep and extensive ulcers is predictive for colectomy, and in active ileocolonic Crohn's disease severe endoscopic lesions have also been associated with an increased risk for penetrating disease[114, 115].

Meanwhile, endoscopic remission is defined as the resolution of friability and ulceration at flexible sigmoidoscopy or colonoscopy for UC, and resolution of ulceration at ileocolonoscopy in Crohn's disease[15]**.** Recent studies have highlighted the need to aim for healing of endoscopic lesions with the goal of preventing structural bowel damage[116]. Absence of ulceration on endoscopic assessment is now considered an optimal target of treatment[15]. Mucosal healing has been associated with improved rates of sustained remission, fewer hospitalizations, surgeries and colorectal cancer, as well as an improved quality of life[117-120].

1.2.5.5 Histology in IBD

Histological features of UC involve diffuse crypt architectural distortion, crypt abscesses, infiltration of neutrophils within the crypt epithelium and mucin depletion[23,121]. Meanwhile, histological features of Crohn's disease include focal crypt distortion, transmural lymphoid aggregates, granulomas not related to crypt injury and muscular hypertrophy[23].

In UC, persistent histologic inflammation has been associated with an increased risk of clinical relapse, hospitalisation, colectomy, and colorectal cancer[122]. Similarly, in Crohn's disease, histologic inflammation may increase clinical relapse, hospitalisation and resection rates. Hence there has been increased interest in the clinical benefits of

achieving ‘complete’ histologic remission, particularly in UC which involves diffuse mucosal inflammation rather than patchy transmural inflammation[122]. However, while mucosal healing has become an established treatment target in IBD, a validated definition of histologic remission has not been established and the prognostic value of histologic remission over mucosal healing has not been confirmed [122]. Randomised controlled trials are required to determine the utility of histologic remission when clinical and endoscopic reemission have been achieved and whether histologic normalisation should be a treatment target in IBD.

1.2.5.6 Conclusion

While it remains an important goal of therapy to monitor and improve clinical symptoms, inducing remission measured by objective means is associated with improved outcomes. Endoscopy is generally considered the gold standard[123] and endoscopic mucosal healing the overall aim of therapy. However, as an invasive procedure, endoscopy is not without risks to the patient, and hence the use of adjunctive non-invasive measures of IBD activity including faecal calprotectin and intestinal ultrasound are typically preferred for regular disease monitoring where feasible. This was the focus of the third study in this thesis, and the literature relating to disease activity monitoring in pregnancy is discussed in Section 1.5.

1.2.6 The Impact of IBD on Fertility and Pregnancy

1.2.6.1 Introduction

IBD can have a substantial impact on a woman’s life, from the threat of a disease flare to the need for regular medical care and disease activity assessment. Moreover, in relation to reproduction, active IBD and surgery involving the pelvis can impair fertility in women with IBD, in addition to disease-related factors that can render women with IBD less likely to have children and more likely to remain ‘voluntarily childless’.

Notably, IBD can also have a substantial impact on the course of pregnancy and can increase the risk of adverse pregnancy outcomes by around two-fold[5]. However, it can be challenging to isolate potential influences on pregnancy outcomes, such as the presence of IBD itself, the use of IBD medications and the impact of disease flares in pregnancy, including the effect of active disease on the mother and the role of inflammatory cytokines[124].

1.2.6.2 The Impact of IBD on Fertility

Voluntary infertility exists amongst women with IBD, with patients opting to remain childless in the setting of disease and medication-related fears and concerns. However, fertility itself is not affected in patients with inactive IBD, except for women who have had pelvic surgery[125-127].

The concept of 'voluntary childlessness' has been coined to describe women with IBD who choose not to have children due to concerns relating to their chronic illness. A systematic review and meta-analysis found that while the involuntary infertility rate was similar to the general population, women with IBD were more likely to remain voluntarily childless[127]. Studies have reported voluntary childlessness rates of up to 18% in women with IBD, compared to 6.2% in the general population in the United States[128,129]. Reasons for this include patient concerns regarding medication safety and potential teratogenicity, disease burden and passing on IBD to offspring[128,130,131].

Active Crohn's disease but not UC has been associated with marginally lower fertility rates[132]. This is likely multifactorial and related to mechanisms including ovarian follicle dysfunction and pelvic adhesions in the setting of Crohn's disease inflammation and/or prior surgery. IBD medications, however, have not been linked to infertility[49]. Interestingly, some IBD medications including prednisolone and adalimumab have been used in fertility treatment in order to dampen exaggerated immune responses that may hamper implantation[133]. This is in keeping with the understanding that treating active inflammation improves fertility.

Surgical procedures involving pelvic dissection and open ileal pouch anal anastomosis formation are performed in close proximity to the pelvic reproductive organs. It has been found that open ileal pouch anal anastomosis surgery is associated with a three-fold increased rate of infertility[134]. A meta-analysis included six studies that provided data on infertility both pre- and post-ileal anal pouch anastomosis surgery, demonstrating infertility rates of 20% prior to pouch surgery and 63% post-operatively[135]. This is thought to be related to pelvic adhesions and scarring causing reduced fallopian tube motility and patency. However, newer laparoscopic pouch surgery is associated with lower rates of infertility in more recent data from retrospective studies[136,137].

The success rate of in vitro fertilisation has been found to be comparable in women with a history of pouch surgery to women without a history of IBD and surgery[138].

Indeed, the chance of a live birth with assisted reproductive technology treatment does not appear to be reduced following surgery in women with UC[139]. However, in Crohn's disease, the chance of a live birth for each embryo transfer is reduced following surgery for Crohn's[139]. This may be due to residual or recurrent inflammation in the post-operative setting with Crohn's disease, whereas surgery for UC removes all inflammation present that may affect pregnancy[139].

1.2.6.3 The Impact of IBD on Pregnancy Outcomes

Adverse pregnancy outcomes in the general population

It is important to frame any discussion of the impact of a disease or its treatments on pregnancy outcomes by first understanding the rates and causes of adverse pregnancy outcomes in the general population. Maternal outcomes include pregnancy complications such as spontaneous abortion and pre-term delivery, while foetal effects include outcomes such as intrauterine growth restriction (small for gestational age and low birth weight), prematurity and congenital anomalies.

In the general population, miscarriage, or spontaneous abortion before 20 weeks gestation, is the most common adverse pregnancy outcome[140]. Miscarriage data is difficult to capture and there are differing rates of miscarriage reported throughout the literature. The recognised miscarriage rate from a survey of Australian women was 25% of live births [140]. Around 8.7% of babies in Australia are born pre-term (before 37 weeks gestation) while approximately 6.7% have a low birthweight (less than 2500g)[141]. Pre-term birth is the leading cause of neonatal death and birthweight is also a key predictor of infant survival as well as health outcomes later in life[140, 141].

Meanwhile, Australian epidemiological data has shown at least one congenital anomaly to be present in around 3.1% of births[142,143]. Congenital anomalies are rare conditions, which often result in long-term morbidity or death and are a major cause of neonatal and infant mortality[142]. The most recent report from the Victorian Congenital Anomalies Register outlined that hypospadias was the most commonly reported condition, followed by obstructive defects of the renal pelvis, hip dysplasia and ventricular septal defect[143].

Risk factors for adverse pregnancy outcomes in the general population include smoking, alcohol or illicit drug intake, very young or advanced maternal age,

gestational diabetes, multiple gestation and underweight or overweight/obese body mass index (BMI) [141, 144].

In particular, there are multiple causes for intrauterine growth restriction, including maternal, placental, foetal or genetic factors. Maternal risk factors include low socioeconomic status, low BMI and poor weight gain, maternal infection and various other maternal diseases such as hypertensive disorders, chronic renal disease and systemic lupus erythematosus[145]. In addition, placental factors such as abnormal vasculature and placental dysfunction, which occurs with pre-eclampsia, have been implicated, as well as foetal factors including infection, congenital anomalies and multiple gestation [145].

Adverse pregnancy outcomes in IBD

It has now been well established in the literature that IBD, particularly when active, can also be associated with pre-term birth and low birth weight [5, 146-148]. A meta-analysis of twelve mostly retrospective case-control studies assessed the risk of adverse pregnancy outcomes in 3907 women with IBD. This study detected a 1.87-fold increase in the incidence of pre-term birth (< 37 weeks gestation) and the incidence of low birth weight (< 2500 grams) was over twice that of normal controls[5]. A more recent meta-analysis, again based on retrospective studies, included 15,007 women with IBD[147]. Similarly, this analysis showed a significant increase in adverse pregnancy outcomes in women with IBD compared to controls, with an OR of 1.85 for preterm birth, OR 1.36 for small for gestational age birthweight and OR 1.57 for stillbirth[147].

Both of these meta-analyses reported increased odds of congenital abnormalities in women with IBD, however it is possible that these rates have been affected by publication bias. Data regarding the association with birth defects has been conflicting, with some studies showing no association[149]. Most recently, a large Canadian retrospective cohort study, including 13,099 women with Crohn's disease and 7,798 with UC, reported the risk ratios for the association between IBD and the risk of congenital abnormalities relative to women with no IBD [150]. This study found that Crohn's disease was associated with 1.90 times the risk of abdominal wall defects and UC with 1.53 times the risk of central nervous system defects[150]. However, there was not a significant association with the risk of birth defects overall. Although this study used hospital administrative data, this meant it could exclude recall bias and provides a large longitudinal cohort. Therefore, these findings suggest a small increased risk of certain birth defects. Further research is required to determine the possible

pathogenesis, which may relate to factors such as the underlying inflammatory or genetic pathways.

A recent large systematic review assessing the risk of adverse pregnancy and obstetric outcomes was published in the last year by Tandon et al. This review, which did not include foetal outcomes, found that gestational diabetes was more common in women with IBD, but an increase in placental disease such as pre-eclampsia was not detected[151]. In this study, the pooled OR for developing gestational diabetes was 2.96 (95% CI, 1.47-5.98, I^2 = 0%) in patients with IBD compared to healthy controls[151]. The mechanism for this is unclear, but it occurred regardless of antenatal corticosteroid use.

For pre-eclampsia, the non-significant OR reported by Tandon et al was 4.65 (95% CI, 0.76-28.35) in IBD patients compared to healthy controls, but this could only be calculated from one included study comprising 75 IBD pregnancies[151]. However, another large cohort study by Mahadevan et al, involving 461 pregnant patients with IBD, as well as a large Danish cohort study, showed different results[152, 153]. These studies demonstrated that IBD may increase the risk of pre-eclampsia[152, 153], a condition that is also related to immune dysregulation[154]. An association between pre-eclampsia and other inflammatory conditions such as systemic lupus erythematosus has been detected [155] and hence there may also be a link with IBD, although this has not been clearly established in the literature.

Published data regarding the effect of IBD on spontaneous abortion are also inconsistent. The same study by Mahadevan et al reported an increase in spontaneous or unknown cause of abortion in their community-based cohort[152]. However, in the analysis by Tandon et al, the pooled odds ratio (OR) was 1.63 (95% CI, 0.49-5.43, I^2 = 90%) for early pregnancy loss in 1030 patients with IBD in comparison to healthy controls in that review. As in the non-IBD population, it is likely that complete data regarding miscarriage rates are problematic to ascertain.

From an IBD perspective, delivery by caesarean section is recommended if a patient has active perianal CD or previous pouch surgery, in order to avoid further perineal injury and preserve anal sphincter function[156, 157]. Caesarean section rates are higher in women with IBD than the general population[5, 151]. In the recent systematic review by Tandon *et al*, the pooled OR of caesarean section in patients with IBD compared to healthy controls was 1.79 (95% CI, 1.16-2.77)[151]. The reason for this is unclear, but

may relate to fears of anal sphincter damage or development of new-onset perianal disease following traumatic vaginal delivery in patients with IBD. Importantly, available data have shown that in women with Crohn's disease and no prior perianal disease, vaginal delivery does not increase the risk of new perianal fistulising disease compared to caesarean section[157, 158].

A recent large Australian population-based study by Shand et al has echoed these international studies in IBD and pregnancy outcomes. This landmark study of 630,742 women who delivered at 20 weeks of gestation or later, reported a prevalence of IBD of 0.31%, including 1960 women with IBD who had 2781 births[159]. Once again, women with IBD were more likely than women without IBD to have adverse outcomes including pre-term birth (adjusted risk ratio (aRR) 1.47, 95% CI 1.30–1.66), a small-for-gestational-age infant (aRR 1.19, 95% CI 1.04–1.36) and delivery by caesarean section (aRR 1.38, 95% CI 1.31–1.45)[159]. However, a limitation of this study was the lack of information regarding disease activity.

Adverse pregnancy outcomes appear to be more pronounced in women who have active IBD at conception or during pregnancy. A recent study by Kammerlander *et al* showed that even with biological treatment, clinically active disease in pregnancy was associated with worse pregnancy outcomes[148]. In this study, in women with UC and disease activity, 19.5% had a child with low birth weight and 29.3% gave birth pre-term[148]. Similarly, in a large Swedish cohort study, there was an increased risk of pre-term birth and low birth weight for patients with both UC and Crohn's disease, and these risks were greater in women with disease flares during pregnancy[160]. Another Scandinavian study has demonstrated that women with UC had an increased risk of adverse pregnancy outcomes compared with the general population and this was associated with disease activity pre-conception[161]. Interestingly, inadequate gestational weight gain, which is associated with small for gestational age infant weight, is more common in women with IBD and disease activity has been shown to contribute to reduced gestational weight gain[162].

1.2.6.4 Conclusion

Fertility is generally normal in women with IBD when inflammation is controlled. However, the risk of adverse pregnancy outcomes including pre-term birth and low-birth weight is increased, especially in active IBD. Possible mediators of adverse pregnancy outcomes in women with IBD include impaired nutrition and increased

underlying inflammation, but the mechanisms behind this complex interplay remain poorly understood.

1.2.7 The Impact of Pregnancy on IBD

1.2.7.1 Introduction

While the effect of IBD on pregnancy has been explored by a host of studies, the effect of pregnancy on IBD remains more uncertain. Historically, pregnancy was thought to be a state of immune suppression and hence was thought to benefit IBD. However, this notion has been challenged by more recent data demonstrating that women with IBD who become pregnant when their disease is active, are more likely to experience ongoing active disease during pregnancy than those who become pregnant when their disease is in remission.

1.2.7.2 Immunological Changes in Pregnancy and IBD

It is known that pregnancy involves complex shifts in maternal inflammatory responses [163-165]. Immunological states change at various stages of pregnancy from implantation to partition. Foetal tolerance requires mediation by both innate and adaptive cells working together for a successful pregnancy[166]. It is thought that implantation requires a pro-inflammatory Th1 environment at the maternal-foetal interface, which is followed by a shift towards a Th2 response for the majority of pregnancy, and again increased shift to a Th1 response before partition[7, 167]. Additionally, the ratio between Th17 cells and regulatory T cells shifts in favour of regulatory T cells during pregnancy[168]. However, the extent to which placental immunological shifts translate to systemic changes is unclear.

It has been previously noted that some autoimmune diseases improve during pregnancy. Patients with autoimmune conditions such as rheumatoid arthritis can have increased Th17 levels and reduced regulatory T cells[168]. The pregnancy-related shifts in favour of regulatory T cells may be responsible for an improvement in some patients with autoimmune conditions during pregnancy, which suggests that pregnancy-associated changes may affect peripheral immune processes[7, 168]. Meanwhile, pregnancy disorders such as pre-eclampsia have also been associated with decreased regulatory T cell levels[154, 168].

It has been widely proposed that a shift towards Th2 responses in pregnancy may contribute to a potential increase in disease relapse in patients with UC, which involves

predominantly Th2 cytokines[167, 169]. There are limited studies in the literature in women with IBD that have examined peripheral immune system and cytokine changes across pregnancy.

A recent study by van der Giessen *et al* studied the peripheral cytokine profiles across pregnancy in 46 IBD patients and 179 healthy controls[170]. This study showed a lack of overall cytokine change during normal pregnancy and that overall cytokine patterns did not cluster separately between patients with IBD and healthy controls[170]. Significant differences for some individual cytokines were observed, although it was not possible to associate the observed changes in this study to either Th1 cytokines (such as IFNγ and TNFα) or Th2 cytokines (such as IL-4, IL-5, IL-6, IL-10 and IL-13). The study noted increased IFNγ levels (Th1) but reduced IL-5 and IL-10 (Th2) levels compared with healthy controls throughout pregnancy and hence did not find evidence of a Th2 shift in peripheral immune responses, which has been commonly hypothesised previously. This study observed an increase in peripheral blood IL-6 levels in heathy pregnancies, which has also been seen in other studies [171]. In contrast, the study showed that in women with IBD some pro-inflammatory cytokines including IL-6 and IL-17 actually decreased significantly with conception[170].

One other small study has recently reported a similar cytokine analysis of pregnant women with IBD (n=28), including serum cytokine levels measured preconception and in the second trimester[172]. This study also observed a significant decrease in pro-inflammatory (Th1 and Th17) cytokines including IL-17A, IL-21, IL-23 and IFN-γ from preconception to trimester two, in women with Crohn's disease but not UC[172]. Additionally, elevated serum levels of IFN-γ in trimester two were associated with neonatal intensive care admission in this small cohort[172]. Interestingly, increased Th1 responses have also been linked with implantation failure during in vitro fertilisation and recurrent pregnancy loss[173]. It is likely that controlling inflammation remains central to optimising pregnancy outcomes for patients with IBD. Interestingly, findings from these recent studies suggest a potential improvement in aspects of the immunological state of pregnant patients with IBD, however, it remains unclear how these changes correlate with disease activity and how they impact the chance of successful pregnancies in IBD.

1.2.7.3 Gut Microbiota Changes in Pregnancy and IBD

Pregnancy itself is also associated with changes in the gut microbiota, which may influence the behaviour of IBD[174]. A study from Finland by Koren et al, which examined

the relative abundance of different gut bacteria in 91 mothers and their offspring, found that in the first trimester of pregnancy the maternal intestinal microbiota exhibited many similarities to healthy non-pregnant controls[175]. However, dysbiosis was seen in the third trimester, with increased Proteobacteria in the majority of women as well as reduced overall bacterial diversity [175]. It has been suggested that these changes in the third trimester may amplify the dysbiosis associated with IBD, and hence potentially worsen inflammation in late pregnancy[7]. Patients with Crohn's disease tend to have a more reduced microbial diversity and more unstable microbiota compared to patients with UC [176], and it has been postulated that this may translate to a diminished effect of pregnancy-related microbiota changes on Crohn's disease activity in pregnancy[7].

The study by van der Giessen *et al* that examined cytokine profiles in pregnant women with IBD, also studied the effect of pregnancy on the microbiomes of patients with UC and Crohn's disease. As has been previously observed, they found lower microbial diversity in IBD patients than controls[170]. Interestingly, their findings between IBD patients and healthy controls indicated that pregnancy with IBD was not associated with an additional pregnancy-related reduction in diversity. Additionally, they noted that while the UC and Crohn's disease microbiota remained different from each other during pregnancy, changes in microbial features became subtler as pregnancy progressed with more similarities in diversity between patients with UC and Crohn's disease. More recently, initial data from the MECONIUM study, assessing the microbiome of pregnant women with IBD and their babies, has shown that both mothers with IBD and their offspring to three months of age had lower bacterial diversity compared with controls[177].

In summary, reduced diversity of the intestinal microbiota is seen in healthy pregnancies as well as in patients with IBD, and changes in microbial diversity in patients with UC and Crohn's disease appear to move towards those seen in healthy females during pregnancy. Further data are required for comparisons of specific bacterial species and in larger cohorts of IBD patients to provide correlations with disease activity and impact on the infant microbiota and disease risk.

1.2.7.4 Inflammatory Bowel Disease Activity During and Subsequent to Pregnancy

The overall effect of pregnancy on inflammatory bowel disease activity remains uncertain in the current literature. It has, however, been recognised that disease

activity at the time of conception is likely to have an impact on disease activity during pregnancy.

An older meta-analysis, which included mostly retrospective studies, found that disease activity during pregnancy is associated with disease at conception. This data, which included 1130 patients with UC, found that the relapse rate in pregnancy was 29% in women who became pregnant while in remission, compared to 55% of patients who continued to have active disease in pregnancy if they became pregnant while their UC was active[8]. Meanwhile, in 519 patients with Crohn's disease, disease relapses were observed in 23% of patients who became pregnant while in remission, compared to 46% of patients who had active disease at the time of conception where their disease remained active in pregnancy[8]. Hence, for women with disease in remission at conception, activity during pregnancy and risk of relapse appears similar to the non-pregnant population[178]. This meta-analysis was limited by significant heterogeneity between studies, a high risk of bias, inclusion of studies prior to the year 1980 with varying methods for assessing disease activity and a low proportion of patients on immunomodulatory or biologic medications. Nonetheless, a recent smaller prospective study has echoed these findings. This study, including 229 women with IBD from the Netherlands, found that active disease at conception was strongly associated with disease relapse during pregnancy (adjusted OR=7.66, 95% CI 3.77–15.54)[9]. This prospective study also found that women with UC were more likely to relapse during pregnancy than women with Crohn's disease.

Similarly, other data have shown that disease relapse is seen more commonly in pregnant patients with UC compared to Crohn's disease. A prospective European cohort study by Pederson et al, including pregnant women with IBD who were mostly in remission at conception, showed that women with Crohn's disease had a similar disease course during pregnancy to age and disease matched non-pregnant controls[179]. However, in this study pregnant women with UC had a higher risk of relapse during the first and second trimesters of their pregnancy than non-pregnant women with UC[179]. The ongoing prospective, multicentre Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry in the United States, conducted by Mahadevan et al, includes greater than 1475 pregnant women with IBD. This registry data, published in abstract form only, has also displayed a higher rate of UC activity relative to Crohn's disease activity during pregnancy[180].

In addition, a recent prospective study from Israel including almost 300 women with IBD who were in remission at conception, has demonstrated the risk of disease relapse according to the Physician Global Assessment to be higher in those with UC compared to those with Crohn's disease (48.1% vs. 31.8%, $p = 0.005$)[181]. The reason for an increase in disease activity during pregnancy in patients with UC compared to Crohn's disease has not been established. It has been postulated that this may relate to differential production of placental pro-inflammatory cytokines, microbiota changes or to less aggressive treatment in UC with 5-ASA monotherapy more commonly prescribed in these patients.

The recent prospective study from Israel, conducted through their 'IBD-Mom' multidisciplinary clinic, also showed that the use of biologic therapy at the time of conception was associated with lower rates of disease relapse (25.0% vs. 43.9%, $p = 0.001$)[181], supporting the concept that treatment efficacy impacts disease behaviour in pregnancy as it does in non-pregnant patients. This study again confirmed the association between active disease in pregnancy and pre-term delivery and lower birthweight[181].

Meanwhile, there is some uncertainty regarding the potential effect of pregnancy on the course of IBD both in the immediate postpartum period and longer-term, and controlled data are lacking. The study by Pederson et al observed an increased risk of flares in women with UC up to six months post-partum[179]. The behaviour of IBD during pregnancy and in the postpartum period is likely to be confounded by reduced adherence to medical therapy, which increases the risk of disease relapse.

Other studies have found a reduction in flares in women with both UC and Crohn's disease in the years following pregnancy. A small cohort of 40 women with IBD (n=40) had a mean 0.46 flares per year for the three years prior to pregnancy, compared to 0.17 in the three years after pregnancy ($p< 0.001$)[182]. In this study, the rate of flares in the three years postpartum reduced both in women with UC and Crohn's disease[182]. Again, data regarding medication continuation in pregnancy is limited, as is multivariate analysis assessing possible confounding effects of variables such as smoking. Another study reported longer term follow up of surgical resections in patients with Crohn's disease following pregnancy. This study found that women with distal ileal and colonic Crohn's who had been previously been pregnant subsequently required fewer surgical resections than a comparison group of Crohn's disease patients with a history of ileal or colonic resection[183].

More recently, a large cohort study from India including 406 women with IBD and median follow up of five years, observed that the long-term course of the disease was worse in patients who had never been pregnant compared to those who had been pregnant [184], suggesting a possible protective effect of pregnancy on subsequent disease course. The finding was significant for patients with UC, whereby women who had never been pregnant had lower rates of long-term remission[184]. Akin to the other longer-term retrospective studies in this area, details regarding disease activity and medication use during each pregnancy were not reported.

1.2.7.5 Conclusion

During normal pregnancy, there are complex and reciprocal changes in both maternal immune cells and gut microbiota, which remain somewhat undefined in women with IBD. Further analysis is required to enhance our understanding of the complex relationship between pregnancy-related immune system and intestinal microbiota changes, circulating cytokine levels, hormonal shifts, disease activity and pregnancy outcomes in immune-mediated conditions including IBD.

The reported effects of pregnancy on the course of IBD during and following pregnancy remain inconsistent. It appears that women in remission at conception are likely to have a similar disease course during pregnancy to the non-pregnant state, however both disease activity at conception and a diagnosis of UC are associated with an increased likelihood of disease flare in pregnancy. Prospective studies will be important to examine the impact of such factors as medication use, previous IBD surgery and objective disease activity markers at conception and during pregnancy, in order to provide a more complete and consistent understanding of the pregnancy-related disease course.

1.2.8 Management of IBD

1.2.8.1 Introduction

As a chronic, relapsing disease, treatment strategies can be divided into induction of remission and treatment of active disease flares, and maintenance therapies (for prevention of disease flares or complications). The majority of patients require lifelong medication, however a significant proportion of patients do not respond or lose response to medical therapies requiring changes in therapy over time.

Before considering these therapies in the setting of pregnancy, their rationale and utilisation in IBD in general will be outlined. The broad principles and goals of IBD treatment overall include achieving improved wellbeing and control of symptoms, minimisation of side effects and prevention of complications such as strictures, fistulae, bowel resection, cancer and hospitalisations[119]. Over the last two decades, management of IBD has evolved immensely, with more ambitious targets to prevent these disease complications, and thus IBD patients are now exposed earlier and more commonly to immunosuppressants and biologic therapies[119].

1.2.8.2 Overview of Current and Emerging Therapies in IBD

Current treatments for IBD include lifestyle modification, nutritional, pharmacological and surgical strategies. Lifestyle modification involves smoking cessation and preventative health strategies to maintain psychological health and prevent bone and skin complications related to both IBD and its therapies. Nutritional therapy, particularly the use of exclusive enteral nutrition over six weeks has been used as a method for inducing remission in Crohn's disease. Pharmacological treatments for IBD largely aim to target or inhibit the aberrant inflammatory and immune system responses associated with the condition. Key pharmacological therapies include aminosalicylates (5-ASA), corticosteroids, immunomodulators such as thiopurines and methotrexate, biologic agents targeting TNF, alpha-4-beta-7 integrin and IL-12/23, and small molecule medications such as JAK inhibitors. The anti-TNF agents have revolutionised the treatment approach to IBD, and paved the way for other biologic therapies targeting different immune pathways activated in IBD (Figure 1.2).

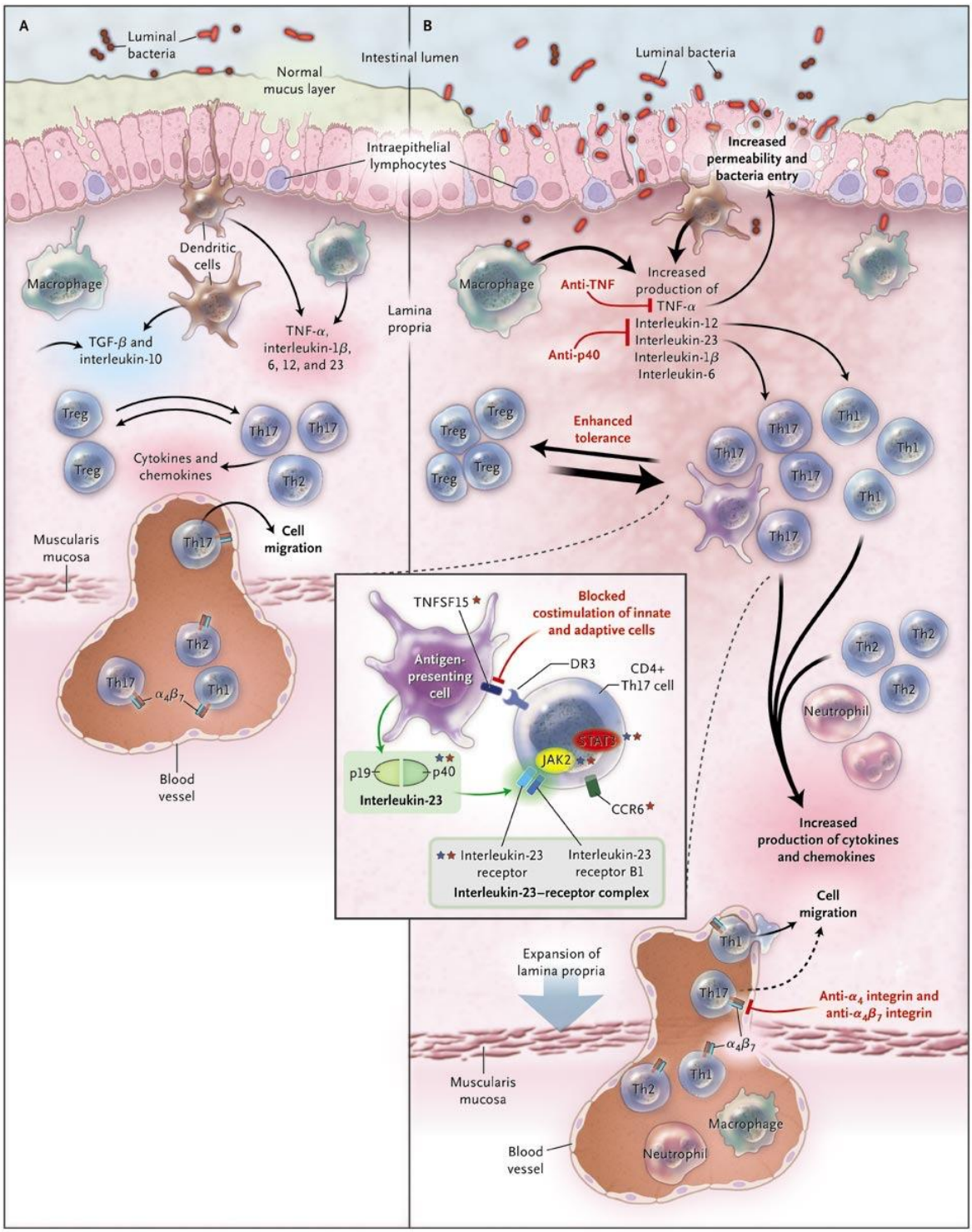

Figure 1.2: Therapeutic Approaches Targeting Intestinal Immune System Pathways

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Insights into typical pharmacological strategies in real-world IBD patients can be gained from epidemiological studies. Spizzo has reported recent data from a local combined hospital and community- based inception cohort, showing that at five years post diagnosis the majority of patients with UC are treated with a 5-ASA drug (90%), while 44% were treated with an immunomodulator and 15% a biologic at five years[185]. These data are similar to recent findings from the large 'Epi-IBD' European multicentre population-based inception cohort, in which 91% of patients with UC were prescribed 5-ASA, 30% an immunomodulator and 12% a biologic medication within the first five years of the disease[22].

Meanwhile, in patients with Crohn's disease after five years of follow up, Spizzo found that 38% were treated with a 5-ASA, 73% an immunomodulator and 38% a biologic drug[185]. Again, this was similar to the 'Epi-IBD' data within patients from Western Europe, with higher rates of immunomodulatory and biological medication use in Crohn's disease compared to UC, but also relatively high rates of 5-ASA prescribing despite limited efficacy in Crohn's disease. Burisch *et al* showed that of the patients with Crohn's disease from Western Europe in the Epi-IBD population cohort diagnosed in 2010, 56% had been prescribed a 5-ASA in the first five years, 66% an immunomodulator and 33% a biologic within five years of diagnosis[72]. The majority of patients on an immunomodulator receive a thiopurine[72].

Whilst pharmacologic agents for IBD treatment have become increasingly targeted, non-pharmacologic therapies have also changed over time[186]. Minimally invasive surgical techniques have developed. For example, outcomes of laparoscopic resection followed by close observation in patients with limited inflammatory ileocaecal Crohn's disease may be equivalent to biologic therapy[187], without the potential risk of immunosuppression.

In light of the emergent association between IBD and gut dysbiosis, dietary therapies are becoming increasingly important alongside anti-inflammatory therapies[188, 189]. For example, current studies are underway to investigate whether manipulation of dietary food content is effective in controlling Crohn's disease in adults as well as paediatric cohorts[190]. An alternative way of altering the microbiota, faecal microbial transplantation, has also gained substantial interest as a potential treatment for IBD. Recent trials have shown modest efficacy with induction therapy in mild-moderate UC[191-193], however questions remain about the optimal donor microbiota, dose, frequency, long term safety and efficacy.

1.2.8.3 Therapeutic Strategies in IBD

Treatment strategies are broadly similar overall in UC and Crohn's disease, with the aim to induce disease remission and then maintain clinical and endoscopic remission. The choice of treatment is influenced by factors such as disease activity and extent, patient preferences and external factors such as co-morbidities[194]. The traditional approach to IBD therapy is termed the 'step-up' treatment strategy (Figure 1.3); whereby simpler, less potent but less toxic therapy is prescribed in the first instance, before escalation to therapies that are potentially more potent but can pose a greater risk of toxicity.

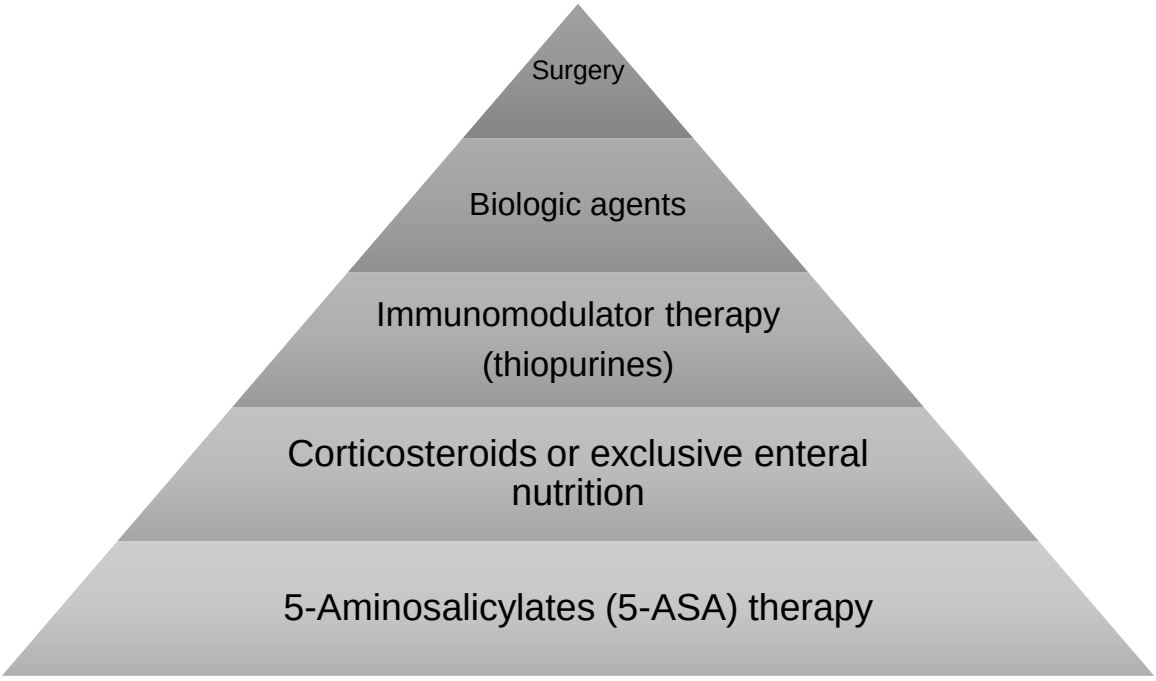

Figure 1.3 The Traditional Pyramid of Therapies used in the Management of IBD

Treatment of IBD has evolved towards a 'top down' approach in high-risk disease. There are other emerging therapies in IBD, however these are not routinely used in pregnancy currently.

Briefly, the conventional approach for mild to moderate UC includes initial induction therapy with oral and topical 5-ASA therapy, followed by consideration after approximately 10-14 days for the addition of oral prednisolone 40mg daily, if there is ongoing rectal bleeding [194]. Prednisolone is typically reduced by 5mg/week and if the patient is unable to wean off steroids then a thiopurine medication is added to

maintenance 5-ASA therapy[194]. If these medications are not tolerated or there are ongoing symptoms after approximately three months, biologic therapy is initiated.

In acute severe UC (bloody stool frequency of six or more daily and evidence of systemic toxicity, defined by the Truelove and Witts criteria), hospital admission for intravenous steroid therapy is indicated [194, 195]. In these cases, flexible sigmoidoscopy is used to confirm disease activity and exclude cytomegalovirus infection, as well as plain abdominal x-ray to exclude toxic megacolon and stool sample analysis to assess for clostridium difficile infection[195]. If there has been an inadequate response to intravenous steroids on day three (defined by the Oxford criteria, which includes a stool frequency of three or more and CRP above 45 mg/L), rescue therapy is indicated with either cyclosporine or infliximab, for which the comparative efficacy is similar but most gastroenterologists are more familiar with infliximab [76, 194]. Colectomy is generally recommended if there is no improvement within approximately four to seven days of rescue therapy or clinical deterioration at any stage [194].

In Crohn's disease, the major differences in the treatment approach includes a limited efficacy of 5-ASA therapy, benefit with exclusive enteral nutrition and greater need for surgery [194]. For example, induction therapy in mild to moderate ileal Crohn's disease includes budesonide or prednisolone. If the patient is unable to taper off steroids within around three months, immunomodulator therapy with a thiopurine or methotrexate is added. Like in UC, if this is not tolerated or there is ongoing evidence of disease activity after approximately three months, biologic therapy is commenced.

More recently, in an effort to prevent bowel wall damage, the end-point of therapy has moved from achieving immediate symptom control to incorporating evidence of mucosal healing (absence of ulceration on endoscopic assessment)[15]. This is referred to as the 'treat to target' strategy and has been associated with lower rates of hospital admissions, surgeries and improved quality of life[196].

Accordingly, the traditional step-up treatment strategy has now been modified in favour of either an accelerated step up or 'top-down' approach, before irreversible damage occurs[119]. This rapidly escalated layering of more aggressive therapies, resulting in more overall immunosuppression, is applied particularly in patients with severe UC or aggressive Crohn's disease where there is evidence for improved outcomes with earlier initiation of combination therapy [197, 198]. Clinical phenotype, serology, endoscopic and radiological markers are used to try to predict which patients will require early

treatment to prevent complications, and conversely, which patients are unlikely to develop disease complications.

1.2.9 Medication Safety in the Non-pregnant IBD population

1.2.9.1 Introduction

The efficacy of more potent immunosuppressive therapies in IBD must be balanced against the increased risks associated with both the commencement and longer-term continuation of these therapies[199]. Thiopurine and anti-TNF therapies carry an increased risk of more serious side effects, most notably infection and malignancy[200, 201]. Patients with risk factors for a more severe disease course are more likely to benefit from aggressive therapies, while less potent yet safer therapies can be used in patients who are less likely to have complicated disease. An overview of these considerations will be followed by a discussion regarding individual medications in relation to pregnancy.

1.2.9.2 Serious Adverse Effects Associated with Immunomodulators and Anti-TNF Therapy

Patients exposed to anti-TNF monotherapy or thiopurine monotherapy have increased risks of serious and opportunistic infections compared with unexposed patients. This risk of serious infections is greater in anti-TNF compared to thiopurine exposed patients (HR, 1.71; 95% CI, 1.56–1.88)[201]. Additionally, combination therapy increases the risks of both serious and opportunistic infections further compared to anti-TNF monotherapy (HR 1.23 and HR 1.96, respectively)[201].

Malignancy is also of concern with these drugs. Anti-TNF therapy and immunomodulators are associated with an increased risk of skin cancers[202]. Cervical dysplasia and cervical cancer has been reported in association with IBD immunosuppressive therapies, hence screening and human papillomavirus vaccination are important for women with IBD[203]. Meanwhile, thiopurine use is also associated with an increased risk of lymphoma, but this risk does not appear to persist following thiopurine discontinuation[204]. Recent data suggest there is also an increased risk of lymphoma with anti-TNF therapies[200, 205]. This risk has been estimated at around 2.5-fold with the use of thiopurine or anti-TNF monotherapy, and up to 6-fold with combination therapy[205]. The absolute risk for these serious side effects remains very low overall, but given the potential for harm these therapies are reserved for patients with moderate to severe disease or refractory disease.

1.2.9.3 Factors Predictive of Severe Disease

Reliably predicting the disease course in an individual patient in order to inform treatment decisions is a challenge, and there has been considerable attention on this matter in recent literature. The prognosis of an individual's disease is largely estimated based on outcomes from population-based studies that include patients treated with current medical therapies.

A validated definition for a severe or complicated disease course in UC is lacking[206]. Outcomes measured include relapse requiring escalation of therapy to anti-TNF, colectomy for refractory disease and the development of colorectal cancer. Clinical predictors associated with increased relapse rates and/or colectomy in patients with UC have been identified in population-based and cohort studies and include younger age at diagnosis and extensive disease [116, 206]. These factors have also been associated with an increased risk of colorectal cancer, while concurrent primary sclerosing cholangitis is also a significant risk factor for the development of colorectal cancer in patients with UC[116, 206]. Serological predictors of the disease course in UC are less well understood than in Crohn's disease.

Similarly, in Crohn's disease, there is no established consensus definition for a severe disease course, however multiple studies have used surrogate markers of severe disease such as surgical resection or recurrence post-surgery. In Crohn's disease, clinical factors consistently associated with an increased risk of resection or disease recurrence include younger age at diagnosis, complicated (stricturing or internal penetrating) disease and fistulising perianal disease[75, 116, 207, 208]. Ileal and upper gastrointestinal disease locations have also been associated with increased risk of surgery[10, 71]. Patients with these risk factors are likely to benefit from early introduction of immunomodulator and/or biological therapy, even if disease activity is mild or moderate[194].

Serological antibodies may also be useful for predicting the disease course in Crohn's disease. Anti-Saccharomyces antibodies (ASCA) have been associated with complicated disease and need for surgical resection [209]. Meanwhile, perinuclear anti-Neutrophil Cytoplasmic Antibodies (pANCA) are commonly associated with UC, and Crohn's disease patients with pANCA-positivity can display a clinical phenotype similar to UC[210].

1.2.9.4 Withdrawal of Immunomodulatory and Anti-TNF Therapies in IBD

Not unlike the decision regarding initiation of more potent therapies in IBD, treatment de-escalation requires an individualised patient approach incorporating patient preference, risk of adverse effects to therapy, current disease state and prognostic factors. This is often a discussion that presents in relation to medication use during pregnancy. There is not sufficient evidence currently to guide treatment withdrawal, but prospective controlled trials are ongoing.

Multiple retrospective and prospective cohort studies have reported outcomes following withdrawal of anti-TNF therapy [211]. In the prospective STORI trial, which included patients with Crohn's disease in clinical remission on combination therapy, the relapse rate was approximately 50% within one to two years after discontinuation of anti-TNF therapy[212]. Reported relapse rates are relatively similar in other studies with varying use of immunomodulator therapy and including patients withdrawn from anti-TNF therapy when in both clinical and endoscopic remission[211]. Similarly, studies in adult patients with UC in clinical remission have also found relapse rates up to around 40% at one year after de-escalation of anti-TNF therapy [213].

Significantly higher clinical relapse rates have also been reported in both UC and Crohn's disease patients after stopping a thiopurine monotherapy compared with continuing the drug[211]. For example, an older randomised clinical trial among patients with Crohn's disease showed the probability of relapse was 5% after one year in those who continued on a thiopurine, compared to around 40% at one year in those patients in the control group[214]. In another randomised controlled trial in patients with UC, the relapse rate was 36% at one year in those who continued on a thiopurine, while almost 60% of patients relapsed after discontinuing the drug while in clinical remission[215].

Current data suggest that predictors for relapse after withdrawal of therapy are similar to identified prognostic factors for severe disease course, including young age at diagnosis, the presence of complicated disease, perianal Crohn's disease, extensive UC and previous surgery[211]. Additionally, objective signs of persisting disease activity including endoscopic lesions, elevated CRP and/or faecal calprotectin are known to be predictors of disease relapse [212].

1.2.9.5 Conclusion

There is considerable heterogeneity in the clinical course of IBD across patients. Although challenging, prediction of the disease course is important for both patients and clinicians alike in order to guide and inform individual treatment choices. Notably, a patient's age at diagnosis along with disease location and extent are known to affect the disease course and prognosis in both UC and Crohn's disease; and, additionally, in Crohn's disease, the disease behaviour is a key factor. Younger age at diagnosis is associated with more extensive and aggressive IBD, while small bowel involvement in Crohn's disease is associated with an increased risk of stricturing and penetrating complications compared to colonic disease.

Patients with these predictive factors may therefore be considered more likely to benefit from early commencement and continuation of more aggressive therapies including biologic and combination therapy, despite the increased risk of serious side effects such as infection. This discussion is paramount in the setting of recommendations for treatment during pregnancy.

1.2.10 Medication Safety in Pregnancy

1.2.10.1 Introduction

Given the importance of controlling active IBD to help regulate the immune response and optimise pregnancy outcomes, most women with IBD require continuation of maintenance medications in pregnancy. Studying the effects of medication use during pregnancy is challenging and needs to include the usual evaluation of disease severity and treatment side effects, as well as the safety in pregnancy, which extends well beyond the assessment of teratogenicity. Medications can have a diverse range of potential effects on maternal and foetal outcomes in addition to birth defects, including spontaneous abortion, stillbirth, preterm delivery and neurodevelopmental effects[213]. These potential adverse effects differ according to the individual drug, the dosage and the timing of exposure during pregnancy.

In general, medication use during pregnancy is common, however large volume data on use of individual medications is rare[213]. Pregnant women are often excluded from clinical trials due to ethical concerns and the vast majority of drugs approved by the US Food and Drug Administration have unknown teratogenic and pregnancy risks in humans[214]. Although some information about potential effects can be acquired from animal studies, most of the evidence concerning foetal effects

comes from post-marketing studies[213]. Many outcomes such as specific congenital malformations are rare, and therefore require large numbers of exposed individuals to adequately assess incidence.

A total of at least 1000 pregnancies is considered by the European Committee for Medicinal Products for Human Use to be representative of widespread exposure and sufficient to capture teratogenic risk[218]. Data are generally under-powered to assess for moderate teratogenic risk and can be insufficient for detecting rarer, more subtle or longer-term outcomes [219] For example, drugs may cause adverse effects that present later in life or developmental effects that may not be captured in medical records. Additionally, retrospective reports are subject to recall bias, and abnormal outcomes may be more likely to be reported. Another issue affecting many studies is the inability to correct for confounding factors associated with drug indication.

In this context, studies of human teratogenicity and pregnancy safety are often limited by inadequate sample size, an absence of comparator reference groups, unreported participation rates, variable data collection methods and limited follow up in order to capture defects not present at birth[217]. Comprehensive pregnancy safety data including longer term effects and rarer events requires large-scale, well-designed, prospective, long term studies, which are complex, time-consuming and expensive to co-ordinate.

Sources of data in the field of IBD medications in pregnancy are largely cohort studies and some case-control studies, with variable sample size and follow-up duration. The available evidence is often retrospective nature and it can be impossible to adjust for the confounding effect of active disease. For some of the older therapeutic agents, there have been studies of sufficient scale to address issues of teratogenicity. However, for newer agents such as vedolizumab, human data are limited. Likewise, longer term data such as neurodevelopmental effects on exposed infants are still emerging. It remains possible that rarer complications may not have been detected due to sample size, reliance on spontaneous reporting and a lack of prospective studies. In the following sections, the literature will be discussed focussing on individual therapies currently used in IBD and their respective pregnancy data. A summary of IBD medications used in pregnancy is presented in Table 1.3.

1.2.10.2 Corticosteroids in IBD

Corticosteroids are used to induce remission in both UC and Crohn's disease[194]. They are potent anti-inflammatory agents, which downregulate inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor (TNF) alpha[220, 221].

Steroids can be administered intravenously in cases of severe disease, as well as in oral formulations including prednisolone and budesonide, or rectally for distal colonic disease. Although effective for inducing remission in both UC and Crohn's disease, steroid use is associated with significant side effects including infection, hypertension and diabetes mellitus, particularly when used long term [221]. Budesonide undergoes approximately 90% first-pass metabolism in the liver and has limited bioavailability [222]. Therefore, it has fewer side effects than prednisolone and is considered an alternative to prednisolone but only in mild to moderately active disease.

1.2.10.3 Corticosteroids in Pregnancy

Corticosteroids may be required to induce remission when there are disease flares during pregnancy. There has been controversy surrounding a possible association of corticosteroids with congenital anomalies following a previous meta-analysis, which showed a small increased risk of oral cleft lip and palate abnormalities with corticosteroid exposure in the first trimester[223], when the foetal lip and palate forms. However, a more recent large Danish cohort study showed no increased risk of cleft lip or palate in 2195 pregnancies with exposure to oral corticosteroids in the first trimester [224].

An older study specific to IBD showed that the frequency of adverse pregnancy outcomes including spontaneous abortion did not appear increased in those exposed to corticosteroid use [225]. The large ongoing prospective multi-centre Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry data provides more recent evidence in the setting of IBD. Preliminary data from an abstract presentation reported that corticosteroids were associated with both maternal and foetal complications with a significant increase in gestational diabetes (OR 2.8), preterm birth (OR 1.8) and low birth weight (OR 2.8), but not with congenital anomalies [226]. Similar findings were also reported in a retrospective database study also presented in abstract form. This data showed that in 546 deliveries exposed to steroids (orally or intravenously) in women with IBD, there was again a significant association with pre-term birth and intrauterine growth restriction, which was not seen with

budesonide[227]. However, in this study there was no adjustment for the potential effects of active disease.

There are minimal data on budesonide or topical steroid use in pregnancy. One very small case series of eight patients with Crohn's disease treated with budesonide did not find an increased risk of adverse pregnancy outcomes[228]. However, budesonide is somewhat less effective for inducing remission, making it a less attractive therapeutic option during pregnancy when rapid induction is required. Rectal corticosteroid preparations are associated with low bioavailability and can provide a safer alternative than oral corticosteroids in the setting of mildly active distal colonic disease.

In terms of longer term follow up, the PIANO registry data also showed a trend towards early infant infection risk with a nonsignificant increase in infant infections in the first four months of life following intrauterine corticosteroid exposure (OR 1.5, 95% CI 0.9-2.7)[226]. The same data does not show any association with increased infection risk at 12 months of age, nor any association with developmental delay at 12 months.

Hence short courses of corticosteroids can be prescribed when necessary to treat active disease, but are not considered an alternative to maintenance therapy for IBD during pregnancy.

1.2.10.4 Aminosalicylates (5-ASA) in IBD

5-aminosalicylic acid (5-ASA) is the main active ingredient in the aminosalicylate medications, and sulfasalazine is a prodrug composed of 5-ASA linked to sulfapyridine. 5-ASA therapies have a variety of different oral and rectal formulations to deliver drug to the disease location[229]. 5-ASA medications act locally on the colonic mucosa, and in certain formulations the distal small bowel mucosa, to reduce inflammation by a variety of anti-inflammatory processes [230].

5-ASA therapy is well-tolerated and effective for both inducing remission in mild to moderate UC as well as for maintenance therapy in UC[229, 231]. Distal disease can be treated with rectal 5-ASA preparations. There is evidence for improved remission rates with combined oral and rectal 5-ASA therapy[232]. 5-ASA medications are prescribed in mild ileocolonic Crohn's disease, however evidence in the literature to support their efficacy in this capacity is limited[177]. 5-ASA therapy is also used for chemoprevention of colorectal cancer in patients with colonic IBD [233].

1.2.10.5 Aminosalicylates in Pregnancy

5-ASA drugs and the prodrug sulfasalazine are some of the oldest medications to be used in the treatment of IBD and they have been widely used in pregnancy. Sulfasalazine may inhibit the absorption of folic acid, therefore higher doses of folic acid are recommended (2 mg/day of folate) [156]. However, multiple human studies including case series, cohort studies and meta-analyses have not linked 5-ASA medications with teratogenicity [149, 234, 235].

Some individual studies have suggested slightly higher rates of congenital anomalies, pre-term birth or low birth weight in women on 5-ASA medications in pregnancy, however it is difficult to delineate the confounding effect of active IBD [234]. A meta-analysis of seven cohort studies, including 642 pregnant IBD patients with exposure to aminosalicylates, demonstrated no significant increase in the risk of congenital anomalies, spontaneous abortion, preterm delivery or low birth weight compared to patients on no medications [235]). There are no published risks relating to topical 5-ASA therapy, for which systemic absorption is minimal.

1.2.10.6 Thiopurines in IBD

Thiopurine medications, including azathioprine and 6-mercaptopurine, are widely used as maintenance therapy in IBD. Azathioprine is a prodrug that is converted to 6-mercaptopurine. It displays complex multistep metabolic pathways (Figure 1.4), which include further conversion by numerous enzymes including hypoxanthine phosphoribosyltransferase (HPRT), into the eventual active metabolite 6-thioguanine nucleotides (6-TGN) [236, 237].

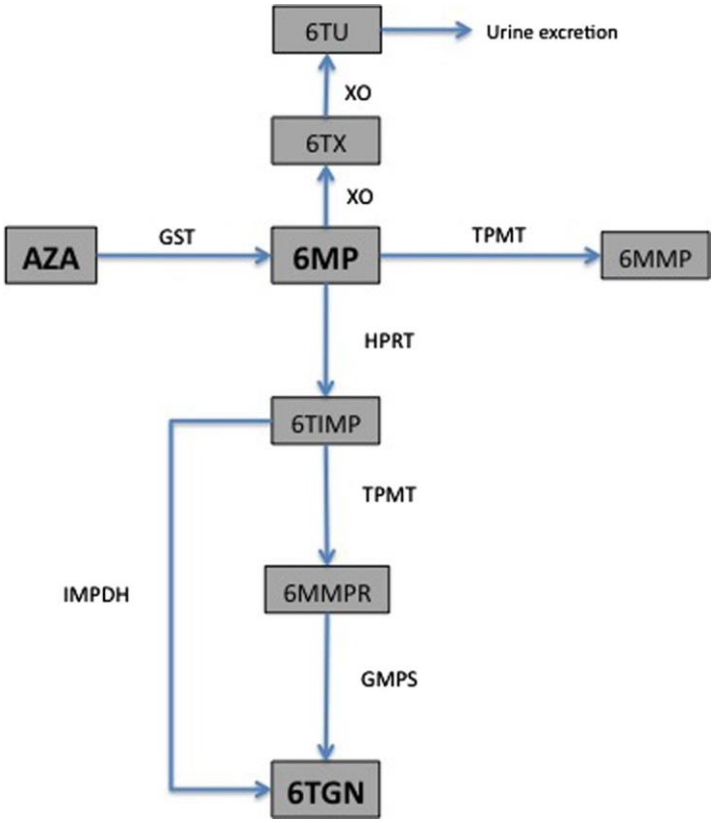

Figure 1.4: Overview of Thiopurine Metabolism

Reproduced from: Monitoring thiopurine metabolites in inflammatory bowel disease, Gonzalez-Lama Y and Gisbert J, Frontline Gastroenterology 2016;7(4):301-7 [237] with permission from BMJ Publishing Group Ltd, 2020.

The mechanism of action of 6-TGN is thought to involve suppression of pro-inflammatory T cell responses as part of its immunosuppressant effects, including induction of T cell apoptosis and inhibition of T cell/antigen-presenting cells complex formation[238]**.** Adverse effects associated with elevated 6-TGN include myelosuppression [239]. Meanwhile, 6-MP can be methylated by the key enzyme thiopurine S-methyltransferase (TPMT), leading to 6-methylmercaptopurine (6-MMP) formation[240]. Hepatotoxicity can be associated with hypermethylation or shunting of the metabolic pathway toward the production of 6-MMP [239].

The recommended weight-based dose is 2–2.5 mg/kg for azathioprine and 1–1.5 mg/kg for 6-MP, however monitoring of thiopurine metabolites is recommended once dosing is stable to ensure the blood metabolite levels are within the therapeutic range[241]. Allopurinol inhibits the metabolism of 6-MP by xanthine oxidase, thus

resulting in increased 6-TGN concentrations[242, 243]. Hence, co-administration with allopurinol has been shown to be effective in those patients who preferentially form 6-MMP[242]. Another option in patients with preferential 6-MMP metabolism is split-dose administration of the thiopurine, which was shown in a small review to significantly reduce 6-MMP levels without reducing 6-TGN in these patients[244].

Thiopurine medications are effective in maintaining steroid-free remission in patients with UC and Crohn's disease [238]. As a consequence of their immune suppressing mechanism of action, risk of infection is increased. The risk of infection associated with thiopurines has been confirmed in a recent large French population study[201]. Both serious and opportunistic infections were increased in the setting of thiopurine therapy, with adjusted hazard ratios of 1.3 (95% CI 1.2–1.4) and 3.7 (95% CI 3.0-4.6), respectively, compared to patients with IBD unexposed to immunosuppressive drugs[201]. The increased infection risk with thiopurine monotherapy largely relates to viral infections.

Thiopurine exposure in IBD patients is also associated with an increased risk of some cancers, including non-melanoma skin cancers (adjusted odds ratio 1.9 (95% CI 1.7–2.1) [202] and lymphoma (adjusted hazard ratio 2.6 (95% 2.0–3.4)[205], as highlighted previously. Additionally, adverse events can include gastrointestinal side effects such as nausea, while pancreatitis is observed infrequently[238].

1.2.10.7 Thiopurines in Pregnancy

In light of the cytotoxic mechanism of action and potential for immune suppression with thiopurine medications, there has been concern regarding foetal effects following antenatal exposure. Initial studies reported an increase in pre-term birth with thiopurine use in mothers with IBD [245-247]. This was reported in two meta-analyses including mostly retrospective studies; both demonstrated a pooled odds ratio of 1.67 for pre-term birth, but no significant association with low birth weight or congenital anomalies in women with IBD exposed to thiopurines [246, 247]. However, these studies were unable to adequately control for the confounding effects of disease activity in pregnancy.

More recently, controlled studies have not shown an association between thiopurine exposure and adverse pregnancy outcomes [248, 249]. A multi-centre retrospective study in women with IBD demonstrated that use of thiopurines (n=187) did not increase the risk of pregnancy or infant complications including spontaneous abortion, congenital anomalies, pre-term birth and low birth weight [249]. This study included two groups for

comparison of pregnancy outcomes, including one receiving medications for IBD other than a thiopurine and another group with IBD receiving no medication; no significant differences were found between the groups[249]. Similarly, the ongoing large prospective PIANO registry, including 337 children with intrauterine thiopurine exposure to date, has not shown an association between thiopurine use and congenital anomalies or pregnancy complications [180].

There have been rare case reports of haematological abnormalities in infants exposed to thiopurine drugs antenatally [250]. A small study by Jharap et al reported infant anaemia following thiopurine exposure *in utero* in 10/16 infants at birth, with a haemoglobin less than 10mmol/L[251]. However, a more recent study has assessed for anaemia in older infants and this study did not detect anaemia at around one year of age [252].

In relation to infection risk in exposed infants, a recent prospective study including 108 infants exposed to a thiopurine showed no increased risk of adverse birth outcomes or infections up to one year of age [253]. However, infants exposed thiopurines in combination with anti-TNF drugs have been shown to be at a slightly higher risk of childhood infections such as varicella zoster [180, 254]. Regarding longer term follow up, a prospective study of 30 children exposed to thiopurines in utero did not report an increased risk of infection up to a median age of 3.8 years [255]. This study, by de Meij et al, also showed no abnormalities in mental or physical development in children up to six years of age [255]. Another small study by Angelberger et al demonstrated that development was normal to a median 3.3 years of age in 15 children whose mothers had IBD treated with a thiopurine during pregnancy and lactation [256].

Thiopurine medications including azathioprine and mercaptopurine are therefore considered safe to continue in pregnancy, with no adverse impact on pregnancy outcomes, infant infection risk or early childhood development in published studies to date. However, the potential association with neonatal haematological abnormalities including anaemia needs further study.

Allopurinol, which can be used to optimise thiopurine metabolism in non-pregnant patients with IBD, has an uncertain medication safety profile in pregnancy and should only be used during pregnancy when there is considered to be no alternative for controlling IBD. Allopurinol-induced teratogenicity has been reported in animal studies, while human data remains limited[257]. A recent review on the safety of allopurinol during

pregnancy included 53 cases of allopurinol exposed infants, highlighting two cases with a very similar pattern of major congenital malformations[257].

The safety of thioguanine, a non-conventional thiopurine medication, also remains uncertain during pregnancy due to very limited data. One retrospective case series including 19 pregnancies in women with IBD on thioguanine reported spontaneous abortion in three pregnancies and a mild congenital abnormality (hypospadias) in one case [258]. Further data is required, however thioguanine is likely to be safe during pregnancy.

1.2.10.8 Methotrexate in IBD

Methotrexate is a dihydrofolate reductase inhibitor, which was organically introduced in the 1940's for treatment of various malignancies[259]. It was then discovered to have broad immunosuppressive properties and for decades has been the base drug for the treatment of rheumatoid arthritis[259]. It was later found that parenteral but not oral methotrexate was effective in the treatment of Crohn's disease.

The current literature supports the use of parenteral methotrexate monotherapy for maintenance of Crohn's disease, although not for UC. It can be used as part of combination therapy to prevent antibody formation towards anti-TNF drugs[260]. Treatment with methotrexate can be limited by side effects including nausea and vomiting as well as hepatotoxicity with prolonged use[261]. It is generally recommended as a second-line maintenance therapy agent following the thiopurines due to both efficacy and safety, although methotrexate may be considered in the setting of targeting extra-intestinal joint manifestations.

Methotrexate is known to be teratogenic in humans and is therefore contraindicated in pregnancy. It is associated with spontaneous abortion and can cause limb defects and craniofacial anomalies when taken during organogenesis as well as developmental delay[262, 263]. Methotrexate should be stopped at least three to six months prior to conception due to its long half-life[263].

1.2.10.9 Anti-TNF Therapy in IBD

Anti-TNF-alpha antibodies, such as infliximab and adalimumab, were developed to inhibit the action of TNF-alpha, a cytokine which is known to play a key role in the

inflammatory cascade in IBD. Infliximab and subsequently adalimumab have now been used for around two decades in IBD therapy to induce and maintain remission in moderate to severe disease. More recently golimumab, traditionally used in rheumatoid arthritis, has also been approved for use in moderate to severe UC.

Infliximab is a chimeric IgG1 monoclonal antibody and adalimumab a fully humanized IgG1 monoclonal antibody. Infliximab is administered intravenously at a standard maintenance dose of 5mg/kg every eight weeks, while adalimumab is given subcutaneously and the standard maintenance dose is 40 mg every other week.

The efficacy of infliximab and adalimumab was first shown in patients with CD in landmark trials including ACCENT I and CHARM [264, 265]. Subsequently, infliximab and adalimumab were also shown to be effective in moderate to severe UC [266, 267]. Current data support the use of anti-TNF therapy for complex perianal fistulising disease, in combination with surgical therapy[268]. Infliximab is also used as salvage therapy in acute severe UC. Anti-TNF medications, while effective and generally safe, are associated with potential adverse events such as hypersensitivity reactions as well as infections and malignancy [261].

Loss of response to anti-TNF medications with anti-drug antibodies can occur. However, it has been shown that combination therapy with infliximab and immunomodulatory therapy is associated with lower immunogenicity to anti-TNF medication and reduced disease-related complications in high-risk patients[177] . Additionally, it can be necessary to increase the dose of anti-TNF agent or shorten the interval between doses in order to overcome low trough medication levels; hence anti-TNF drug level monitoring is important. Higher trough levels may also be required, for example in patients with perianal fistulising Crohn's disease[269]. Therapeutic drug monitoring will be further discussed in relation to pregnancy in Section 1.7, as part of the background literature review for the fifth study in this thesis.

1.2.10.10 Anti-TNF Therapy in Pregnancy

There are a multitude of studies in the literature relating to pregnancy outcomes in the setting of prenatal anti-TNF therapy exposure. The first series of pregnancy outcomes in women with Crohn's disease (n=55) as well as rheumatoid arthritis who were exposed to infliximab was published by Katz et al in 2004, with rates of spontaneous abortion and birth defects consistent with the background population [270]. Since then, several large registries, cohort studies, meta-analyses and systematic reviews have

confirmed that women with IBD who are exposed to anti-TNF therapy during pregnancy do not have increased rates of adverse pregnancy outcomes including spontaneous abortion, pre-term birth, low birth weight or congenital anomalies [180, 254, 271-274].

The most recent meta-analysis, published in 2016, included six high quality observational studies, one of which was retrospective. This meta-analysis, with a total of 1242 pregnancies in women with IBD including 482 exposed to anti-TNF therapy, showed no increased risk of adverse pregnancy outcomes compared with disease-matched controls [271]. This manuscript also reported on a total of 19 published studies that reported rates of congenital abnormalities. Pooled data from these studies included 957 live births with exposure to anti-TNF, with an overall proportion of 2.71% with congenital abnormalities and no significant difference to population data[271]. These findings are consistent with the ongoing prospective PIANO registry, for which the preliminary data have been presented to date. These data include over 500 women who have been exposed to anti-TNF therapy in pregnancy with no increased risk of adverse pregnancy outcomes reported[263, 272]. Further complete publication of the detailed PIANO registry findings is eagerly awaited.

More recently, Luu et al reported outcomes data relating to 1457 pregnancies exposed to ant-TNF drugs in the retrospective EVASION study, based on information from the French national health system database[275]. This study found that anti-TNF therapy in pregnancy increased the rate of maternal infections (adjusted OR 1.31), however this risk is similar in non-pregnant women on anti-TNF agents[275, 276]. In addition, this study reported that maintaining anti-TNF therapy beyond 24 weeks gestation did not increase the risk of maternal complications, while cessation of these drugs before gestational week 24 increased the risk of disease flare[275]. The issue regarding optimal timing for the last intra-partum dose of anti-TNF agents remains controversial, with conflicting advice offered in the existing European guidelines compared to advice from America and Canada [156, 277].

It has been established in the described studies that birth outcomes are not adversely affected by antenatal anti-TNF exposure, however there remains concern regarding subsequent infection risk and effects on the developing immune system in exposed infants. Active transport of maternal immunoglobulin G (IgG) antibodies across the placenta is mediated by the fragment crystallisable (Fc) receptor (FcRn), providing immunity for the newborn[278]. IgG antibodies are transported across the placenta from

early in the second trimester and transfer increases throughout the pregnancy[279]. The anti-TNF agents, infliximab and adalimumab, are IgG1 antibodies, which is the most efficiently transported sub-class. Hence, while transfer is minimal in the first trimester during the crucial period for organogenesis, it is increased particularly in the third trimester, with infliximab and adalimumab levels in the infant often exceeding those of the mother[254, 280-282]. The landmark multi-centre ERA study, including 80 pregnant women who received anti-TNF therapy in pregnancy, demonstrated that infliximab levels in umbilical cord blood were 1.97 times the mother and adalimumab levels 1.21 times greater[254]. The ERA study also showed that infant anti-TNF levels were inversely related to the duration since the last intrapartum dose [254]. Consistent findings regarding placental transfer have been reported in a subsequent Dutch cohort study [282].

Furthermore, from the ERA study we learnt that infliximab and adalimumab remained detectable in exposed infants for a median 7.3 and 4.0 months, respectively [254]. Despite this prolonged clearance time, the rate of infections up to one year of age was not increased in infants exposed to anti TNF monotherapy. Infant infections were, however, higher in infants exposed to combination therapy with anti-TNF and thiopurine medications (relative risk 2.7, 95% CI 1.09–6.78)[254]. Similar findings have been demonstrated in the PIANO cohort, with higher infliximab and adalimumab levels in infants compared to mothers and infant clearance times of six months reported for anti-TNF drugs[281]. Data from the PIANO registry has also shown an increased infection risk in infants following intrauterine exposure to combination therapy but not with anti-TNF monotherapy [180]. The PIANO registry data presented to date, however, has shown no increased infant infection risk up to 12 months of age associated with anti-TNF exposure in the last 10 weeks of pregnancy[272]. Both the ERA study and the PIANO registry have also shown normal infant development to 12 months of age[254, 283].

These data regarding infant and childhood infections have been echoed in recent large cohorts. The multicentre, retrospective TEDDY cohort, which included 388 children with antenatal anti-TNF exposure, did not show an increase in serious infections over a mean follow up of four years when compared to unexposed children born to mothers with IBD [284]. Similarly, the large French health database study (EVASION) also detected no increased infection risk in the first year of life in infants exposed to anti-TNF *in utero* (n=799 children)[275]. Additionally, preliminary follow up data from a pilot study planned as an extension of the PIANO registry, including 104 children (82 exposed to a biologic agent and/or thiopurine) aged 5-10 years, reported no septic complications or malignancies [285].

Likewise, infant vaccine response to inactivated vaccines does not appear to be affected by intrauterine anti-TNF exposure despite the presence of detectable anti-TNF levels in exposed infants. Beaulieu et al reported vaccine titres amongst infants born to 50 women enrolled in a small sub-study from the PIANO registry, with no significant difference in serologic response to the Haemophilus influenzae type b (Hib) vaccine and tetanus toxoid in biologic exposed compared to unexposed infants of mothers with IBD [286]. However, live vaccines should be avoided in the setting of detectable anti-TNF levels in infants; there has unfortunately been a case report of an infant death due to disseminated BCG following live vaccination at three months after intrauterine infliximab exposure[287].

Similarly, limited longer-term follow up data have shown developmental outcomes equivalent to the normal population in infants exposed to anti-TNF drugs. A study from the Czech Republic reported that 72 children at a median age of 35 months had similar psychomotor development compared to a control group of children born to women without IBD or anti-TNF exposure [288]. This study also showed no significant difference in infection, allergy or vaccination response between these two groups[288]. Further long-term data from the PIANO study has reported normal developmental milestones in children up to 4 years of age[283, 289].

In conclusion, there is no current evidence of harm related to continuing anti-TNF into the third trimester. Infant infection, development and response to inactivated vaccines are equivalent to unexposed populations. While increased disease flares have been observed when discontinuing anti TNF before 24 weeks [275], other studies have shown no effect on maternal disease activity when stopping anti-TNF before 25 to 30 weeks gestation [290-292]. However, a recent large retrospective database study has analysed the risk of disease flares in women with IBD in steroid-free remission who discontinued infliximab 'early' in pregnancy (more than 90 days before delivery) compared to those who continued infliximab 'late' in pregnancy (within 90 days of delivery)[293]. This study, including 68 patients in the early pregnancy infliximab discontinuation group and 318 patients in the late group, showed that discontinuation of infliximab more than 90 days before delivery resulted in an increased risk of disease flare with significantly more oral steroid prescriptions required for these patients as well an increase in pre-term birth[293]. Hence, when considering all of these data, patients in sustained remission can choose to have the last intrapartum anti-TNF dose administered at around week 30 for infliximab and week 34 for adalimumab, in order to maintain disease remission in the

mother but minimise foetal drug exposure [277]. For women with ongoing disease activity or those who have not been in sustained remission, anti-TNF therapy can safely be continued throughout pregnancy, given that neonatal outcomes are unaffected.

1.2.10.11 Vedolizumab in IBD

Vedolizumab is a humanised IgG1 monoclonal antibody that binds to the alpha-4-beta-7 integrin and prevents interaction with mucosal cell adhesion molecule-1 (MAdCAM-1), selectively inhibiting migration of lymphocytes into the gut [294].

The GEMINI trials have demonstrated the effectiveness of vedolizumab for induction and maintenance therapy in both UC and Crohn's disease[295, 296]. Since its inception around five years ago, vedolizumab is being increasingly used for moderate to severely active IBD. Vedolizumab is associated with less systemic side effects given its gut-selective mode of action and also has low immunogenicity compared to anti-TNF agents [261, 297, 298].

1.2.10.12 Vedolizumab in Pregnancy

Initial data relating to vedolizumab in pregnancy remain somewhat limited as it is a relatively new agent in the IBD treatment paradigm. In comparison to the anti-TNF agents, pregnancy data in the case of vedolizumab is restricted by the limited number of pregnancies to date and shorter follow up of infant outcomes.

Like the anti-TNF drugs, vedolizumab is an IgG1 monoclonal antibody and, as such, is not expected to cross the placenta until at least 16 weeks gestation[279]. In keeping with this knowledge, both the animal studies and limited human data presented have not shown an increased risk of congenital abnormalities associated with vedolizumab. Animal data is available from pregnant monkeys administered high dose vedolizumab, which found no evidence of teratogenicity or abnormalities in overall development in infants up to six months of age[299]. Human data from the vedolizumab clinical development trials included 24 pregnancies with five elective terminations, four spontaneous abortions and eleven live births documented [300]. There was a congenital corpus callosum agenesis anomaly reported, however this was in the setting of a single vedolizumab dose 79 days prior to conception in a healthy volunteer with extensive obstetric risk factors[300].

More recently, a retrospective multi-centre study was conducted in Europe (the CONCEIVE study), which reported outcomes in 79 vedolizumab exposed pregnancies and compared them to outcomes in those exposed to anti-TNF or combination anti-TNF and immunomodulator therapy [301]. Given that MADCAM1 is expressed in the human placenta during the first trimester, there has been theoretical concern regarding a potential risk of miscarriage associated with vedolizumab [302]. With its gut-specific mode of action, theoretically there is less concern regarding risk of infant infections following intrauterine vedolizumab exposure, except perhaps for gut-related illnesses. In the CONCEIVE study, the miscarriage rate was 16%, which was similar to the other groups and also similar to the background population. There were 64 live-born infants in the vedolizumab exposed group including three (5%) with a congenital abnormality and two (3%) who were small for gestational age [301]. Only three (5%) vedolizumab exposed infants in this relatively small study had documented infections up to one year of age requiring hospitalisation, none of which were severe gastroenteritis[301]. There were no significant differences in these pregnancy and infant outcomes compared to the other groups who were exposed to anti-TNF therapy or combination therapy.

Ongoing prospective data will be important to confirm these initial findings, which have thus far not shown an increase in adverse pregnancy outcomes or infant infections associated with vedolizumab.

1.2.10.13 Ustekinumab in IBD

Ustekinumab is an IgG1 monoclonal antibody that targets the p40 subunit on the IL-12 and IL-23 cytokines [303]. It was initially used in psoriasis and more recently has been approved for use in Crohn's disease in Australia.

The recent UNITI and UNIFI trials have demonstrated the efficacy of ustekinumab for the induction and maintenance of moderately to severely active Crohn's disease and UC[304, 305]. Maintenance ustekinumab is administered at a dose of 90 mg subcutaneously every 8 weeks. Like vedolizumab, immunogenicity appears low and the infective risk is lower than anti-TNF in large psoriasis registries[261, 303].

1.2.10.14 Ustekinumab in Pregnancy

Being the newest biologic agent to be approved for use in patients with IBD, data relating to use of ustekinumab in pregnant women with IBD are very limited. Animal

study data, which included high-dose ustekinumab administered to cynomolgus macaques, showed no adverse foetal effects[306].

The majority of data relating to ustekinumab in human pregnancies pertain to women treated for psoriasis, for which a lower dose is generally prescribed. In addition, the drug was commonly ceased around or soon after conception, rather than continued throughout pregnancy. Nonetheless, a recent abstract has presented the available pregnancy outcome data reported to the manufacturer up until April 2019, including from registries and clinical studies[307]. This data reported 479 pregnancies resulting in 341 live births with exposure to ustekinumab within three months of conception or during pregnancy. However, only 12.1% of women continued the drug throughout pregnancy[307]. The rates of spontaneous abortion (18.4%) and congenital abnormalities (3.8%) were similar to the general population and did not differ between psoriasis and IBD cases[307]. The risk of infant infections is unknown, and, similarly, there are no data yet relating to childhood development.

1.2.10.15 Tofacitinib in IBD

Janus Kinase (JAK) inhibitors are newer emerging therapies targeting multiple cytokine signalling pathways in IBD. Unlike the biologic proteins, which require intravenous or subcutaneous delivery, they are orally-administered small molecule drugs, which would be expected to cross the placenta from conception[308]. Various JAK inhibitors are in development for different inflammatory conditions, with only tofacitinib currently approved for use in moderate to severe UC.

Tofacitinib is a JAK1 and JAK3 inhibitor, which was initially studied and used for rheumatoid arthritis and psoriasis. The OCTAVE trials have since demonstrated the efficacy of tofacitinib for both induction and maintenance therapy in moderate to severe UC[309]. It is administered at a dose of 5mg or 10mg twice daily. Adverse drug reactions include elevated cholesterol levels and increased infection risk, such as for opportunistic herpes zoster infection with 10mg twice daily dosing[309].

1.2.10.16 Tofacitinib in Pregnancy

Tofacitinib was found to be teratogenic in animal studies at supratherapeutic doses and is therefore contraindicated in pregnancy at present. Feticidal and teratogenic effects were observed in pregnant rats and pregnant rabbits who received tofacitinib during

organogenesis at exposures 73-times and 6.3-times greater than the 10mg twice daily human dose, respectively[310].

Human data regarding tofacitinib exposure in pregnancy are extremely limited. Eleven cases of maternal exposure in the first trimester were reported from tofacitinib clinical trials in women with UC[311]. Pregnancy outcomes documented in these cases were similar to both the general population as well as the limited data from clinical trials and post marketing experience in rheumatoid arthritis and psoriasis cases[311]. Ongoing pregnancy safety information is required from prospective registry data before conclusions can be made regarding tofacitinib use in human pregnancy.

1.2.10.17 Cyclosporine in IBD

Cyclosporine is a calcineurin inhibitor that can be used as an effective rescue therapy in steroid-refractory acute severe UC as an alternative to infliximab. Cyclosporine has a rapid onset of action and short half-life, however is also associated with a risk of complications including seizures and nephrotoxicity [195].

1.2.10.18 Cyclosporine in Pregnancy

Cyclosporine must often be continued during pregnancy in women with a history of other autoimmune conditions or organ transplants [312]. A large meta-analysis has reported no difference in the prevalence of major malformations in cyclosporine-exposed newborns compared to the background population [312].

In IBD, cyclosporine has a role as rescue therapy to avoid colectomy in severe colitis during pregnancy [313, 314]. In non-IBD patients, use of cyclosporine in pregnancy has been associated with complications such as pre-term birth, maternal hypertension and pre-eclampsia [315]. However, it is not clear whether these complications are related to maternal disease or cyclosporine, and as such cyclosporine should be considered for women with severe refractory colitis in pregnancy.

1.2.10.19 Surgery in IBD

Surgical resection may be indicated in UC and Crohn's disease, for example in severe UC that fails to respond to medical therapy, when a proctocolectomy and eventual ileal pouch-anal anastomosis is most commonly performed[316]. Surgery in Crohn's disease may also be performed when medical therapy is unable to achieve disease control, for example in symptomatic ileal stenosis or penetrating disease[317].

1.2.10.20 IBD Surgery in Pregnancy

There are extremely limited data regarding the safety of IBD surgery during pregnancy. Abdominal surgery has been linked to spontaneous abortion and pre-term birth in retrospective studies, but these data do not separate the confounding effects of underlying disease states and indication for surgery [156, 318].

When the mother is acutely unwell, this is of greater risk to maternal and foetal safety and hence the indications for urgent surgery during pregnancy are the same as for non-pregnant IBD patients. When surgery is required for severe, refractory disease with concerns regarding complications such as toxic megacolon, obstruction, abscess or perforation, it should not be delayed due to pregnancy. The risks of surgery need to be weighed against the risk of active disease, and should be performed when indicated with multidisciplinary team involvement, regardless of timing in pregnancy.

1.2.10.21 Conclusion

Given the effectiveness of combination therapy in achieving remission in patients with moderate to severe Crohn's disease and refractory UC, the current treatment approach in IBD is to intervene early and aggressively with immunomodulator and/or biologic therapies. However, with this shift in the treatment paradigm, many more women with IBD are exposed to these therapies during pregnancy.

The current literature demonstrates that 5-ASAs, thiopurines and anti-TNF drugs are not associated with adverse pregnancy outcomes, while the data are more limited regarding vedolizumab and ustekinumab, but their risk is also considered to be low. The main driver of adverse pregnancy outcomes is active disease, supporting the continuation of maintenance medical therapies in IBD, especially in patients with predictive risk factors for severe IBD. Thus, as drug therapies and treatment strategies have continued to evolve, there is a continuing need to use these emerging drug therapies during pregnancy, albeit with less established pregnancy safety data available for the newer drugs.

Table 1.3 Summary of Risks of Adverse Maternal and Foetal effects of Common IBD Medications Prescribed during Pregnancy

Drug	Fertility/ Miscarriage	Congenital anomalies	Intrauterine growth	Infant infections	Infant development	Relevant studies in IBD
Corticosteroids	No	No	No *(likely related to disease activity)*	Possible trend at four months of age	No	Truta et al *n=546 (in abstract form)*[227] Mogadam et al *n=102* [225] PIANO registry *n=979 (total IBD patients, in abstract form)*[226]
Aminosalicylates	No	No	No	Unknown but no theoretical concerns	Unknown but no theoretical concerns	Meta-analysis Rahimi et al *n=642* [252]
Thiopurines	No	No	No	Increased in combination with anti-TNF	No	Meta-analysis Hutson et al *n=482* [247] Casanova et al *n=187* [249] PIANO registry *n>335* [180] Kanis et al *n=108* [253]
Anti-TNF	No	No	No	Increased in combination with thiopurine	No	Meta-analysis Shihab et al *n=957* [271] PIANO registry *n>500* [180] EVASION Study *n=799* [275] ERA study *n=80* [254] TEDDY cohort *n=388* [284]
Vedolizumab	Theoretical risk, not shown thus far *(limited data)*	No *(animal studies, limited human data)*	No *(limited data)*	No *(limited data)*	Unknown	Mahadevan et al (clinical trials data) *n=24* [300] CONCEIVE study *n=79* [301]
Ustekinumab	No *(limited data)*	No *(animal studies, limited human IBD data)*	Unknown	Unknown	Unknown	Geldhof et al *n=135* [307] *(in abstract form)*

1.2.11 IBD Medications and Lactation

1.2.11.1 Introduction

Breastfeeding itself brings positive effects for both mother and child, particularly in the setting of IBD. Breastfeeding in infancy brings the potential associated benefits of reducing gut microbial dysbiosis and protecting against IBD in later life [319]. Lactation is considered compatible with the majority of IBD medications, with the exception of methotrexate and tofacitinib. The rate of breastfeeding in the PIANO registry was 75% (591 out of 787 patients), however, women on biologic therapy and/or thiopurines were less likely to breastfeed than those not on these medications, while women with more active disease breastfed for a shorter duration [320].

1.2.11.2 Corticosteroids During Lactation

Corticosteroids at low doses are excreted into breastmilk in small amounts. However, prednisolone when required at higher doses above 20mg can result in higher levels in the breastmilk, and hence it has been recommended to avoid breastfeeding for three to four hours after high dose prednisolone[263]. This recommendation stems from an old study from Sweden, which included six lactating women on prednisolone therapy at doses from 10-80mg daily. Women had blood and breastmilk prednisolone concentrations measured over six hours following a dose of prednisolone, and milk concentrations were approximately 10-20% of serum levels[321]. This study found that peak milk and serum prednisolone concentrations occurred approximately one hour after a dose was given, then concentrations decline and are usually undetectable in the breastmilk after four hours. Budesonide has minute levels in breastmilk[321].

1.2.11.3 Aminosalicylates During Lactation

5-ASA medications are excreted into the breastmilk at low levels[322]. Rarely in case reports, diarrhoea has been reported in exposed infants, but 5-ASA medications are generally well tolerated and are compatible with lactation [263].

1.2.11.4 Thiopurines During Lactation

Thiopurines including azathioprine and mercaptopurine can be detected at low levels in breastmilk. A Danish study included eight women with IBD who were prescribed 75-200mg of azathioprine and underwent measurement of 6-meraptopurine concentrations in plasma and breastmilk [323]. Plasma concentrations peaked within

three hours of the dose and breastmilk concentrations within four hours, with significantly lower concentrations in breastmilk [323]. Individual peak values in plasma and breastmilk both showed a wide inter-individual variation, reflecting the large variation in drug bioavailability. However, based on the maximum concentration detected in breastmilk in this study, which occurred in a patient receiving 200mg azathioprine daily, the infant daily dose via breastfeeding equated to <1% of the maternal dose [323].

While reassuring, measurement of 6-mercaptopurine in breastmilk does not assess the active metabolite, 6-thioguanine nucleotide (6-TGN). A small study from New Zealand aimed to address this by measuring 6-TGN concentrations in four lactating women taking azathioprine and in their three-month-old infants [324]. Women had therapeutic 6-TGN levels, whereas in the exposed infants, no 6-TGN or 6-MMP was detected in infant blood [324].

1.2.11.5 Anti-TNF Agents During Lactation

Monoclonal antibodies used in the treatment of IBD are all considered compatible with breastfeeding. This is due to low levels detected in breastmilk and their molecular structure, which is thought to preclude oral absorption[263]. Ingestion via breastmilk is likely to result in degradation by infant gastric acids and poor oral absorption in the gastrointestinal tract[325].

Once again, the most comprehensive lactation data in the literature pertaining to monoclonal antibodies used in IBD relates to anti-TNF therapies. In one small case series, infliximab levels were detected in the breastmilk of three lactating women with Crohn's disease at levels <0.5% of maternal levels [326]. In another case report, adalimumab levels were detected in the breastmilk of a lactating mother, with a peak concentration at six days post dose and levels <1% of maternal serum levels [327].

A more recent multicentre study performed as part of the PIANO registry by Matro et al, assessed drug level concentrations the breastmilk of 72 lactating mothers receiving biologic medications, including 29 women on infliximab. The maximum breastmilk infliximab concentration was detected between 24 to 48 hours post infusion (range 0.15–0.74 ug/mL)[320]. Nineteen/29 (66%) mothers had at least one breastmilk sample with a detectable infliximab concentration and in those women who submitted samples

at 168 hours post infusion, five out of eight women had detectable breastmilk concentrations[320].

In the same study, 21 women on adalimumab had breastmilk samples collected and only two had detectable levels[320]. However, this study obtained breast milk samples out to only 48 hours following adalimumab dose for most mothers, which may limit detection in breastmilk given that peak concentration can occur up to around six days. Nonetheless, peak breastmilk adalimumab concentrations were seen 12-24 hours post dose with concentrations ranging from 0.45–0.71ug/mL in these two women[320]. In the seven women who did provide breastmilk samples out to seven days, no adalimumab was detected[320].

Survey data from the PIANO registry study, which included 824 women with IBD, showed that breastfed infants exposed to biologic medications or combination therapy had similar milestone achievements and infection rates compared to unexposed infants or infants who were not breastfed [320].

1.2.11.6 Vedolizumab During Lactation

Similar studies regarding vedolizumab in lactation also show very low levels in the breastmilk and no additional concerns regarding infant outcomes.

A study of five mothers with IBD who were breastfeeding while receiving vedolizumab therapy has shown that levels in breastmilk were low. Vedolizumab levels in breastmilk peaked at days three to seven after vedolizumab infusion, and the peak milk concentration in breastmilk was less than 1% of the maternal serum concentration[328]. In all five infants, normal developmental milestones were recorded at three-and-a-half to ten months of age[328]. Similar findings were reported in another small series of five vedolizumab-treated breastfeeding women, with breastmilk vedolizumab levels again not surpassing 1% of maternal serum levels [329]. Normal infant development was reported up to ten months of age with no increase in infections.

1.2.11.7 Ustekinumab During Lactation

Similarly, in limited data to date, ustekinumab has been detected at low levels in breastmilk. The multicentre study performed as part of the PIANO registry included six ustekinumab-treated women with IBD who had breastmilk levels measured.

Ustekinumab levels were detected in four out of six samples with peak concentrations ranging from 0.72–1.57 ug/mL at 12-72 hours after the injection [320].

1.2.11.8 Cyclosporine During Lactation

Data regarding lactation in relation to cyclosporine is extremely limited. Cyclosporine is known to be excreted in breastmilk and infant blood cyclosporine concentration is usually low, although therapeutic blood concentrations can occur following exposure through breastmilk [330]. It is thought to be compatible with breastfeeding but monitoring of infant levels is advised in expert recommendations [263].

1.2.11.9 Conclusion

Lactation is considered safe with most IBD medications, including prednisolone, 5-ASA therapy, thiopurines and monoclonal antibodies, although limited studies exist in the literature[263]. Low levels of these medications can be detected in breastmilk; however, this is not thought to be clinically significant and women with IBD should be supported to enable breastfeeding. Additionally, biologic medications in breastmilk are not considered to be orally absorbed.

1.3 Exploration of Pregnancy-Related Concerns Amongst Women with IBD

1.3.1 Introduction

Amid the increasing prevalence of IBD and the expansion of immunosuppressant and biologic medications used during pregnancy, it is pertinent to recognize and explore the concerns of women with IBD who are pregnant or wishing to conceive, and in turn improve the pregnancy-related education delivered by treating gastroenterologists.

Despite the increasing and reassuring pregnancy data regarding IBD medications, many women harbour fears regarding harmful foetal effects relating to medication use in pregnancy. A study by Mountifield et al, which surveyed 219 women with IBD by postal questionnaire, highlighted that women with IBD had greater concerns regarding the effect of IBD medications than active IBD in pregnancy[14]. A questionnaire-based Australian study by Selinger et al found that reluctance to use medication during pregnancy and consideration of voluntary childlessness were prevalent in a significant proportion of women with IBD[131]. This study also observed that these women were commonly concerned regarding infertility, a finding which was noted in a further study

by Mountifield et al including 255 Australian patients ages 18-50 years, again surveyed by postal questionnaire[130]. Similar findings have been documented in another European questionnaire-based study, which also found that women with IBD have misperceptions about fertility and pregnancy[331].

1.3.2 Qualitative Research Relating to IBD and Pregnancy

Qualitative research enables an informed understanding of the complexity of the experiences of women with IBD, allowing physicians to explore the lived experience of a health condition, gain broader insights beyond the biomedical paradigm and optimise clinical interactions[332]. While quantitative data based on physician-designed questionnaires has been represented in the literature, there is a lack of in-depth qualitative data examining maternal concerns and experiences amongst women with IBD in the current era of widespread immunomodulator and biologic medication use[333].

A study conducted in the United States in 2013 indicated that over half of this cohort of women with IBD (n=129) reported disease-related pregnancy concerns such as the effect of IBD medications, however the nature of these concerns was not able to be explored in detail through this telephone survey[334]. A more recent qualitative study conducted in the United Kingdom including 22 mothers with IBD identified that both having IBD and being a mother impacted participants' sense of self and demanded similar lifestyle changes such as adapting to "unpredictability"[335]. However, while this study addressed the practical difficulties of motherhood and having IBD, it did not explore issues relating to IBD and pregnancy such as medication concerns.

Another recent American study incorporated thematic analysis of social media and online forum posts that related to patients' experiences of IBD medication use during the reproductive period[336]. Fears of IBD medications in pregnancy were highlighted including general concerns regarding birth defects and risk of miscarriage [336]. This study noted that many patients seemed frustrated by unsatisfactory counselling from their gastroenterologists and insufficient knowledge from some obstetric care providers[336]. Meanwhile, an interview-based study of eight Japanese women who had IBD and children ranging in age from seven months to seven years reported that these women predictably faced adversity at times of IBD flares[337]. Similarly, these patients also reported receiving inconsistent information from treating clinicians, as well as an inability to find accurate information on the internet about IBD medications[337].

1.3.3 Conclusion

Women are frequently worried about the adverse impact of medication or disease on fertility and pregnancy, when in fact fertility is generally normal in IBD patients and medications are considered safer than active IBD. A deeper understanding of how women with IBD inherently feel about and experience pregnancy is required to establish what drives their concerns. The patient perspective may influence a wide range of outcomes including compliance with medication and therefore, disease control; whether to have more children and when; and maternal psychological health across pregnancy.

1.4 Education and Psychological Care of Women with IBD in Relation to Pregnancy

1.4.1 Introduction

Patients with IBD require education in order to actively participate in clinical decision making. This is particularly crucial around the time of pregnancy, when patients have to wrestle with these additional pregnancy-related concerns and considerations. Accordingly, there has been growing interest in promoting education regarding pregnancy for IBD patients.

1.4.2 Pregnancy-related Knowledge in IBD

It is known that a lack of pregnancy-related knowledge can be associated with negative views surrounding having children and even an increased rate of voluntary childlessness amongst women with IBD[131, 338]. Multiple studies in the literature have shown that patients with IBD have poor levels of knowledge regarding the safety of maintenance IBD medications and the importance of active IBD being treated prior to and during pregnancy[13, 338-340]. The first of these studies in 145 women with IBD was used to validate the Crohn's and Colitis Pregnancy Knowledge Score (CCPKnow), and found that around 50% of women had poor knowledge levels using this tool. More recently, a large prospective global study also found that women with IBD had limited pregnancy-related knowledge[338].

Restricted knowledge has been linked to poor medication compliance. Studies in women with both UC and Crohn's disease by Julsgaard et al have found non-compliance with maintenance therapy during pregnancy occurs frequently, and a common reason for non-compliance in pregnancy is the fear of medication adverse

effects on the baby[341, 342]. Women who reported receiving pre-pregnancy counselling had higher rates of medication compliance in pregnancy[342]. In a previous survey from Canada of female IBD patients of childbearing age, almost 20% of respondents reported stopping a prescribed IBD medication while attempting to conceive or while pregnant and only half said they received counselling regarding IBD medications in pregnancy[343]. Another recent retrospective Canadian study analysed medication adherence in pregnancy using dispensed prescription medication data[344]. Similarly, this study found that 25% (41/159) of women with IBD who had been adherent in the year prior to pregnancy were either not adherent or ceased their medications during pregnancy[344]. However, details regarding antenatal counselling and education were not included in that study.

It has been shown that education and counselling can improve pregnancy-related knowledge. Previous Australian work by Mountifield et al, has demonstrated that pregnancy knowledge can improve when re-tested immediately after a once-off group education session using the CCPKnow tool, although the longer-term recall of this knowledge is not known[345]. In addition, this study found that less than half of those with IBD received information regarding reproductive matters from their specialist, with many relying on their general practitioner (GP) for information[345]. However, it is known that a significant proportion of GPs are uncomfortable in general with managing IBD and also with many commonly used IBD medications[346]. The CCPKnow tool has also been used to demonstrate that GPs and obstetricians have inadequate pregnancy-related knowledge in IBD including use of IBD medications[347].

More recently, a small number of case studies have demonstrated the possible benefit of IBD pregnancy clinics where women with IBD are reviewed regularly prior to conception and during pregnancy [348, 349]. A recent prospective Dutch study demonstrated that a specialised pre-conception and pregnancy care clinic, including follow-up before, during and after pregnancy, can reduce disease relapse rates during pregnancy, and rates of low birthweight[349]. However, this approach is costly, labour intensive and may disrupt the continuity of patient care.

In addition to the arrival of dedicated IBD pregnancy clinics, a recent Canadian study presented the value of an online intervention for improving pregnancy-related knowledge. This study, including 78 male and female patients with IBD who completed pre and post-intervention pregnancy knowledge scores, showed that an online educational portal can improve patient knowledge [350]. Online education may provide an

adjunct to the counselling delivered as part of clinical care with the treating gastroenterologist.

Pregnancy-related counselling is indeed recommended by all major international guidelines regarding IBD management in pregnancy[49, 156, 277]. However, there is no specific advice about how this should be implemented and penetration of these guidelines has appeared limited[331]. Despite increased awareness, not all women have access to pre-pregnancy counselling or protocolised IBD pregnancy clinics and the availability and quality of counselling is variable. Questions therefore remain regarding when, by whom and how pregnancy and IBD information should be delivered, as well as the impact of this information on patient wellbeing.

1.4.3 Psychological Health and Quality of Life in Women with IBD in Relation to Pregnancy

In the context of pregnancy-related fears, concerns and physiological adaptations, it is conceivable that women with IBD may have significant depression or anxiety, which may affect health-related quality of life (HRQoL). Notably, it has been shown that in the general IBD population, improved disease-related knowledge is associated with greater anxiety levels, and that stress and anxiety can drive reduced HRQol in patients with IBD[351, 352]. However, the potential impacts on psychological distress and quality of life in women with IBD who are pregnant or planning a pregnancy remain undefined.

The concept of the brain-gut axis and the association between IBD generally and mental illnesses such as anxiety and depression has now been well recognised[353-355]. The Hospital Anxiety and Depression Scale (HADS) is an instrument that has been used extensively to identify anxiety and depression in patients with chronic health problems including IBD[356]. Anxiety and depressive symptoms are identified more commonly in IBD patients than the general population, and female gender has been associated with worse HADS scores in patients with IBD[357]. It is also appreciated that the perinatal period can, in the general population, be associated with increased emotional distress and mental illness. A recent meta-analysis found a prevalence of 18% for self-reported anxiety symptoms in pregnant women during the first trimester [358]. In relation to IBD, there has been a recent large retrospective study measuring mental health diagnoses across pregnancy. This study, based on health administrative data, found an increased risk of new onset mental illness in the postpartum period in women with IBD[359].

Similarly, patients with IBD can have impaired quality of life and in addition pregnancy itself can affect health-related quality of life [360, 361]. HRQoL has been shown to be adversely affected in patients with IBD in a recent meta-analysis[360].Recently, the assessment of quality of life has become a frequently measured endpoint in clinical trials in IBD, most commonly using the disease specific IBDQ questionnaire[362] and the SF-36[363] as a generic HRQoL questionnaire. Numerous studies utilising these tools have demonstrated worse HRQoL in patients with IBD compared to healthy controls. In particular, active disease and female gender are associated with lower HRQoL scores[357].

It has also been highlighted in a large survey study that IBD, particularly in women, can disrupt quality of life and sexuality, even when the disease is in remission[364]. In a separate study, women were more likely than men to experience negative effects of their disease on body image, libido, and sexual activity[365]. Additionally, In the setting of the physical and emotional adaptations occurring during normal pregnancy, HRQoL scores in pregnant women can be poorer than in non-pregnant women[361]. One small, retrospective study has examined HRQoL across pregnancy in patients with IBD. In this study of 32 patients, HRQoL scores improved in half of these patients, remained stable in 14 (44%) and in 2(6%) worsened during pregnancy[366]. Meanwhile, recent data from a small Canadian cohort, presented in abstract form, has shown that HRQoL was reduced in women with clinically active IBD in late pregnancy[367].

1.4.4 Conclusion

Pregnancy itself is a significant life event for any woman and can be associated with considerable psychological challenges. In the context of IBD, where there are additional pregnancy-related management considerations and patient concerns relating to chronic illness, women may be particularly susceptible to mental illness and reduced quality of life in the perinatal period. Prospective data relating to potential effects on a woman with IBD's psychological wellbeing and health-related quality of life (HRQoL) prior to conception and during pregnancy are lacking. Enhanced pregnancy knowledge and psychological care are warranted in this vulnerable patient group. The impact of pregnancy-relating counselling on patient knowledge, psychological wellbeing, quality of life and pregnancy outcomes has not been evaluated in the current literature.

1.5 Assessment of Disease Activity in Pregnancy

1.5.1 Introduction

In light of the potential variability and unpredictability in disease activity and adverse impact of active disease on pregnancy, individual disease activity monitoring throughout pregnancy is paramount. However, evaluation of IBD during pregnancy can be difficult, as the standard methods of assessment are not validated during pregnancy or are ideally avoided due to potential risks to the foetus[368]. Evidence regarding markers of inflammation and assessment during pregnancy in women with IBD are somewhat limited in the literature, but available data are summarised below and in Table 1.4.

Clinical symptoms of IBD are challenging to interpret in the setting of pregnancy. It is known that the majority of women experience gastrointestinal symptoms during pregnancy, regardless of IBD history [369]. Symptoms of IBD can overlap with pregnancy-related symptoms, such as fatigue, nausea and bloating. Hormonal fluctuation has been reported to alter symptom severity in women with IBD [370]. Additionally, bowel motility can be slowed in pregnancy[369], which may conceal symptoms of active disease.

1.5.2 Serological Biomarkers in IBD During Pregnancy

Routinely available blood tests such as CRP, haemoglobin and albumin are frequently used as markers of inflammatory activity in IBD, however these values can change during pregnancy, impeding their utility. Studies have shown increased levels of IL-6 cytokines in pregnancy and, similarly, CRP can be elevated even in normal pregnancy [171, 371]. In a study by Klajnbard et al, including 391 healthy Caucasian women with uncomplicated pregnancies, CRP levels were mostly stable throughout pregnancy but were higher than the standard reference range [372]. Higher CRP levels have also been documented in the setting of maternal obesity, pre-eclampsia and pre-term labour[373-375]. In addition, other serological biomarkers including albumin and haemoglobin are affected by physiological adaptations in pregnancy; albumin levels decrease throughout normal pregnancy and mild anaemia with a haemoglobin down to 110g/L is normal in the pregnancy state[372, 376].

1.5.3 Faecal Calprotectin During Pregnancy

Faecal calprotectin is widely used as a sensitive marker of inflammation, particularly in colonic IBD. Although it is generally more sensitive and specific than CRP for identifying IBD activity in general, data regarding faecal calprotectin are more challenging to interpret in pregnancy. Knowledge in this sphere is restricted by the unavailability of routine endoscopy in pregnant patients as a gold standard and the limitations of using the clinical assessment as a comparison, particularly during pregnancy due to the reasons outlined previously. However, several studies have demonstrated that faecal calprotectin is likely to remain accurate in pregnancy for detecting active disease[377, 378].

The first of these includes the sub-analysis of 46 pregnant women with IBD from the ERA study, which showed that a faecal calprotectin >250μg/g correlated with active disease when using the Physician Global Assessment[379]. A limitation of this method, however, is that the faecal calprotectin result may not necessarily be independent to the clinician's assessment. Another study, presented in abstract form, included 75 patients with IBD and found that calprotectin >200μg/g had a sensitivity and specificity of over 80% for detecting disease activity (based on clinical assessment which included CRP and disease activity indices), but an elevated calprotectin level did not predict relapse in this study[380]. More recently, the retrospective study by Kammerlander et al, has shown that faecal calprotectin concentrations are higher in patients deemed to have clinically active disease[381]. There is also evidence in the literature that in women without IBD, calprotectin is not increased in pregnancy, suggesting that unlike CRP, calprotectin is not altered by the physiological changes of pregnancy [382], and remains a useful test for monitoring disease activity.

1.5.4 Imaging in IBD During Pregnancy

Imaging in pregnancy for women with IBD is complicated by safety concerns for the foetus as well a lack of IBD-specific pregnancy data. Abdominal and pelvic CT scans are associated with significant ionizing radiation, which at high doses has been linked to malformations, neurodevelopmental abnormalities and carcinogenesis[383]. The foetus is most susceptible to malformations during the period of major organogenesis and early foetal development (2-15 weeks gestation) and with exposure to doses above 100mGy, based on animal data [384, 385]. The most sensitive time for risk of neurodevelopmental abnormalities is 8-15 weeks gestation and again with radiation doses of at least 100mGy [385]. The estimated foetal dose exposure from a single

abdominal CT scan is 35mGy and up to 50mGy for a pelvic CT [386]. The risk of childhood cancer is thought to increase with increasing doses of radiation but remains low overall[386].

In relation to non-contrast MRI, there is no associated ionising radiation and there been no reported adverse effects of MRI exposure on the developing human foetus[386, 387]. There are theoretical concerns regarding the effects of exposure to the electromagnetic field and damage to foetal hearing. However, a recent large, retrospective Canadian study, which identified births of more than 20 weeks gestation from 2003 to 2015 and compared first-trimester MRI (n=1,737) to no MRI exposure (n=1,418,451), found no significant increase in the risk of neonatal death, congenital anomalies, cancer or hearing loss following first trimester MRI [388].

For patients with IBD, the usual MR enterography protocol incorporates use of the contrast medium gadolinium. There are foetal safety concerns related to gadolinium, which has been found to be teratogenic in animal studies at high doses[387]. As free gadolinium is toxic, it is given with a chelating agent. However, it is thought that gadolinium can cross the placenta and dissociate from this agent, remaining in the amniotic fluid where it can be swallowed by the foetus and then re-enter the circulation, resulting in prolonged exposure[389]. Interestingly, the same Canadian study assessing antenatal MRI exposure showed higher rates of rheumatologic, inflammatory and infiltrative skin conditions up to 4 years of age in those exposed to MRI with gadolinium (n=397) compared to no MRI exposure (adjusted hazard ratio, 1.36)[388]. However, this study did not include a control group who underwent MRI without gadolinium.

Given that the safety regarding gadolinium in pregnancy is uncertain, it is not recommended to be used in pregnancy. Although the optimal MR enterography protocol includes administration of gadolinium, it can be performed without gadolinium, and parameters other than contrast enhancement can be evaluated including bowel wall thickness and hyperintense signal on T2-weighted images [390]. Only one small study relating to patients with known or suspected Crohn's disease (n=9) has assessed the use of non-contrast MRI in pregnancy[391]. This very small study found that reliable diagnostic information could still be obtained using a modified MRI protocol without gadolinium[391]

Meanwhile, intestinal ultrasound, a radiation-free and generally non-contrast imaging modality, is notionally considered ideal for use in pregnancy[392]. However, practically,

there is concern regarding bowel views being impeded by the growing foetus. Hence, the accuracy and feasibility of intestinal ultrasound during pregnancy is yet to be established. There has only been one study documenting the use of intestinal ultrasound in 91 pregnancies in women with Crohn's disease but not UC[393]. This study reported clinical symptoms in relation to ultrasound findings, but did not incorporate faecal calprotectin, which is more reliable as a marker of disease activity[393].

1.5.5 Endoscopy in Pregnancy

Finally, endoscopy is rarely performed in pregnancy due to safety concerns for both other and foetus, as it is an invasive procedure and often requires anaesthetic sedation. Hence, data regarding endoscopy in pregnancy are limited, and tend to be retrospective or from small case series.

A recent Swedish population-based cohort study reported no increased risk of stillbirth or congenital malformation associated with any endoscopy during pregnancy, but did report an increased risk of preterm birth and small for gestational age infants [394]. However, although the risk of adverse pregnancy outcomes associated with endoscopy remained rare overall, this study was based on registry data and was not able to take into account indication for endoscopy or disease activity, which can affect pregnancy outcomes.

In relation to endoscopy in pregnant patients with IBD specifically, a systematic review and small prospective cohort study by de Lima et al concluded that lower gastrointestinal endoscopy appears to be of low risk, based on the limited available data in this field [395, 396]. This prospective study, including 42 patients who underwent 47 lower gastrointestinal endoscopies (35 sigmoidoscopies, 12 colonoscopies) during pregnancy, demonstrated no increase in adverse outcomes for the mother or the newborn relating to endoscopy when compared to controls matched based on age, medication and disease activity [395]. Similar findings from Mahadevan's group have been presented in regard to flexible sigmoidoscopy in pregnant IBD patients (n=48) in a retrospective cohort, with no adverse obstetric events reported[397].

1.5.6 Conclusion

Safe and accurate monitoring of disease activity during pregnancy is imperative, but not always straightforward. Faecal calprotectin is more useful than CRP, while endoscopy and computed tomography (CT) present potential concerns regarding risks

to the foetus, as does small bowel MRI with gadolinium. Ultrasound is an ideal and promising technique for use in pregnancy, however the accuracy and feasibility of GIUS for monitoring IBD during pregnancy has not been assessed.

Table 1.4 Summary of Available Biomarkers and Investigations for IBD During Pregnancy

Biomarker	Considerations in Pregnancy
Serum inflammatory markers	Values altered in normal pregnancy: - CRP in pregnancy: up to ~22 mg/L [372] - Albumin in pregnancy: down to ~23 g/L in late pregnancy [376] - Hb in pregnancy: down to 110 g/L [372]
Faecal calprotectin	Helpful to detect relapse; values normal in normal pregnancy [377, 378]
Radiographic imaging	Radiation risk associated with CT [386] Safety concerns regarding gadolinium for small bowel MRI with contrast [388] Intestinal ultrasound ideal modality in terms of safety, however feasibility and accuracy in pregnancy *unknown*
Endoscopy	Limited safety data in pregnancy; flexible sigmoidoscopy low risk if indicated to investigate severe distal colonic disease [395]

1.6 Maternal Thiopurine Metabolites in Pregnancy and in Exposed Neonates

1.6.1 Introduction

Despite good neonatal outcomes associated with IBD medications in pregnancy, clinicians and patients often aim to minimise maternal and infant exposure where possible without compromising maternal disease control. It is hypothesised that the physiological changes associated with pregnancy may alter the pharmacokinetics of medications in pregnancy, including thiopurines, which may in turn affect their efficacy and maternal-foetal safety.

1.6.2 Pharmacokinetics of Thiopurine Medications

Measurement of the thiopurine metabolites 6-thioguanine nucleotides (6-TGN) and 6-methylmercaptopurine (6-MMP) are important to guide therapy with thiopurine medications [239, 241]. 6-TGN and 6-MMP levels are associated with thiopurine efficacy and can predict toxicity [398]. 6-TGN levels >235 pmol/8x10^8 RBCs have been associated with therapeutic response in monotherapy, while 6-MMP levels >5700 pmol/8x10^8 RBCs are associated with hepatotoxicity[239].

Patients with intermediate or absent TPMT enzyme activity produce substantially higher levels of 6-TGN, which can result in profound myelosuppression[236]. Additionally, concomitant medications can alter thiopurine pharmacokinetics. 5-ASA medications can inhibit TPMT activity, and concurrent therapy with 5-ASA and thiopurine medications has been associated with increased 6-TGN levels [399].

1.6.3 Pharmacokinetics of Thiopurine Medications in Pregnancy

There is a paucity of data on the pharmacokinetic effects of pregnancy on thiopurine metabolism. One study by Jharap et al involving 30 women with IBD who were taking thiopurines during pregnancy, indicated that maternal 6-TGN levels decreased while 6-MMP levels showed a non-statistically significant increase across pregnancy[251]. It is possible that this may relate to pregnancy-induced changes in drug clearance or drug-metabolising enzymes, such as a potential increase in TPMT activity during pregnancy. However, further data are required to confirm the pattern of thiopurine metabolite levels in pregnancy.

1.6.4 Infant Clearance of Thiopurine Metabolites following Intrauterine Exposure

The small study by Jharap et al also assessed the placental transfer of thiopurine metabolites, documenting that infant 6-TGN levels were detected in infants at birth and were lower than maternal levels [251]. The time to clearance of thiopurine metabolites in exposed infants remains unknown and the potential association with neonatal anaemia remains unclear.

1.6.5 Conclusion

Further study is required in an expanded cohort in order to examine thiopurine pharmacokinetics during pregnancy and subsequent placental transfer, as well as to explore the potential association with neonatal anaemia. Additionally, neonatal thiopurine clearance time and the impact on haematological and liver function tests in neonates following *in utero* thiopurine exposure have not been studied. These data are necessary for safe yet efficacious treatment of mothers with IBD.

1.7 Therapeutic Drug monitoring of Infliximab, Adalimumab, Vedolizumab and Ustekinumab During Pregnancy

1.7.1 Introduction

The measurement of serum anti-TNF drug levels and anti-drug antibodies is now commonly employed in order to optimise the use of these drugs and hence therapeutic outcomes. However, the impact of pregnancy on biologic levels in patients with IBD is undefined.

1.7.2 Therapeutic Drug Monitoring of Anti-TNF Agents

A number of studies have shown a correlation between anti-TNF concentrations and improved outcomes in patients with IBD, supporting the role of therapeutic drug monitoring in anti-TNF therapy [400]. Recent consensus guidelines suggest aiming for a maintenance trough infliximab concentration above 3µg/mL and adalimumab concentration above 5µg/mL for luminal IBD [401] . It is known that the clearance of anti-TNF drugs can be increased by various factors including detectable anti-drug antibodies, increased body weight, lower albumin concentrations and more severe disease activity [402-404] .

Only one small Canadian study by Seow et al has documented anti-TNF drug levels in the pregnant population. This study, which included fifteen women with IBD who received infliximab and ten women treated with adalimumab, observed that infliximab levels increased during pregnancy[405]. Median trough infliximab levels of 8.5µg/ml, 10.31µg/mL and 21.03µg/mL in trimesters one, two and three, respectively were reported in this study. The authors found that after adjusting for albumin, CRP and BMI, maternal infliximab levels increased by 4.2ug/mL each trimester[405]. The mechanism behind this finding was unknown, and there was no significant difference in adalimumab levels noted during pregnancy.

The volume of distribution of monoclonal antibodies is relatively small and they remain mainly within the plasma and extracellular fluid due to their large molecular size[406]. During pregnancy, it is known that plasma volume increases by around 40-50%[406, 407]. However, it remains unclear whether the pharmacokinetics of anti-TNF medications are substantially altered in pregnancy and further data are required.

1.7.3 Therapeutic Drug Monitoring of Vedolizumab and Ustekinumab

The role of therapeutic drug monitoring for vedolizumab and ustekinumab remains undefined [297, 400].

Data regarding vedolizumab levels are emerging from clinical trials and real-world cohorts, and maintenance vedolizumab trough levels above 14ug/mL have been associated with improved patient outcomes including endoscopic remission[408]. There have been no studies evaluating vedolizumab levels during pregnancy to date.

In regard to ustekinumab, dose-exposure relationships have been described [409], however there are insufficient data to recommend therapeutic target concentrations. Only two case studies have reported ustekinumab drug levels in pregnancy, including one patient on standard 8-weekly ustekinumab continued until 30 weeks gestation and another on 4-weekly dosing until 33 weeks [410, 411]. In these two cases, ustekinumab trough levels appeared stable across pregnancy [410, 411].

1.7.4 Placental Transfer and Time to Clearance of Vedolizumab and Ustekinumab

Little is known about the placental transfer of vedolizumab and ustekinumab. Additionally, vedolizumab and ustekinumab have an uncertain time to clearance in exposed infants.

The unpublished PIANO registry data found that, unlike anti-TNF drugs, vedolizumab levels were actually lower in seven infants than in their mothers at delivery[412]. One other small case series of two mother-baby pairs also found that cord blood vedolizumab levels were lower than maternal levels[413]. The elimination half-life of vedolizumab is known to be longer than that of infliximab and adalimumab[414]. Follow up levels were only available in one of these infants in the case series, which showed a very low level of 0.10ug/mL at six months[413]. Birth outcomes were normal, as was infant development at 12 months of age and there were no hospitalisations required for infant infections in these two cases[413].

Similarly, data regarding the placental transfer of ustekinumab is scarce, however, as it is also an IgG1 molecule, the drug is thought to be actively transported across the placenta in the second and third trimesters[278, 279]. The PIANO registry data, presented in abstract form, included three patients on ustekinumab in pregnancy with the mean cord blood level being almost two-fold higher than the mean maternal level[412]. In the

case reports of two cord blood ustekinumab levels in patients with Crohn's disease treated with ustekinumab, the cord blood levels were also higher than the maternal serum level [410, 411]. The time to clearance is unknown.

1.7.5 Conclusion

Evidence regarding the pharmacokinetics of biologic medications in pregnancy is lacking. Placental transfer and time to clearance of vedolizumab and ustekinumab have not been established. An improved understanding of the impact of pregnancy on the pharmacokinetics of these drugs and the placental transfer of vedolizumab and ustekinumab is important for optimal disease control and maternofoetal outcomes in patients with IBD.

1.8 Overall Research Design

1.8.1 Overall Thesis Hypotheses

1. That pregnancy, a pivotal time in a woman's life, may be rendered more complex in the setting of IBD and IBD medications
2. Lack of knowledge and fear of adverse impact on pregnancy may result in maternal anxiety and reduced health-related quality of life
3. Pregnancy-related knowledge can be improved following a single educational consultation
4. Objective markers of inflammation including gastrointestinal ultrasound are likely to be useful in monitoring disease activity in pregnancy
5. Drug levels of immunosuppressant medications including thiopurines and biologic medications may change throughout pregnancy due to alterations in pharmacokinetics and pharmacodynamics
6. Cord blood thiopurine metabolites, vedolizumab and ustekinumab levels are likely to correlate with maternal levels
7. Infant vedolizumab clearance may be longer than infliximab and adalimumab due to the longer half-life of vedolizumab
8. Babies exposed to thiopurines *in utero* may be predisposed to anaemia

1.8.2 Overall Thesis Aims

1. To explore the impact of IBD on reproductive planning and pregnancy from the patient's perspective through in-depth interviews
2. To improve pregnancy-related knowledge, anxiety and health-related quality of life in women with IBD through an individualised patient education intervention
3. To evaluate the accuracy and feasibility of gastrointestinal ultrasound for assessment of IBD during pregnancy
4. To determine the pharmacokinetics of thiopurine and biologic medications during pregnancy
5. To determine the impact of maternal thiopurine metabolites levels during pregnancy on infant outcomes up to six months including cord blood levels, time to clearance and impact on blood parameters including full blood count and liver function tests in neonates exposed to thiopurines *in utero*

6. To determine the impact of maternal vedolizumab and ustekinumab levels during pregnancy on infant outcomes including cord blood levels and time to clearance

1.8.3 Details of the Studies in this Thesis

Chapter 3: Addressing Pregnancy-Related Concerns in Women with Inflammatory Bowel Disease

A qualitative study using in-depth interviews to explore participants' experiences and perceptions regarding IBD and pregnancy.

Chapter 4: Education and Psychological Care of Women with IBD in Relation to Pregnancy

A prospective study of women with IBD who were pregnant or planning a pregnancy to evaluate the effectiveness of a single gastroenterologist-led educational intervention for improving pregnancy-related knowledge. Secondary outcomes include the effect on patient anxiety and depression, quality of life, medication adherence and satisfaction.

Chapter 5: Monitoring Inflammatory Bowel Disease in Pregnancy using Gastrointestinal Ultrasonography

A multi-centre study to determine the feasibility and accuracy of GIUS in the assessment of IBD during pregnancy progression.

Chapter 6 Maternal Thiopurine Metabolism during Pregnancy and Neonatal Clearance and Outcomes

A prospective observational study to characterise the impact of pregnancy on thiopurine metabolism as well as evaluate neonatal thiopurine metabolite levels and neonatal outcomes following *in utero* thiopurine exposure.

Chapter 7 Biologic Drug Levels Across Pregnancy and Vedolizumab and Ustekinumab Levels in Infants following Intrauterine Exposure

A prospective observational study to measure levels of infliximab, adalimumab vedolizumab and ustekinumab levels during pregnancy in women with IBD, and vedolizumab and ustekinumab levels in exposed infants.

2 Methodology

This chapter provides an outline of the methodology selected to complete this research including the overall study design and procedures. Each of the five studies in this thesis has been submitted for publication in peer-reviewed journals and further detail regarding the methodology of the individual studies is presented within the relevant study chapters.

2.1 Overall Study Design and Population

The first study in the thesis is a qualitative study, which employed in-depth interviews to explore participants' experiences and perceptions regarding IBD and pregnancy. Given the lack of qualitative data in the field, this study was completed at the beginning of the candidature to provide the foundation for performing the patient-centred educational intervention described in the subsequent study. Participants known to the general IBD service at St Vincent's Hospital, Melbourne who had recently been pregnant were recruited for this aspect of the research.

The following four studies of the thesis pertaining to the pregnancy-related educational intervention, intestinal ultrasonography, thiopurine metabolite and biologic drug levels are prospective in nature and included participants recruited to the *Pregnancy in Crohn's and Colitis: Observations, Levels and Outcomes* (PICCOLO) study cohort. Female patients with IBD aged 18-45 who were pregnant or planning a pregnancy in the next 12 months were recruited from August 2017 to January 2020. The research was conducted through the St Vincent's Hospital Melbourne IBD and Pregnancy service, which was newly established as part of this thesis.

Briefly, enrolled participants in the educational component of the study attended the intervention and then completed follow-up outcome measures at one month. Patients who were or became pregnant in the study period were enrolled for disease activity monitoring including intestinal ultrasonography during pregnancy. Patients who were taking a thiopurine and/or biologic medication (infliximab, adalimumab, vedolizumab or ustekinumab) who were pregnant within the study period were enrolled for measurement of maternal thiopurine metabolites and/or biologic drug levels across pregnancy, from pre-conception to postpartum. Pregnancy outcomes were also prospectively collected. Follow up of infant outcomes including thiopurine metabolites

and biologic drug levels was performed for infants exposed *in utero* to a thiopurine, vedolizumab and ustekinumab.

Participants were referred to the prospective PICCOLO study through:

i. Major Melbourne metropolitan public hospital IBD outpatient clinics and private gastroenterologists
ii. Adult IBD Clinicians registered as part of the IBD Melbourne collaborative research group
iii. Members of the Australian and New Zealand Inflammatory Bowel Disease Consortium (ANZIBD) if pregnant on vedolizumab or ustekinumab
iv. Obstetricians or general practitioners

IBD Melbourne is a special interest group of around 20 IBD gastroenterologists; the group fosters networking and collaborative research opportunities across IBD centres in greater Melbourne. The study was not advertised through obstetric or general practice networks; hence the majority of study referrals were from gastroenterologists.

2.2 Study Procedures

Baseline data were collected including patient demographics and medical and obstetric histories for individual participants. Study data were prospectively collected according to each study as detailed in the subsequent chapters, including study questionnaires, clinical disease activity assessments and maternal and infant thiopurine metabolites and biologic drug levels. Pregnancy and infant outcomes questionnaires were completed by telephone or face to face with assistance from the study nurse, or online by study participants.

Arrangements were made for study blood samples for maternal and infant thiopurine metabolite concentrations to be processed through the St Vincent's Hospital Pathology laboratory and analysed by South Australia Pathology, Adelaide (as per the existing agreement for thiopurine metabolites performed through St Vincent's Pathology). Blood samples to determine maternal and infant biologic drug levels were analysed at the Monash University Central Clinical School laboratory at The Alfred, Melbourne. Mothers were offered to have infant blood tests as part of the study collected by experienced staff at The Royal Children's Hospital Pathology, Melbourne.

2.3 Data Collection and Management

A clinical database was designed and implemented to facilitate online data collection and storage using the REDCap (Research Electronic Data Capture) platform. REDCap is a secure web-based research data collection tool provided through the Health Informatics Department at the University of Melbourne. The advantage of REDCap is the ability to electronically send surveys for self-completion by study participants via an email link when relevant, for example in order to provide feedback following the educational intervention and record pregnancy outcomes in this study.

All other electronic data were kept in an appropriate password-protected database on the secure server at St Vincent's Hospital, Melbourne. Participants were assigned a unique study identifier. Paper files including study visit documentation and clinical results were stored securely in the Department of Medicine at St Vincent's, Melbourne. Access to the database and clinical data were limited to the study team.

2.4 Evaluation of Methodology and Sources of Error

In relation to the qualitative study, a combination of opportunistic and purposeful sampling was used to recruit patients until data saturation was attained, including in women with both Crohn's disease and UC. The sample size for qualitative studies involving in-depth interviews is typically small, however interviews were conducted until thematic saturation was achieved. Possible selection bias was restricted by the recruitment of consecutive patients, defined only by their recent pregnancy timing and not by other factors such as disease severity, hence incorporating a range of potential patient experiences. There is the possibility of recall bias given the data was collected retrospectively but the interview schedule incorporated targeted, open-ended questions and patients participated anonymously, thus optimising the environment for authentic participant responses. Additionally, the primary researcher was not involved in patient care so as not to influence the results.

Prospective observational studies were also included in this thesis. There are inherent limitations of observational studies in establishing causal relationships when compared to randomised controlled trials, but these could not be practically or ethically performed in the setting of pregnancy.

A prospective interventional pre-test/post-test study design was chosen to evaluate

the effectiveness of the pregnancy-related educational intervention for women with IBD. In the setting of the current literature demonstrating poor pregnancy-related knowledge amongst patients with IBD, it was not deemed ethical to randomise a control group of women to receive no dedicated counselling when they were already pregnant or imminently planning a pregnancy. Therefore, a follow-up duration of one month was selected in order to maximise the internal validity of the study and restrict other contributory factors to patient outcomes, such as external sources of education through multiple medical visits or other potential influences on quality of life after a longer timeframe.

In the third study, the accuracy of intestinal ultrasonography in pregnancy was determined in comparison to matched faecal calprotectin measurements. Ethical constraints in pregnancy limited other disease activity assessments such as colonoscopy and cross-sectional imaging. Faecal calprotectin was chosen as the best available objective marker of disease activity as it not altered by pregnancy. However, faecal calprotectin can be normal in the setting of active mucosal or stricturing disease, which may have underestimated the reported accuracy of our intestinal ultrasound findings.

A limitation of the final two prospective observational studies, which measured thiopurine metabolites and biologic drug levels across pregnancy and in exposed infants, was their small sample sizes. These data, however, provide the largest cohorts in the literature to date. There were also limited maternal observations, with some patients not completing blood tests at every time point. However, appropriate statistical modelling was performed to assess maternal metabolite and drug levels in relation to timing during pregnancy, which has accounted for missing values and controlled for the potential effect of other clinical variables.

2.5 Collaborations

A collaboration was formed with Dr Jacqui Richmond, who is a Senior Fellow at the Department of Nursing, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, in order to guide the accomplishment of the first study in this thesis. She has extensive qualitative research experience in hepatology and she provided specific advice and expertise regarding the design of the qualitative study and interpretation of the interview data.

A collaboration was undertaken and a multicentre study facilitated with national gastrointestinal ultrasonography experts to investigate ultrasound findings across pregnancy in IBD patients. Collaborative investigators included Associate Professor Jakob Begun at Mater Hospital, Brisbane and Dr Robert Bryant at Queen Elizabeth Hospital, Adelaide, who provided additional data from their respective institutions. Additionally, we collaborated with Professor Peter Gibson and his experienced team from the Monash University Central Clinical School laboratory at Alfred Health to perform analysis of samples for anti-TNF, vedolizumab and ustekinumab levels as part of the fifth study in this thesis.

3 Addressing Pregnancy-Related Concerns in Women with Inflammatory Bowel Disease: Insights from The Patient's Perspective

3.1 Introduction

The prevalence of inflammatory bowel disease (IBD) is rising and the peak incidence overlaps with childbearing years[1]. Fertility is normal in patients with quiescent IBD, with the exception of women who have had pelvic surgery. The best pregnancy outcomes for women with IBD occur when their disease is in remission, for which most require maintenance medication[2]. The therapeutic options in IBD have expanded, with increasing use of immunosuppressant and biologic medications during the reproductive period[3,4]. While the majority of IBD medications are considered safe during pregnancy and lactation[5], newer agents have limited pregnancy safety data, and many women harbor fears regarding harmful foetal effects[6].

Fear of infertility and reluctance to use medication during pregnancy were prevalent in a significant proportion of Australian women with IBD in a questionnaire-based study[7]. However, these data were collected using physician-designed surveys, which do not allow for dynamic patient discussion and may have missed concerns important to patients but not obvious to physicians. Another approach using telephone surveys of American women with IBD reported that over half had pregnancy concerns related to their IBD such as the effect of IBD medications, but the nature and reasons behind these concerns were not explored[8].

Pregnancy is a significant life event that can be associated with considerable psychological challenges and women with IBD are particularly vulnerable to mental illness in the perinatal period[9]. Qualitative research enables a deeper understanding of the complexity of the experiences of women with IBD, and allows physicians to explore the lived experience of a health condition and gain broader insights beyond the biomedical paradigm[10]. This is particularly crucial around the time of pregnancy, when patients have to wrestle with additional pregnancy-related concerns and considerations, which often go unrecognised or are concealed from the treating medical team. How women with IBD feel about and experience pregnancy may

influence a wide range of outcomes including compliance with medication and therefore, disease control; whether to have more children and when; and maternal psychological health across pregnancy. Understanding the detail behind these concerns may allow IBD physicians to address these topics in their routine pregnancy counselling, acknowledge with patients that their concerns are valid, and communicate discussions with primary care and obstetric providers to educate appropriately and provide patient-centred and consistent care for these women.

Qualitative research examining the pregnancy-related concerns and perceptions of women with IBD in the era of widespread immunomodulator and biologic medication use does not exist[11]. Therefore, we performed a qualitative study to explore the current impact of IBD on reproductive planning and pregnancy from the patient's perspective in order to identify key themes that should be addressed in pre-conception counselling and psychological care for women with IBD during the reproductive period.

3.2 Methods

The current study used semi-structured interviews to explore participants' experiences and perceptions of IBD and pregnancy. We explored the patient journey from becoming pregnant to completing their pregnancy and caring for a newborn in the setting of IBD. Participants were asked to describe their feelings about taking IBD medications during their pregnancy and while lactating and the impact of IBD on their pregnancy and peri-partum experience.

Interviews were conducted between August and December 2017. Women with IBD who had been recently pregnant (within the previous two years) were invited to participate. Participants were recruited from the patient cohort known to the IBD service at a tertiary IBD centre (St Vincent's Hospital Melbourne) through a combination of both stratified purposeful and opportunistic sampling.

Participants were given the option of completing the interview in person or via telephone. Interview questions were informed by a review of the literature and the authors' clinical experience and developed by the multi-disciplinary research team (see Appendix I: Interview Schedule). Interviews were conducted by the first author (EF), who had not been involved in patient care, and were audio-recorded and transcribed

verbatim.

Interview transcripts were coded for key themes and a coding framework was developed drawing on predetermined areas of interest and themes that emerged in the data. These emergent themes were identified using standard thematic analysis techniques; passages of text were coded by reading and reviewing the interview transcripts[12]. This process of repeated reading and data selection was in keeping with traditional iterative coding techniques.

Ethical considerations:

Ethics approval was granted through the St Vincent's Hospital Ethics Committee (reference number 094/17). Interviewees provided written consent to participate. Participants were not offered any reimbursement.

3.3 Results

Fifteen participants with a confirmed diagnosis of IBD who had given birth within the last two years were interviewed (65% response rate). Interviews lasted approximately 45 minutes (range 25-65 minutes).

Ten women had Crohn's disease (CD) and five women had ulcerative colitis (UC). The median age at the beginning of pregnancy was 30 years (range 20-42 years) and median IBD duration was seven years (range 4-30 years). All participants had been prescribed maintenance medication for their IBD. Eleven participants were taking a thiopurine medication (azathioprine or 6-mercaptopurine) during pregnancy or had taken a thiopurine prior, while eight participants were prescribed biologic therapy either before or during their pregnancy.

Key themes have been reported chronologically according to the participant's pregnancy journey from pre-conception through to the post-partum period (Table 3.1). Participants' quotations are denoted by diagnosis (CD or UC) with assigned study numbers in order to preserve their anonymity.

Table 3.1 Key themes and sub-themes

Prior to pregnancy • Fertility concerns relating to IBD and IBD medications • Timing of pregnancy impacted by active IBD
During pregnancy • Anxiety throughout pregnancy regarding adverse pregnancy outcomes and disease flares • Fears regarding effects of IBD medications on children exposed *in utero* • Limited information from GPs and obstetric team regarding IBD
Post-partum • Concerns and conflicting advice regarding breastfeeding • Difficulty caring for a newborn due to IBD

Prior to pregnancy:

Fertility concerns relating to IBD and IBD medications

Eight participants had concerns regarding their ability to conceive, relating both to their previous medication use and history of IBD:

"'We miscarried at twelve weeks… That's when we were on the [azathioprine]...For it to take seven months to fall pregnant…I didn't think that [pregnancy] was going to happen at all."

Participant 14, UC

In these participants, their apprehension regarding fertility persisted at times despite being informed that their fertility should not be affected.

Timing of pregnancy impacted by active IBD

Five participants recognised that their IBD had impacted on the timing of their pregnancy. Women reported either trying to conceive promptly during a period of disease remission due to fears of a disease flare derailing their pregnancy, or having to postpone their plans for pregnancy due to active IBD:

"'I was always told I should…have no active illness before becoming pregnant, because of all those terrible consequences…the small, sickly baby…But… it didn't

seem like there was going to be any point at which I didn't have some active disease… it was not looking like an actual reality to me, and I was getting older."

Participant 13, UC

One participant also expressed her difficulties with sexual intimacy in the setting of perianal Crohn's disease:

"The Crohn's affected relationship aspects as well, so everything just was put on hold…I have a recto-vaginal fistula…[After] that big surgery …my surgeon [told] me: 'You can't be intimate for three months'…when the time came I was really scared …I almost had the mentality where I didn't want to be intimate at all."

Participant 7, CD

During pregnancy:

Anxiety throughout pregnancy regarding adverse pregnancy outcomes and disease flares

Seven participants expressed anxiety and persistent uneasiness relating to their IBD during pregnancy. These participants were mostly concerned regarding the possibility of a flare or complication during pregnancy or adverse outcome for their baby. As one participant explained, anxiety regarding IBD in pregnancy can be protracted:

"Once I got pregnant, I did become very anxious…not for myself but for my baby…I was anxious for the entire pregnancy… I kind of felt a bit cheated that I didn't enjoy my pregnancy."

Participant 8, UC

Concern regarding effects of IBD medications on children exposed in utero

Twelve participants were concerned about potentially harmful effects of their IBD medications on their babies. This was despite advice that these medications were thought to be lower risk to the foetus than that of active IBD. Participants alluded to the universal paranoia and myriad of recommendations for pregnant women in general regarding medication use, and discussed the pervasive awareness of not wanting to take any medications during pregnancy, for IBD or otherwise. Such was the influence of taking medications during pregnancy, that seven participants began talking about IBD medications in pregnancy prior to being directly asked about the topic. Two women reported stopping their thiopurine pre-conception despite advice that is was considered safe in pregnancy.

Specific concerns regarding the use of IBD medications during pregnancy included the possibility of causing birth defects, as one participant explained:

"I know there was definitely a negative connotation with the mercaptopurine, so I always thought 'Is there residual stuff hanging around that could cause some birth defect?'… even until the day he was born I thought 'he's going to have two heads or something'."

Participant 1, CD

In addition, the possible effect on the developing baby's immune system was raised as another explanation for feeling uncomfortable with the use of IBD medications in pregnancy:

"Ideally, I would like to have been on no medication…I was concerned about [my baby]… it could potentially have an impact on her in the future…some kind of an effect on suppressing her immune system… It is something that you would think of down the line if she was to develop something, could it have been as a result of taking medications while you are pregnant?"

Participant 9, CD

Participants commonly referred to a sense of uncertainty and not feeling reassured due to limited studies involving pregnant women exposed to IBD medications and the potential for unknown long-term effects in the future for their children:

"You're so worried about the Crohn's, and the medications, that you are instilled with a lot of fear, because the doctors don't know… studies haven't been done on women with Crohn's disease that are pregnant, so you feel like a guinea pig... I don't know the effect it's going to have on my child…If it affects me, that's fine, I'm responsible for myself, but to know that you're taking a medication that can have side-effects, on your child…That's what worries me the most."

Participant 7, CD

Participants described a revised acceptance for medication during the reproductive stage due to their prevailing concern for the unborn child:

"I really didn't want to be on any medication, and I know that was completely unscientific, but it was…an emotional decision, rather than an intellectual one. Being pregnant…it's like your brain's not quite so logical, you just get this sort of overwhelming, protective thing in your life, 'I don't want low-risk, I want no-risk'…you would protect your baby at the expense of yourself… [the doctor]…will come up with the statistics, but…I still don't know if it's a good thing. I think they probably said that to women using thalidomide."

Participant 6, CD

Limited information from GPs and obstetric team regarding IBD

Nine participants experienced a perceived lack of knowledge or conflicting advice from their general practitioner (GP) and/or obstetric team regarding their IBD and/or medications during pregnancy, which augmented pre-existing anxiety and uncertainty. For instance, women taking a thiopurine medication were often advised it was a 'Category D' or unsafe medication in pregnancy by primary care physicians or members of the obstetric team. As one participant outlined regarding the advice she received about taking azathioprine in pregnancy (which was prescribed by her specialist and considered safe):

"My normal doctor said, 'You can't, you're on high-risk medication'. I said, 'No, my specialist wouldn't have prescribed it to me if I wasn't allowed on it', and he goes 'It's not safe, it's in the list.' It was really stressful."

Participant 14, UC

Post-partum:

Conflicting advice regarding breastfeeding

Nine participants expressed concern regarding breastfeeding while on IBD medications or had been given inaccurate advice from a primary care doctor or member of the obstetric team regarding the safety of their IBD medications and lactation. Some women disclosed that breastfeeding while on medications was something they felt negatively about as they felt they had more of a choice about exposing their baby to medications then than *in utero*.

"I think breastfeeding, while taking the medication, had been more of a concern to me…I wonder if it's about him being out, and it's optional now for him to be impacted by those medications. …You can read all the studies that you want, but at the end of the day…it feels intuitive that it would have some impact, if it's passing through to him".

Participant 13, UC

Difficulty caring for a newborn due to IBD

Nine participants raised concerns regarding a flare post-partum and their ability to care for their baby in the setting of their IBD, or had indeed faced additional challenges due to their IBD during what is already a time of immense adjustment and fatigue. Participants expressed worries about having time away from their children due to hospital admission, wanting to remain healthy for the sake of their children and described increased difficulties faced due to suffering from IBD while caring for a newborn. Four participants volunteered that they had experienced issues with bowel

urgency or incontinence particularly after pregnancy, which was then more difficult to manage when caring for young children:

"Oh, it was so hard…I'd be in the middle of breastfeeding her, I'd have to put her down in her bassinet and run to the toilet… I couldn't do it on my own, like physically couldn't care for her."

Participant 8, UC

3.4 Discussion

This is the first qualitative study to evaluate the concerns facing women with IBD in relation to pregnancy in the setting of currently available IBD medications. Our study highlights that women with IBD have a range of concerns about fertility, management during pregnancy, and the post-partum period including lactation and managing symptoms with a newborn. Their apprehension persisted despite receiving regular obstetric and tertiary IBD care.

The most pressing worry for most of these women with IBD was the potential effect of their medication, rather than their IBD itself, on their pregnancy and offspring. This was demonstrated in the majority of women expressing concern regarding IBD medication use in pregnancy and is in keeping with previous data showing that female patients report concerns about the effect of IBD medications despite good safety data for the majority of medications. Conversely, fewer women reported concerns about the adverse effect of IBD flares on the foetus, consistent with previously reported poor knowledge of the risks of spontaneous abortion, growth restriction, and premature birth[6].

Our study details specific medication-related fears, which included negative effects on the child's immune system, and a lack of data meaning that women could not be "100% certain" that the medications are entirely safe for their children. These results show that in some women, fears regarding medication persisted despite reporting adequate knowledge regarding medication safety. Participants reported a strong cultural sense that taking medication while pregnant seemed unnatural and contradicted the "maternal instinct" to "protect" their unborn children. There was a sense of distrust among participants regarding the possibility of unproven health consequences for their babies in the short term and also as yet unknown outcomes in

the longer term. Moreover, these fears regarding medication existed in women with IBD regardless of disease severity or medication type. For example, women on 5-ASA agents as monotherapy can feel apprehensive regarding medication use during pregnancy and lactation. Similarly, the majority of women in a previous Australian study assessing medication adherence in pregnancy generally believed that using any medication in pregnancy was not risk-free[13].

With regard to fertility, our data also shows that many women with IBD are concerned about the impact of medication or disease activity, when, in fact, fertility is generally normal in patients with IBD[14]. This apprehension regarding infertility can be sustained despite being informed otherwise. The assumption that one will be infertile translates into a higher rate of unplanned pregnancies in women with chronic diseases[15] and therefore a lack of IBD-specific pregnancy care. Participants also worried about miscarriage once they were pregnant. Other concerns included physical symptoms related to disease flares such as faecal urgency or incontinence and difficulties with sexual intimacy. This persisting anxiety may be in part related to women with IBD feeling “sick” and “not normal” and the public perception that this may then translate to infertility or unsuccessful pregnancies. The study uncovered a perceived incompatibility between having IBD and enduring the physicality of pregnancy and motherhood.

Compounding the anxiety amongst this patient group is the inconsistent information that can at times be provided by treating doctors. This is contributed to by the fact that many of the medications used in IBD are not labelled as ‘safe’ within national medication classification systems, despite literature demonstrating safety and international society guidelines. These warnings can be raised by electronic prescribing platforms but do not take into account the clinical indication for a medication. To counteract this the United States Food and Drug Administration is no longer using these pregnancy risk categories. However, once concerns have been raised, it is often difficult to reassure patients regarding safety.

There is a paucity of qualitative data exploring current maternal concerns amongst women with IBD. A recent American study that incorporated analysis of social media and online forum posts related to patients’ experiences of IBD medication use during the reproductive period, found similar themes to the current study[16]. In particular, fear of IBD medications in pregnancy were highlighted including general concerns

regarding birth defects and risk of miscarriage[16]. Likewise, this study noted that many patients seemed frustrated by insufficient knowledge from some obstetric care providers[16]. An interview-based study of eight Japanese women who had IBD and children ranging in age from seven months to seven years reported that these women predictably faced adversity at times of IBD flares[17]. In addition, these patients also reported receiving inconsistent information from treating clinicians and an inability to find accurate information on the internet about IBD medications[17]. One other large study that examined social media posts relating to biologic therapies in IBD, found that patients expressed their concerns regarding pregnancy safety in online discussions[18].

The novel finding of our study is the powerful knowledge generated regarding how women with IBD inherently feel about reproduction and IBD and the manner in which pre-conception advice is delivered, which did not always accommodate patient circumstances or preferences even though this is essential for shared decision-making. Our data suggest that physicians providing pregnancy information and advice for women with IBD should explore and acknowledge the patient's beliefs, and use a more personal and less scientific approach, for example with open questioning regarding specific patient concerns and how they are coping during the process of trying to conceive, throughout pregnancy and post-partum. There was a sense that at times the treating clinician was not seen to recognize the importance of discussing specific maternal fears and personal circumstances during these consultations. Counselling should acknowledge our patient's potential fears, allow opportunities for them to express their concerns, provide regular reassurance and offer referral for peri-natal psychological care for anxiety when indicated (Table 3.2). This candid awareness of the patient experience with strong patient-physician rapport is particularly significant given the known increased risk of new onset mental illness in women with IBD during the perinatal period[9].

A limitation of our study is the small sample size, however in-depth interviews were conducted until data saturation was reached. The high response rate amongst a group of women with young babies to participate in an interview highlights the significance of reproductive issues for women with IBD. Although there is the potential for recall bias because the data was retrospectively collected, the study produced rich data, possibly because it provided a low-risk context for participants to discuss their impressions, given that any findings would be anonymously reported. Women were recruited from a high-level tertiary service providing

pregnancy advice and would be expected to represent the best-case scenario. Women with less access to counselling may have amplified concerns.

The current study has generated a thorough assessment of female patients' perspectives of IBD in relation to conception, pregnancy and caring for offspring. In particular, this research has emphasised the unique fears and lingering anxieties regarding IBD medications in the setting of pregnancy. These important insights should be used to enhance pre-pregnancy counselling for women with IBD by encouraging a non-judgmental patient-centred approach designed around patient concerns and beliefs incorporating the themes identified in this study.

Further Discussion

This study aimed to evaluate the entire pregnancy experience and hence included women with IBD who had delivered their babies.

Participants were not asked to complete formal IBD and pregnancy knowledge scores or anxiety scales in the qualitative study, however this would be interesting to correlate with the qualitative interview findings.

Future qualitative study could incorporate semi-structured interviews with women who are currently pregnant to reduce recall bias. Additional qualitative research in the future could also include interviewing young women with IBD who have never been pregnant in order to explore the potential anxieties and misperceptions that may exist in this group.

Table 3.2 Suggested advice for patient-centred care of women with IBD in the childbearing years

Prior to pregnancy • At the time of diagnosis reassure patient that reproductive outcomes are very good when IBD is well controlled and that most IBD medications are low risk • Encourage open communication and opportunities to discuss fears and desires • Ask patient about pregnancy plans and request that they attend for pre-conception counselling six months prior • Initiate pre-conception education with patient, particularly regarding IBD medications, encourage partner/other family members to attend if appropriate, provide written information • Acknowledge that you are providing recommendations from an IBD perspective, there are other factors to consider including personal choices and circumstances
During pregnancy • Discuss with patient that they may face a more complex pregnancy journey than women without a chronic illness and encourage them to communicate their concerns • Provide ongoing education and reassurance regarding the safety of IBD medications in pregnancy and regular monitoring of disease activity • Assess anxiety levels, for example with open ended questions: o "Have you been worrying a lot about your medications / your IBD?" • Offer psychological support and counselling when indicated to address anxiety • Recommend IBD nurse helpline as resource for patients during pregnancy
Post-partum • Breastfeeding should be encouraged and discussion initiated regarding medication safety during lactation to address possible patient fears or contradictory advice • Patients should be reviewed to monitor for post-partum disease flare and post-natal anxiety

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4 A Single Educational Intervention Improves Pregnancy-Related Knowledge and Emotional Health Among Women with IBD who are Pregnant or Wishing to Conceive

4.1 Introduction

Inflammatory Bowel Disease (IBD) commonly affects women during their childbearing years[1]. It is now established that the majority of medications used to treat IBD are safe to continue in pregnancy, while active IBD can have an adverse impact on pregnancy outcomes[2]. However, it has been shown that patients have poor levels of knowledge regarding the importance of disease control prior to conception and during pregnancy, as well as the safety of IBD medication use during pregnancy[3-6]. Poor pregnancy-related knowledge has been associated with negative views about pregnancy and childbirth and an increased rate of voluntary childlessness amongst women with IBD[6,7]. Pregnancy is a momentous life event for any woman and can itself be associated with considerable psychological challenges. In the context of IBD, there are additional pregnancy-related management considerations and patient concerns relating to chronic illness. A recent large retrospective study based on health administrative data found an increased risk of new onset mental illness including anxiety during the postpartum period in women with IBD[8]. Prospective data relating to psychological wellbeing and health-related quality of life (HRQoL) prior to conception and during pregnancy are lacking in women with IBD.

There is increasing awareness about the importance of education for IBD patients as part of participatory health care and shared decision-making models. Pregnancy-related counselling is recommended by all major international guidelines regarding IBD management in pregnancy[9-11], but there is no specific advice about how this should be implemented and adherence to guidelines appears limited[12].

There has been considerable interest in improving the education and care of pregnant women with IBD in order to improve pregnancy outcomes for both mother and baby. Previous Australian work demonstrated that pregnancy-related knowledge can improve when re-tested immediately after a once-off group education session, but the longer-term recall of this knowledge was not assessed[13]. More recently, a Canadian study

including male and female patients with IBD showed that a novel online educational portal can improve pregnancy-related knowledge[14]. However, this model alone lacks the aspect of personalised care that is necessary at an important and potentially anxiety-provoking stage in a woman's life. Face-to-face patient education, which can be offered via telemedicine, remains fundamental to the care of patients with IBD and patients have high levels of trust in information received from the treating specialist compared to other sources[15].

A small number of case studies have demonstrated the benefit of IBD pregnancy clinics where women with IBD are reviewed regularly prior to conception and during pregnancy. A recent prospective Dutch study demonstrated that a specialised pre-conception and pregnancy care clinic, including follow-up before, during and after pregnancy, can reduce disease relapse rates during pregnancy, and rates of low birth weight[16]. However, this approach is labour intensive and may disrupt the continuity of patient care. Despite increased awareness, not all women have access to pre-pregnancy counselling or protocolised IBD pregnancy clinics and the availability and quality of counselling is variable. The efficacy of a more individualised but less intensive model has not been evaluated.

We hypothesised that a single, simple educational intervention delivered by a gastroenterologist can improve pregnancy-related knowledge, provide patient satisfaction and maintain optimal pregnancy outcomes for women with IBD who were pregnant or wishing to conceive. We also postulated that there is a high proportion of depression and/or anxiety in these women, which may affect HRQoL. We aimed to measure patient anxiety and depression, and HRQoL and to evaluate the effect of education on these outcomes.

4.2 Materials and Methods

Study design:

This was a prospective interventional pre-test/post-test study that evaluated the effectiveness of a single session, gastroenterologist-led patient education consultation in improving pregnancy-related knowledge in women with IBD. Secondary outcomes included the effect on patient anxiety and depression, HRQoL, medication adherence and participant satisfaction.

Study recruitment was facilitated through clinical referrals from local care providers of females with IBD aged 18-45 who were pregnant or planning a pregnancy in the next 12 months. Participants were recruited from September 2017 to July 2019 from both public hospital clinics and private specialists.

At baseline (pre-intervention) data were collected regarding medical and obstetric history, psychological comorbidity, education and employment status, age at diagnosis, pregnancy and medication history and whether patients reported receiving previous preconception counselling. Clinical assessment at baseline was recorded, including baseline faecal calprotectin, the Physician's Global Assessment (PGA) as well as either the Harvey Bradshaw Index (HBI) for women with Crohn's disease (CD)[17] or the Simple Clinical Colitis Index (SCCAI) for women with ulcerative colitis (UC)[18].

The intervention:

The educational intervention was provided via a half-day clinic run second weekly with a single gastroenterologist per clinic. The intervention incorporated a one-on-one information session using a pro forma for evidence-based advice and structured discussion relating to IBD and pregnancy (Appendix II). All participants received the same information centred around the defined pro forma. The discussion was then personalised to focus on those areas identified by the patient to be of greatest concern. The individual educational intervention was delivered by a gastroenterologist (SB or EF) during a single visit using either an in-person approach or via telemedicine in a dedicated clinic time. Up to one hour was allocated, which included disease assessment and study data collection.

Education was provided on standardised topics including the effect of IBD on fertility and pregnancy, inheritance of IBD, the effect of pregnancy on IBD and the need and options for disease monitoring during pregnancy. Detailed medication safety information was provided for pregnancy and lactation and a discussion regarding mode of delivery was held. Information delivered was aligned with international guidelines and expert consensus reviews[9,10,19].

Recommendations were provided regarding the importance of quiescent disease to optimise pregnancy outcomes. Only medications known to be teratogenic were recommended to be ceased. General reproductive health advice was provided including folic acid supplementation and smoking and alcohol avoidance. Discussion included how patients were coping with their disease and its impact on reproductive

planning. Participants and their partners had the opportunity to address specific concerns.

Following the session, communication regarding the discussion was provided directly to referring doctors including the patient's gastroenterologist, planned obstetric clinician and general practitioner. All patients were informed that they should continue to be seen by their regular treating gastroenterologist as planned. Written information was not provided as part of the study in order to avoid influencing the follow-up knowledge survey results.

Evaluation of the Educational Intervention:

Prior to the intervention, participants were asked to complete the CCPKnow (Crohn's and Colitis Pregnancy Knowledge Score, a validated IBD and pregnancy knowledge assessment tool)[3], Hospital Anxiety and Depression Scale (HADS)[20], HRQoL questionnaires, using both the RAND 36-Item Short-Form Health Survey 1.0 (SF-36)[21] and IBDQ[22], as well as a medication adherence scale. Participants were requested to repeat the CCPKnow, HADS, HRQoL and medication adherence surveys one month after the intervention. A participant satisfaction score was also collected following the intervention.

Surveys were completed either on paper or online and study data were collected and managed using the REDCap electronic data platform at the University of Melbourne. Follow-up results were included if the participant had completed the follow up survey within two months (60 days) of the intervention. At six months post the intervention, participants who were not pregnant at the time of the intervention were asked to complete a simple series of questions assessing their conception and pregnancy successes or plans.

In those women who were or became pregnant in the study period, pregnancy outcomes were captured via an online or telephone questionnaire and/or details from medical records. Pregnancy outcomes included spontaneous abortion, intrauterine death, live birth, mode of delivery, pre-term birth (<37 weeks), neonatal birth weight, congenital anomalies and APGAR scores.

Primary outcome:

The primary outcome was the change in patient knowledge following the intervention

as measured by the CCPKnow questionnaire at one month post the intervention. Selinger et al developed and validated the CCPKnow questionnaire, which provides a standard measure of pregnancy-related knowledge in IBD[3]. The questionnaire includes 17 multiple-choice questions covering aspects including inheritance of IBD, medication during pregnancy, mode of delivery and breastfeeding; with scores out of 17 categorised as follows: poor (0–7), adequate (8–10), good (11–13), and very good (14-17).

Secondary outcomes:

Psychological status was measured with the HADS, an instrument that has been used extensively to identify anxiety and depression in patients with physical health problems. It includes a 14-item questionnaire and each item is scored 0-3, with a sub-score of 0-21 for anxiety (HADS-A) and 0-21 for depression (HADS-D)[20]. These sub-scores can be categorised as normal (0–7), possible (8–10) and probable (15–21) anxiety or depression with a sub-score >7 suggestive of clinically-relevant anxiety or depression, respectively. The total HADS score has been used to indicate global psychological distress, with higher scores suggestive of more distress[23].

HRQoL was measured prospectively using the generic RAND SF-36 and the disease-specific IBDQ. The SF-36 is a 36-item instrument containing eight health scales[21]. Average scores within each scale are calculated, with a range from 0-100 and higher scores represent better HRQoL. The IBDQ has 32 items, each scored 1-7, and four health domains[22]. Average scores can be calculated for the four domains, as well as a total score of 32-224 with higher scores indicating better HRQoL.

A self-designed questionnaire regarding medication adherence was developed based on Julsgaard et al previous dedicated study in this area[24,25]. Women were asked to report their average intake of prescribed medication: 0–49%, 50–80%, or >80% of the recommended dose. They were asked to select the reason(s) for reduced adherence (if applicable) from: fear of negative effect on fertility/foetus, quiescent disease, forgetfulness, other.

Participant satisfaction with the intervention was measured using a 7-point Likert scale from extremely dissatisfied to extremely satisfied.

Statistical considerations:

Data are reported as median [interquartile range (IQR)] or number (%). Between group differences were compared by $\chi 2$ test and Wilcoxon rank-sum test, as appropriate. Within subject differences pre- and post-intervention were compared using McNemar's chi-squared test and Wilcoxon signed-rank test, as appropriate. Linear regression analysis was used to identify variables associated with pregnancy knowledge. Statistical analysis was performed using STATA version 15.1 (STATA LP College Station, TX, USA). A p value < 0.05 was considered statistically significant.

Ethical considerations:

Ethical approval for the study was obtained from the Human Research Ethics Committees at St Vincent's Hospital Melbourne (HREC/17/SVHM/116) and patients provided written informed consent.

4.3 Results

100 consecutive women with IBD (59% CD, 37% UC, 4% IBDU) were included who attended the educational intervention and competed the baseline pregnancy knowledge assessment. An additional twelve women accepted the invitation to participate in the educational intervention but then subsequently cancelled or did not attend, while one other patient elected to attend the intervention but declined enrolment in the study (100/113 (88.5%) included).

Participants were referred from gastroenterologists in Melbourne, Australia with affiliations across eight different IBD centres. 43/100 (43%) of enrolled participants were referred from private gastroenterologists. 21/100 (21%) of participants resided in regional Australia outside of a major city and 6/100 (6%) elected to attend the intervention via telemedicine.

Patient characteristics are shown in Table 4.1. Half of the participants (50%) were pregnant at the time of the intervention, with a median gestational age of 12 weeks (IQR 10-18 weeks). In 15/50 (30%) of cases this was reported as an unplanned pregnancy. In 28/50 (56%), the participant's IBD had been in remission for at least six months prior to pregnancy.

The majority of patients (73%) were in remission at baseline according to the Physician Global Assessment (PGA). 91 (91%) participants had a baseline faecal calprotectin. The median calprotectin in those with a normal PGA was 22.0 μg/g (8.9-52.6μg/g) compared to 336.0 μg/g (IQR 93.0-757.0 μg/g) in those with active disease (p<0.001). Median clinical disease activity indices were normal; with a median HBI of 1 (IQR 0-2) for women with CD and median SCCAI of 0 (IQR 0-2) in women with UC or IBDU. Approximately one third of women (32%) had poor knowledge scores (0-7) at baseline. There was no significant difference in the rate of poor baseline CCPKnow scores (defined as 0-7) according to age, socioeconomic area (according to the Socio-Economic Indexes for Areas (SEIFA index)), body mass index (BMI), education status, age at diagnosis, disease activity according to PGA, disease phenotype or medication type including biologics. Likewise, there was no difference between those participants who were currently pregnant or had been previously pregnant at the time of the intervention, compared to those who were not pregnant or had never been pregnant. There was a trend for women who were currently pregnant with a planned pregnancy to have better knowledge scores than those with unplanned pregnancies (p=0.06). Participants who were members of the national patient support and advocacy group or were healthcare workers also demonstrated better knowledge scores at baseline (p<0.05). Meanwhile, patients who had a history of a bowel resection or termination of pregnancy had lower baseline knowledge scores (p<0.02).

Table 4.1 Patient Characteristics for Total Cohort and According to Baseline CCPKnow Score

Median (IQR) or n (%)	**Total cohort n=100**	**Poor knowledge (n=32)**	**At least Adequate knowledge (n=68)**	**p-value**
Age (years)	31.8 (28.9-34.5)	31.2 (27.2-32.4)	32.3 (29.4-36.1)	**0.016**
SEIFA Index	7.0 (5.0-9.0)	7.0 (4.5-9.0)	8.0 (6.0-9.0)	0.10
Marital Status				
Single	6 (6.0%)	3 (9.4%)	3 (4.4%)	0.50
Married/cohabiting	86 (86.0%)	26 (81.2%)	60 (88.2%)	
Other	7 (7.0%)	3 (9.4%)	4 (5.9%)	
Unknown	1 (1.0%)	0 (0.0%)	1 (1.5%)	
Education				
Basic school level	3 (3.0%)	2 (6.2%)	1 (1.5%)	0.26
Upper secondary	22 (22.0%)	9 (28.1%)	13 (19.1%)	
Tertiary education	34 (34.0%)	12 (37.5%)	22 (32.4%)	
Tertiary education, >4 years	32 (32.0%)	6 (18.8%)	26 (38.2%)	

Other	4 (4.0%)	1 (3.1%)	3 (4.4%)	
Unknown	5 (5.0%)	2 (6.2%)	3 (4.4%)	
Occupation				
Non-Health care worker	76 (76.0%)	28 (87.5%)	48 (70.6%)	**0.04**
Health care worker	22 (22.0%)	3 (9.4%)	19 (27.9%)	
Missing	2 (2.0%)	1 (3.1%)	1 (1.5%)	
Ethnicity				
Non-Caucasian	12 (12.0%)	6 (18.8%)	6 (8.8%)	0.14
Caucasian	87 (87.0%)	25 (78.1%)	62 (91.2%)	
Missing	1 (1.0%)	1 (3.1%)	0 (0.0%)	
BMI	23.5 (20.8-28.4)	24.8 (20.9-28.7)	23.3 (20.7-27.2)	0.30
Previous conception counselling	47 (47.0%)	10 (31.2%)	37 (54.4%)	0.086
Provider of previous conception counselling				
Gastroenterologist	44 (44.0%)	10 (31.2%)	34 (50.0%)	0.83
IBD Nurse	1 (1.0%)	0 (0.0%)	1 (1.5%)	
Obstetrician	1 (1.0%)	0 (0.0%)	1 (1.5%)	
The Internet	1 (1.0%)	0 (0.0%)	1 (1.5%)	
Member of national patient support and advocacy group	17 (17.0%)	1 (3.1%)	16 (23.5%)	**0.01**
Disease Characteristics				
Crohn's Disease	59 (59.0%)	21 (65.6%)	38 (55.9%)	0.31
Ulcerative Colitis	37 (37.0%)	11 (34.4%)	26 (38.2%)	
IBD unspecified	4 (4.0%)	0 (0.0%)	4 (5.9%)	
History of bowel resection	18 (18.0%)	12 (37.5%)	6 (8.8%)	**<0.001**
Age at Diagnosis				
Under 16 years	12 (12.0%)	2 (6.2%)	10 (14.7%)	0.22
17-40 years	88 (88.0%)	30 (93.8%)	58 (85.3%)	
Current medication				
5-ASA	32 (32.0%)	6 (18.8%)	26 (38.2%)	0.051
Oral Steroids	2 (2.0%)	0 (0.0%)	2 (2.9%)	0.33
Thiopurine	57 (57.0%)	16 (50.0%)	41 (60.3%)	0.33
Biologic	54 (54.0%)	17 (53.1%)	37 (54.4%)	0.90
PGA score				
Remission	73 (73.0%)	24 (75.0%)	49 (72.1%)	0.76
Mild	16 (16.0%)	4 (12.5%)	12 (17.6%)	
Moderate	10 (10.0%)	4 (12.5%)	6 (8.8%)	
Severe	1 (1.0%)	0 (0.0%)	1 (1.5%)	
Faecal calprotectin μg/g	31.6 (11.3-116.0)	29.0 (20.6-62.0)	38.1 (9.6-141.0)	0.80
Currently pregnant	50 (50.0%)	17 (53.1%)	33 (48.5%)	0.67
Planned pregnancy	35 (70%)	9 (28.1%)	26 (38.2%)	0.059
Disease in remission at least 6 months prior to pregnancy	28/50 (56%)	9 (28.1%)	19 (27.9%)	0.75
Previous pregnancy	49 (49.0%)	14 (43.8%)	35 (51.5%)	0.47
Live birth	28 (28.0%)	5 (15.6%)	23 (33.8%)	0.059

Stillbirth	1 (1.0%)	0 (0.0%)	1 (1.5%)	0.49
Miscarriage	27 (27.0%)	7 (21.9%)	20 (29.4%)	0.43
Termination	9 (9.0%)	6 (18.8%)	3 (4.4%)	**0.019**
Crohn's Disease Location (Montreal)				
L1, ileal	26 (26.0%)	13 (40.6%)	13 (19.1%)	0.11
L2, colonic	11 (11.0%)	2 (6.2%)	9 (13.2%)	
L3, ileocolonic	22 (22.0%)	6 (18.8%)	16 (23.5%)	
Upper Gastrointestinal Crohn's disease	2 (2.0%)	1 (3.1%)	1 (1.5%)	0.67
Perianal Crohn's disease	16 (16.0%)	6 (18.8%)	10 (14.7%)	0.85
Surgery for perianal fistula and/or fistula	14 (14.0%)	3 (9.4%)	11 (16.2%)	0.36
Disease behaviour CD (Montreal)				
B1, Non-stricturing non-penetrating	38 (38.0%)	12 (37.5%)	26 (38.2%)	0.67
B2, Stricturing	19 (19.0%)	8 (25.0%)	11 (16.2%)	
B3, Penetrating	2 (2.0%)	1 (3.1%)	1 (1.5%)	
Disease extent UC (Montreal)				
E1, Proctitis	8 (8.0%)	1 (3.1%)	7 (10.3%)	0.38
E2, Left-sided colitis	12 (12.0%)	5 (15.6%)	7 (10.3%)	
E3, Pancolitis	17 (17.0%)	5 (15.6%)	12 (17.6%)	
Extra intestinal manifestations	31 (31.0%)	8 (25.0%)	23 (33.8%)	0.35
Smoker				
Current smoker	7 (7.0%)	3 (9.4%)	4 (5.9%)	0.30
Past smoker	26 (26.0%)	5 (15.6%)	21 (30.9%)	
Never smoker	65 (65.0%)	22 (68.8%)	43 (63.2%)	
Unknown	2 (2.0%)	2 (6.2%)	0 (0.0%)	

SEIFA: Socio-Economic Indexes for Areas; BMI body mass index; IBD: inflammatory bowel disease; PGA: Physician's global assessment

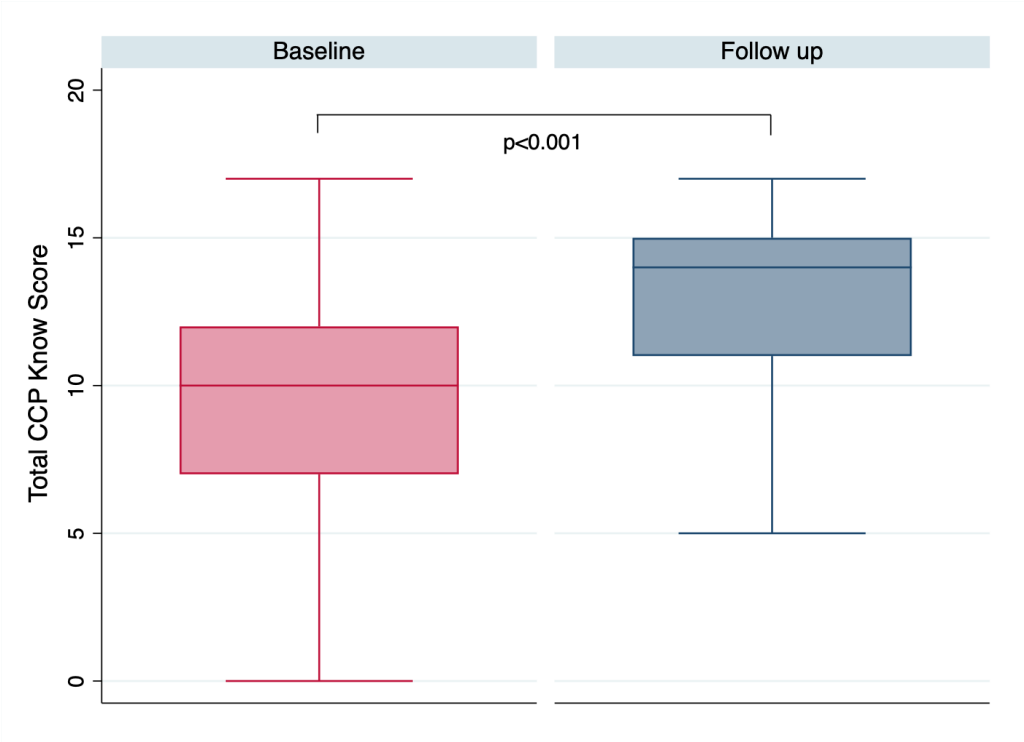
Effect of the Intervention on Pregnancy-Related Knowledge:

82 participants (82%) completed the one month follow up CCPKnow survey; 18 patients did not complete the follow up surveys within two months. The median follow-up duration was 33.5 days (IQR 29-39 days). There was no significant difference in the median baseline CCPKnow score (10/17) for those who completed the follow up compared to those who did not (p=0.60).

Overall, the median CCPKnow score post-intervention was significantly higher than the median score pre-intervention. The median score following the intervention was 14/17 (IQR 7-12) compared to 10/17 (IQR 11-15) prior to the education (p<0.001) (Figure 4.1). There was no significant difference in the median follow up scores for the patients who attended via telemedicine and those who attended in person (p=0.69).

Additionally, regardless of which clinician delivered the intervention, there was no significant difference in median follow up scores (p=0.19).

Figure 4.1 Total CCPKnow Scores Prior to and Following the Educational Intervention



Prior to attending the intervention, 12/100 (12%) participants had very good knowledge levels (score 14/17 or higher), while one month following the intervention 43/82 (52%) had very good knowledge. 32/100 (32%) had poor knowledge levels (CCPKnow score 7/17 or lower) at baseline, compared to only 4/82 (5%) following the intervention (p<0.001) (Table 4.2).

Possible predictive factors for women with poor knowledge levels at baseline were determined using linear regression modelling. Patient age, current unplanned pregnancy and history of previous termination were found to be significant on univariate modelling while socioeconomic index, disease activity according to PGA and medication adherence were not significant. Patient age remained significant (p=0.03) on multivariate modelling with the above variables, with younger age associated with lower knowledge scores.

In detail, responses to 13 out of 17 CCPKnow questions significantly improved following the intervention (Table 4.3). There was no significant change in four questions: 1, 4, 5 and 7 (Table 4.3). One of the IBD inheritance questions (question 1) showed no change, with 75/100 (75%) of participants answering correctly at baseline and then 58/82 (71%) being correct at follow up. However, the subsequent question, which also related to inheritance (question 2), did show a significant improvement with only 35% of participants answering correctly initially and then 78% correct at follow up testing ($p<0.001$). In questions 4 and 5, which related to disease activity, knowledge levels were excellent at baseline and remained so, with over 90% of the cohort answering these questions correctly at follow up. Similarly, almost all women at baseline were aware that pregnant women with IBD 'should continue some medications' (question 7).

Table 4.2 CCPKnow Scores Pre and Post the Educational Intervention

CCPKnow score	Pre-intervention (n=100)	Post-intervention (n=82)	p-value
Poor (0-7)	32 (32.0%)	4 (5%)	**<0.001**
Adequate (8-10)	27 (27.0%)	8 (8.0%)	
Good (11-3)	29 (29.0%)	27 (27.0%)	
Very good (14-17)	12 (12.0%)	43 (43.0%)	

Table 4.3 Per Question Analysis of Scores Pre and Post the Intervention

Question	Response	Baseline (n=100)	Follow up (n=82)	p-value
INHERITANCE				
1. Inflammatory bowel disease is more likely to affect a child if mother or father are suffering from it	Correct	75 (75.0%)	58 (70.7%)	0.38
2. The risk of passing on inflammatory bowel disease to a child is less than 10%	Correct	35 (35.0%)	64 (78.0%)	**<0.001**
FERTILITY				
3. Men with inflammatory bowel disease usually do not have problems with infertility	Correct	44 (44.0%)	61 (74.4%)	**<0.001**
DISEASE ACTIVITY				
4. IBD should be well controlled before becoming pregnant	Correct	93 (93.0%)	81 (98.8%)	0.63
5. Women with inflammatory bowel disease should delay trying for a baby until their disease has been controlled by medication	Correct	87 (87.0%)	77 (93.9%)	0.18

6. Active inflammatory bowel disease during pregnancy should be treated with some types of drugs to protect the pregnancy	Correct	67 (67.0%)	71 (86.6%)	**<0.01**
DRUGS				
7. Pregnant women with inflammatory bowel disease should continue some medications	Correct	94 (94.0%)	81 (98.8%)	1.00
8. Infliximab or Adalimumab are generally seen as 'probably safe' in pregnancy	Correct	59 (59.0%)	63 (76.8%)	**<0.01**
9. The drug Methotrexate should always be stopped 3-6 months before trying for a baby	Correct	24 (24.0%)	40 (48.8%)	**<0.001**
10. During pregnancy mesalazine is safe and should be continued	Correct	38 (38.0%)	48 (58.5%)	**<0.01**
11. During pregnancy azathioprine or 6-mercaptopurine can be continued	Correct	53 (53.0%)	56 (68.3%)	**<0.01**
MODE OF DELIVERY				
12. Women with inflammatory bowel disease can have a vaginal delivery in most cases	Correct	63 (63.0%)	76 (92.7%)	**<0.001**
13. Peri-anal disease that occurs after a normal vaginal delivery is more likely if a woman suffered from it previously	Correct	26 (26.0%)	39 (47.6%)	**<0.001**
PREGNANCY OUTCOMES				
14. Women suffering from IBD often give birth a bit early	Correct	35 (35.0%)	54 (65.9%)	**<0.001**
15. Birth defects in babies of mothers with IBD occur slightly more often than in babies of mothers without inflammatory bowel disease	Correct	25 (25.0%)	53 (64.6%)	**<0.001**
16. The chances of having a healthy baby for mothers suffering from IBD are very good	Correct	78 (78.0%)	79 (96.3%)	**<0.001**
BREASTFEEDING				
17. Mothers suffering from IBD may have tiny amounts of medication in their breast milk	Correct	54 (54.0%)	72 (87.8%)	**<0.001**

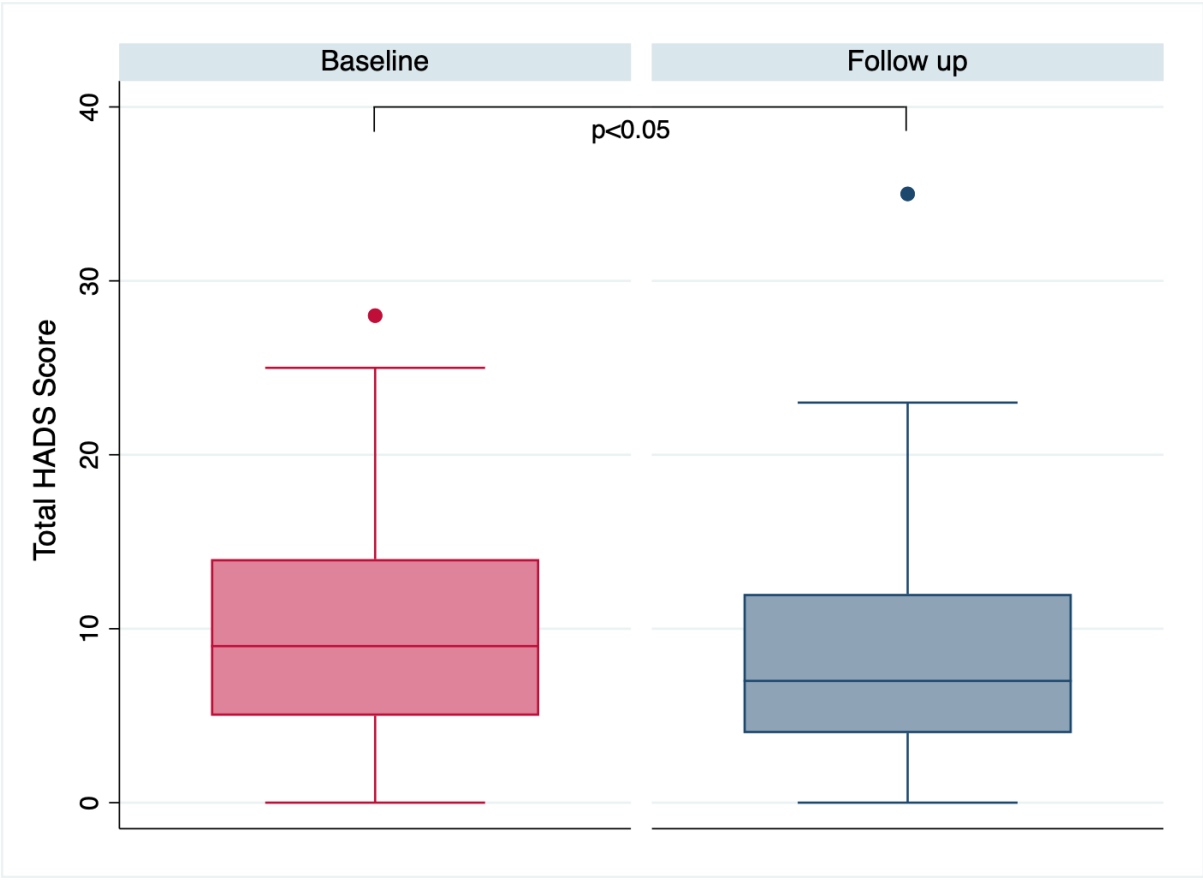
Effect of the Educational Intervention on Patient Depression and Anxiety scores:

Baseline and follow up HADS scores are shown in Table 4.4. In 39% of the cohort, baseline HADS-A scores were suggestive of anxiety (HADS-A > 7). There were no significant differences in patient characteristics whether or not the baseline HADS-A score was normal, including no difference in baseline CCPKnow score, disease activity by PGA, faecal calprotectin level, patient age or current pregnancy status. HADS-A and HADS-D scores were stable following the intervention. There was a statistically significant improvement in global HADS scores following the educational intervention ($p<0.05$) (Figure 4.2).

Table 4.4 HADS Scores Pre and Post the Intervention

	Baseline (n=100)	Follow up (n=81)	p-value
Total HADS Anxiety Score, median (IQR)	6 (4 - 9)	6 (3 - 8)	0.16
HADS-A score			
Normal	60 (60.0%)	59 (72.8%)	0.06
Possible	26 (26.0%)	17 (20.7%)	
Probable	13 (13.0%)	5 (6.1%)	
Missing	1 (1.0%)	19	
Total HADS Depression Score, median (IQR)	3 (1 - 5)	2 (1 - 4)	0.05
HADS-D score			
Normal	90 (90.0%)	76 (93.8%)	0.68
Possible	3 (3.0%)	3 (3.7%)	
Probable	6 (6.0%)	2 (2.4%)	
Missing	1 (1.0%)	19 (19.0%)	
Total HADS Score, median (IQR)	9 (5 - 14)	7 (4 -12)	**<0.05**

Figure 4.2 Total HADS scores Prior to and Following the Educational Intervention



Effect of the Educational Intervention on Health-Related Quality of Life:

There was a significant improvement across all dimensions of the IBDQ and the total median IBDQ improved from 176 to 186 ($p<0.05$) (Table 4.5). There was a significant improvement in the dimensions of 'Emotional well-being' and 'General Health' using the SF-36 instrument ($p<0.05$) (Table 4.6).

Table 4.5 IBDQ Sub-scores and Total Score Pre and Post the Intervention

IBDQ score, median (IQR)	Baseline (n=97)	Follow up (n=81)	p-value
Bowel systems	5.5 (4.9 - 6.11)	6 (5.5 - 6.5)	**<0.001**
Emotional health	5.33 (4.5 - 6)	5.75 (5.08 - 6.25)	**<0.001**
Systemic systems	4.4 (3.4 - 5)	4.8 (4.2 - 5.6)	**<0.01**
Social function	6.8 (6 - 7)	7 (6.4 - 7)	**<0.05**
Total	176 (155 - 186)	186 (171 - 198)	**<0.001**

Table 4.6 SF-36 Sub-Scores for Each Dimension Pre and Post the Intervention

SF-36 Sub-score, median (IQR)	Baseline (n=98)	Follow up (n=82)	p-value
Physical functioning	92.5 (80-100)	94.72 (80-100)	0.07
Role limitations due to physical health	100 (25-100)	100 (50-100)	0.24
Role limitations due to emotional problems	100 (33.33-100)	100 (66.66-100)	0.12
Energy/Fatigue	45 (30-65)	50 (35-70)	0.05
Emotional well-being	76 (60-84)	82 (68-88)	**<0.05**
Social functioning	81.25 (62.5-100)	75 (75-100)	0.79
Pain	77.5 (67.5-90)	77.5 (67.5-90)	0.81
General Health	55 (40-70)	60 (40-75)	**<0.01**

Medication Adherence:

81/91 (89%) patients who were prescribed a regular medication for their IBD reported being adherent (>80% of daily dose or equivalent) at baseline. This was similar after the intervention with 69/75 (92%) respondents reporting good adherence. Medication adherence rates and reason(s) for non-adherence, where applicable, are reported in Table 4.7.

Table 4.7 Medication Adherence Rates Pre and Post the Intervention

	Baseline (n=91)	**Follow up (n=74)**	**p-value**
Please estimate your daily intake of prescribed medication on average			
>80% of daily dose	81 (89%)	69 (93%)	0.18
50-80% of daily dose	4 (4%)	4 (5%)	
0-49% of daily dose	6 (7%)	1 (1%)	
If non-adherent, reason(s) for non-adherence			
Fear of a negative effect on fertility or foetus	5 (50%)	1 (20%)	1.00
Quiescent disease	0 (0%)	1 (20%)	1.00
Forgetfulness	4 (40%)	4 (80%)	1.00
Other	2 (20%)	1 (20%)	1.00

Patient Satisfaction:

Overall, 93% of participants were satisfied with the intervention, while 2% were 'neutral' and 5% dissatisfied. The majority (66/82, 80%) of participants were 'extremely satisfied' with the educational intervention.

Six-month Follow-up:

Of those who were not pregnant at the time of the intervention, 20/50 (40%) had become pregnant within six months after their visit, 22/50 (44%) were not pregnant (12/22 (55%) were trying to conceive) and 8/50 (16%) lost to follow up/withdrawn at six months.

Pregnancy Outcomes:

Fifty patients were pregnant at time of intervention and 20 patients became pregnant within six months of the educational intervention. Pregnancy and birth outcomes are currently available for 66/70 participants who had a live birth and are similar to the background population. Pregnancy outcomes are shown in Table 4.8. 95% of women took folic acid supplementation in pregnancy. The majority of babies were born at term with normal birthweight and normal Apgar scores. In addition, 5/70 (7%) reported spontaneous abortions following the visit, all in the first trimester.

Table 4.8 Pregnancy outcomes to date (live births n=66)

	Median (IQR) or n (%)
Gestation at delivery (weeks)	39 (38-40)
Pre-term birth (<37 weeks)	4 (6%)
Birth weight (grams)	3280 (2990-3640)
Low birth weight (<2500g)	5 (8%)
Birth length (cm)	50 (49-51.5)
Mode of delivery	
Caesarean section- emergency	11 (17%)
Caesarean section- elective	20 (30%)
Vaginal birth	26 (39%)
Vaginal birth instrumental	9 (14%)
APGAR score at 1 minute*	9 (8-9)
APGAR score at 5 minutes*	9 (9-9)
Congenital abnormality	3 (5%)
Gestational diabetes	3 (5%)
Pre-eclampsia	5 (8%)
Fertility treatment prior to pregnancy	8 (12%)
Folic acid supplement at least 1 month prior to pregnancy	46 (70%)
Folic acid supplement during pregnancy	63 (95%)
Iron infusion during pregnancy	22 (33%)
Smoking history	
Yes, daily	1 (2%)
Yes, not every day	1 (2%)
No, ex-smoker	15 (23%)
No, never smoker	48 (73%)
Unknown	1 (2%)
Alcohol during pregnancy	4 (6%)

**Available in 53/66 participants*

4.4 Discussion

This study demonstrates the effectiveness of a simple, accessible and repeatable educational intervention to address disease-specific knowledge deficits in women with IBD who are pregnant or planning to conceive. Emotional health improved and high levels of patient satisfaction were reported in the study cohort following the intervention.

We demonstrated that in women planning to conceive or pregnant, overall knowledge levels are reasonable for most, but can improve further with tailored education. In our study, a third of the cohort had poor knowledge at baseline, which decreased to less than 5% a month after the educational intervention. Baseline knowledge levels in our

cohort were superior to those reported in previous studies, which did not restrict study inclusion to pregnant patients or those considering pregnancy[3,4,13]. The current study enrolled women attending IBD specialists and IBD clinics, and thus the cohort might be expected to have better IBD and pregnancy knowledge than those receiving general gastroenterology or primary care. With all of these women receiving specialist care, this highlights a deficit in pregnancy-related education within general IBD healthcare. Additionally, knowledge levels may be poorer and gains even greater in a more general IBD population. Even if women attended our intervention when already pregnant or having previously received pregnancy-related counselling from their treating specialist, there remained shortcomings in baseline pregnancy-related knowledge, suggesting that important knowledge gains can still be made with this simple education session. In the current study, we have identified that patients with unplanned pregnancies, a history of termination of pregnancy and younger patients may be more likely to have poor pregnancy-related knowledge. Meanwhile, participants who were members of the national patient support and advocacy group or were healthcare workers more commonly had adequate baseline knowledge scores. These data can enable the intervention to be further targeted to those patients who may possess the lowest knowledge.

We have documented that a significant proportion of women with IBD in the setting of planning for pregnancy or being currently pregnant have persistent symptoms of anxiety. It has been shown in the general IBD population that improved disease-related knowledge is associated with greater anxiety, and that high levels of anxiety may drive reduced HRQoL in patients with IBD[26]. However, in contrast to other studies whereby anxiety may be amplified following general disease education, patient anxiety was not exacerbated after the education session in our study. There was no significant improvement in anxiety after the educational intervention, suggesting that anxiety related to IBD and pregnancy is not only related to knowledge levels and can persist throughout the pregnancy and chronic illness journey. In addition, there were no associations with the presence of anxiety at baseline and patient variables such as knowledge score, current pregnancy and disease activity found in the present study.

While anxiety can remain significant, we found that the quality of life of women in our cohort was good overall, but was further improved after a pregnancy-specific education session, especially in the domain of emotional health. HRQoL may be negatively impacted by both pregnancy and IBD in general, particularly active IBD[,27,28]. A small, retrospective study that examined HRQoL across pregnancy in 32 women with IBD,

found HRQoL scores improved in half of these patients, remained stable in 14 (44%) and in 2(6%) worsened during pregnancy[29]. Meanwhile, recent data from a small Canadian cohort, has shown that HRQoL was reduced in women with clinically active IBD in pregnancy[30]. Unlike other older studies, which found that HRQoL can worsen after disease-related education[31], our targeted educational intervention did not impair the quality of life in women with IBD who are pregnant or planning pregnancy. Our cohort was largely in remission, which may account for the satisfactory HRQoL scores overall. Still, in the setting of patients being mostly in remission at the time of the intervention, quality of life and emotional wellbeing appeared to improve following the educational intervention.

The majority of our cohort reported being adherent to their medication and therefore a statistically significant change in adherence rates could not be shown. However, in the minority of patients who were non-adherent at baseline (n=10), five women cited fear of adverse effects on fertility or pregnancy before attending the education intervention, compared to only one participant afterwards. In a previous survey from Canada, almost 20% of women with IBD of childbearing age reported stopping an IBD medication while attempting to conceive or while pregnant, and only half said they received counselling regarding IBD medications in pregnancy[32]. Our pregnancy-specific medication adherence questionnaire is based on earlier retrospective Danish studies relating to medication adherence pre-conception and in the setting of pregnancy[24,25]. These two studies, in women with Crohn's disease and UC, showed a high concordance between self-reported medical treatment using this questionnaire and a prescription database[24,25]. The other advantage of this questionnaire is that it incorporates the influence of pregnancy-specific fears on patient medication adherence. Consistent with our pre-intervention data, these studies identified that of the patients who were non-adherent in pregnancy, half reported a fear of medication effect on the foetus[24,25]. Julsgaard et al also found that women with UC who reported receiving counselling were less likely to be non-adherent during pregnancy,[24] but this was not the case in the study of women with Crohn's disease[25]. Similar to our findings, the recent Canadian study assessing an online educational portal regarding IBD and pregnancy also had high pre-intervention rates of medication adherence[33]. This study, using a generic medication adherence questionnaire, did not show a statistically significant difference following their online intervention[33]. We have demonstrated that in a well-educated cohort, excellent medication adherence can be achieved with a numerical decrease in women reporting non-adherence due to fears of adverse effects on fertility or the foetus.

The strengths of our study were that all facets of pregnancy-related knowledge were covered, but the discussion was also tailored to patients' needs, providing an opportunity to ask questions and build rapport. We have shown that satisfaction levels were very high with this individualised approach. The education session can be delivered in-person or by telemedicine, allowing the program to be readily available to regional patients. The cohort was a representative sample with a range of obstetric histories, disease severity and medication types, suggesting that our findings should be translatable to other cohorts. Our educational package was specifically developed for this study, based on the topics integrated in the 'CCPKnow' as well as themes and specific concerns identified through in-depth interviews with patients[34]. This pro forma can be used as a template to guide structured discussion (Appendix II). Areas where knowledge did not improve, which need particular focus in future counselling, include the risk of pre-term birth, and the risk of recurrence of perianal disease after vaginal delivery. Similarly, the issue of mildly increased risk of birth defects in IBD remains controversial, and it is important to explain the background risk in the general population in order to contextualise this information for patients and to emphasise that a possible minor increased risk is not associated with IBD medications[35].

Limitations of our study include selection bias and short duration of follow up. Women interested in attending an education session may be more motivated to improve their knowledge than those who decline referral. We chose follow-up at one month to maximise the internal validity of the study and restrict other contributory factors (such as external sources of education or influences on quality of life over time), rather than a longer follow up potentially involving multiple contacts within the healthcare system during the peri-partum period. We believed this was more meaningful than checking retention immediately, but also long enough that patients could make decisions regarding their preferences for pregnancy. The patients who were lost to follow-up may have impacted our findings, for example if these women had less improvement in knowledge, however, there was no significant difference in their baseline knowledge scores. The limitations of our model of pregnancy education include the time required per patient, limiting the number of patients able to access the service, and the failure of the intervention to reduce anxiety. Potential opportunities for ongoing research arising from the present study may include validation in additional cohorts with poor baseline knowledge, and inclusion of a comparison group who do not receive the face-to-face intervention. This intervention could be adapted to be provided as a generic online education session, however this would result in a loss of individualisation. No study has

compared the two models of online and personalised education for improving knowledge and emotional wellbeing in this vulnerable patient group. In fact, patients may benefit from initial online education followed by a personalised interview using the model established in the current study.

4.5 Conclusion

Universally, access to a dedicated IBD and pregnancy service for all women with IBD is limited. Hence, we advocate for a simpler, less resource intensive model consisting of this single individualised consultation, which can be delivered either in-person or via telemedicine, with clear communication regarding the recommended pregnancy treatment plan for both the patient and their wider treating team. Our model, which incorporates telemedicine, currently provides a pregnancy and IBD education service fortnightly to a city of around four million people and surrounding regional areas, and could be administered by a general gastroenterologist with an interest in this field. We believe this approach is logistically and financially more feasible than numerous specially set-up clinics looking after IBD patients throughout pregnancy. Uptake of this educational intervention has the potential to not only improve pregnancy knowledge, but also to optimise patient satisfaction, promote medication adherence, and enhance quality of life for women with IBD. Further research is required to evaluate the role of newer models of education provision such as an online decision aid and whether this can enhance our current model. The factors driving persistent anxiety in women with IBD approaching pregnancy are likely to be complex and also need to be explored to ensure appropriate support for this population.

Further Discussion

For this study, missing data was assumed to be missing at random and no multiple imputation was performed. The total number of participants with missing follow up data are reported. A limitation of our study includes the potential selection bias from participants who were lost to follow up, for example if these participants had demonstrated a lesser improvement in their knowledge scores; however, the lost to follow up group was relatively small and there was no significant difference in their baseline knowledge scores.

Another limitation is the sample size. Formal power calculation was not conducted for the CCPKnow and HADS parameters for this pre-test/post-test study. The small sample size may have resulted in under-powering and hence, for example, the research may not have been able to detect a significant improvement in patient anxiety following the intervention. Future studies in larger cohorts with a control group who do not receive the intervention would be beneficial.

Four CCPKnow questions did not show significant improvement following the intervention and these were all questions where the majority of participants knew the correct response prior to attending the intervention. For example, most women were aware at baseline regarding the recommendation to control IBD using medications in pregnancy. These topics were still covered in the educational intervention pro forma.

In addition, there was no difference between changes in CCPKnow among those who had an improvement in their HADS compared to those who did not have an improvement in their HADS (median change in CCPKnow score 3/17 in both groups, $p>0.05$). It is likely that receiving additional information and reassurance through the intervention may help improve psychological wellbeing and that patient anxiety in this context exists somewhat distinctly to patient knowledge level.

Interestingly, there was no significant association between poor CCPKnow score and having a baby with low birth weight. Median CCPKnow score following the intervention was 15/17 in patients with low birth weight babies compared to 13/17 in patients with normal birth weight babies ($p>0.05$).

In the earlier study by Mountifield el al [13], there was a more pronounced improvement in patient knowledge scores with 56% of females having poor knowledge prior to the group education session compared to 2% immediately after the education. However, this is to be expected, due to the differences in study design when compared against the current study. In the previous study, participants were captured while attending a general IBD patient information evening rather than for specific pregnancy-related counselling, hence at baseline they tended to have poorer pregnancy-related knowledge than this cohort. Additionally, in the study by Mountifield et al, follow up knowledge questionnaires were completed directly following the presentation rather than assessing knowledge retention at one to two months following the session.

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5 Monitoring Inflammatory Bowel Disease in Pregnancy using Gastrointestinal Ultrasonography

5.1 Introduction

Inflammatory Bowel Disease (IBD) often affects women in their prime childbearing years. Management of the pregnant patient is challenging and requires consideration of both maternal and foetal wellbeing. It is now established that active IBD can lead to adverse pregnancy outcomes[1-3]. Safe and accurate monitoring of disease activity during pregnancy is imperative, but not always straightforward. Pregnancy can affect the interpretation of traditional symptoms and biomarkers[4], while some modes of assessing IBD, such as endoscopy and computed tomography (CT), present potential concerns regarding risks to the foetus[5,6].

Gastrointestinal ultrasonography (GIUS) is increasingly used as part of IBD care. GIUS can be used to identify disease activity in both the small and large bowel as well extra-luminal complications and stricturing disease[7,8]. GIUS can accurately assess disease activity and extent in non-pregnant patients with Crohn's disease (CD) and ulcerative colitis (UC) proximal to the rectum[9]. GIUS has been shown to have similar diagnostic accuracy for evaluating ileal and colonic inflammation and disease complications compared with magnetic resonance imaging and CT[10].

As a radiation free and non-invasive imaging modality, ultrasound is the safest imaging technique for use in pregnancy. It is also the preferred diagnostic modality by patients[11]. In practice, bowel views can be impeded by the gravid uterus, creating some uncertainty regarding the accuracy of GIUS for IBD assessment in pregnancy. The role of GIUS for monitoring of IBD in pregnancy has not yet been established[9] and it is underutilised in clinical practice. A Canadian study of 91 scans in pregnant patients, which included women with CD but not UC, found that GIUS could detect subclinical inflammation in pregnancy, however there were only a small number of patients (n=11) with active sonographic disease reported in this study[12].

Hence, we aimed to determine the feasibility and accuracy of GIUS in the assessment of IBD in pregnancy and how these change with pregnancy progression.

5.2 Materials and Methods

We performed a multicentre observational study across three Australian GIUS centres to evaluate the feasibility and accuracy of GIUS for monitoring of IBD in pregnancy. The study included women with a confirmed diagnosis of ileal and/or colonic IBD who underwent at least one GIUS assessment during pregnancy. Patients with disease known to be limited to the upper gastrointestinal tract or rectum or concurrent *Clostridioides difficile* infection were not included. Participants underwent GIUS in both the first and second trimesters where possible.

Clinical and Biochemical Assessment:

Baseline information including demographics and disease phenotype was documented as well as the presence of clinical disease activity at the time of GIUS defined by the Physician Global Assessment (PGA) as well as either the Harvey Bradshaw Index (HBI) or Simple Clinical Colitis Activity Index (SCCAI) where possible. In the absence of endoscopic data or cross-sectional imaging to determine disease activity, faecal calprotectin (FC) greater than 100μg/g was used to define the presence of disease activity during pregnancy[13-16]. A matched FC result was recorded within two weeks of each GIUS.

Gastrointestinal Ultrasound:

GIUS examinations were performed by one of four gastroenterologists (JB, RB, EF, EW) with adequate training and expertise in the procedure[17] using either a SuperSonic Aixplorer (SuperSonic Imagine, Aix-en-Provence, France), Aloka Prosound F75 (Aloka, Tokyo Japan) or a Toshiba Aplio 500 (Toshiba, Tokyo, Japan) ultrasound machine with a high-frequency linear probe.

Clinicians made an assessment of the adequacy of bowel views (adequate/inadequate) in four colonic segments (sigmoid, descending, transverse, ascending) and the terminal ileum (TI). Where relevant, ileal measurements at the ileocolic anastomosis and/or distal ileum were reported. Any location(s) in which the views were impeded by the gravid uterus were documented to determine the feasibility of obtaining adequate IUS views throughout pregnancy.

Bowel wall thickness (BWT) (mm) and colour Doppler blood flow were recorded in each bowel segment and the presence or absence of intra or extra-mural complications of

disease including stenosis, bowel dilatation and phlegmon/abscess were reported for all scans.

Assessment of disease activity on GIUS was made for each ultrasound performed. Disease activity on GIUS was defined as BWT greater than 3mm[9,10,18]. Colour Doppler blood flow (vascularity) was also measured in all areas where BWT was > 3mm and a Limberg score was assigned, with a score of 2 for short stretches of vascularity, 3 for long stretches of vascularity and 4 for long stretches of vascularity reaching into the mesentery[19,20].

In scans with adequate views of involved segments, sonographic disease activity was compared to biochemical disease activity as defined by elevated FC (>100μg/g) in order to objectively assess the accuracy of GIUS findings. Results were excluded from the analysis of GIUS accuracy if there were inadequate colonic views in the setting of colonic disease, and similarly in scans with inadequate ileal views for patients with ileal Crohn's disease.

Statistical considerations:

Data are reported as median [interquartile range (IQR)] or number (%). Between group differences were compared by $\chi 2$ test and Wilcoxon rank-sum test, as appropriate. Correlation between FC and maximal BWT in any affected segment was assessed using Spearman's correlation coefficient. The accuracy of IUS as compared to FC was determined through the calculation of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) within a 95% confidence interval (CI). Cohen's kappa coefficient was calculated to assess agreement between the two diagnostic tests. A univariate ordinal logistic regression model was fitted to examine the association between PGA and BWT, with the standard errors allowing for intragroup correlation due to multiple scans per person. Statistical analysis was performed using STATA version 15.1 (STATA LP College Station, TX, USA). A p value < 0.05 was considered statistically significant.

Ethical statement:

Ethical approval for the study was obtained from the Human Research Ethics Committees of the participating hospitals. Data was prospectively recorded as part of the PICCOLO study and patients provided written informed consent before inclusion at St Vincent's Hospital Melbourne (HREC/17/SVHM/116), while data was retrospectively

collected from the other two sites, Mater Hospital Brisbane and Queen Elizabeth Hospital, Adelaide (reference HREC/18/MHS/75 and HREC/17/RAH/78, respectively).

5.3 Results

Ninety pregnant patients with IBD were included (57 CD, 29 UC). Patient characteristics are shown in Table 5.1. In total, 127 GIUS examinations were included between May 2016 and August 2019 with assessment of all five bowel segments. Ten patients attended one GIUS in first trimester (gestational weeks 4-13), 38 patients had one GIUS in the second trimester (gestational weeks 14-26), 27 patients underwent GIUS in both first and second trimesters, while six patients had one scan performed in the third trimester only (Table 5.1). 71 of 127 (55.9%) scans were performed in the second trimester of pregnancy (median gestation 19 weeks).

Table 5.1 Patient characteristics (n=90)

	n (%) or median (IQR)
Age (years)	31 (29-34)
Pre-pregnancy BMI (kg/m^2)	23.4 (21.3-28.4)
Disease duration (years)	7.6 (2.8-11.8)
Diagnosis: **-Crohn's Disease** **-Ulcerative Colitis** **-IBD unclassified**	 57 (63%) 29 (32%) 4 (4%)
UC extent (n=29): **-Left-sided** **-Extensive**	 16/29(55%) 13/29(45%)
IBDU extent (n=4): **-Extensive**	 4/4 (100%)
CD location (n=57) **-Ileal** **-Colonic** **-Ileocolonic**	 21/57 (37%) 13/57 (23%) 23/57 (40%)
Upper gastrointestinal CD	3/57 (5%)
CD behaviour (n=57) **-Non-stricturing, non-penetrating** **-Stricturing**	 38/57 (67%) 19/57 (33%)
Previous ileocolic resection	11/57 (19%)
Timing of GIUS in pregnancy **-One scan in Trimester 1** **-One scan in Trimester 2** **-Two scans Trimesters 1 and 2** **-One scan in Trimester 3**	 10 (11%) 38 (42%) 27 (30%) 6 (7%)

-Two scans in Trimester 2	5 (6%)
-Two scans Trimesters 1 and 3	1 (1%)
-Two scans Trimesters 2 and 3	1 (1%)
-Three scans (with two scans in Trimester 2)	2 (2%)

BMI, body mass index; CD, Crohn's disease; GIUS, gastrointestinal ultrasound; IBDU, inflammatory bowel disease unclassified; UC, ulcerative colitis

Feasibility of GIUS views across pregnancy:

Adequacy of GIUS views were determined for each bowel segment. The gestational week of pregnancy at these times were recorded. Rates of adequate GIUS views per segment across pregnancy are shown in Table 5.2.

Overall, in 88/127 (69%) scans, adequate views were possible across all five bowel segments at a median gestation of 16.5 weeks (IQR 10-21 weeks), while in 39/127 (31%) scans there was at least one segment with inadequate views at a median 22 weeks gestation (IQR 20-26 weeks) ($p<0.001$). There was no significant difference overall in the median pre-pregnancy BMI for scans with complete views compared to those without (23.3 vs. 23.6 kg/m^2, $p=0.46$).

Trimester 1: weeks 4-13

Thirty-nine patients underwent a GIUS during the first trimester of pregnancy (gestational weeks 4-13). Adequate views were obtained in all bowel segments in all but two patients, both of whom had a pre-pregnancy BMI > 28kg/m^2; in both of these patients, there were two segments not adequately visualised (Table 5.2). In these two patients GIUS views were impeded by body habitus rather than the pregnancy state according to the ultrasonographer's assessment.

Early Trimester 2: weeks 14-19

A total of 28 scans were performed for 27 patients during the early second trimester (gestational weeks 14-19). Adequate views were achieved in all bowel segments during the early second trimester, with the exception of three patients who had had a pre-pregnancy BMI of >31kg/m^2; in these three patients, adequate TI views were not obtained and there were inadequate transverse colon views in one of these patients (Table 5.2).

Late Trimester 2: weeks 20-26

A total of 51 scans were performed for 49 patients during the late second trimester (gestational weeks 20-26). Views throughout the colon remained adequate in the majority of scans (45/51, 88%) in the late second trimester of pregnancy. However, it became increasingly difficult to obtain adequate views of the terminal ileum. It was possible to adequately assess the terminal ileum late in the second trimester (including in gestational week 26) in 30/51 (59%) scans. In 23/30 (77%) of these scans where the TI could be seen, the TI was normal.

Trimester 3: 27-33 weeks

Nine patients had a GIUS performed between 27 and 33 weeks gestation. Adequate colonic views were possible in most patients (7/9, 78%). However, adequate views of the terminal ileum were not obtained in any patients at this stage of pregnancy. Views were limited due to the gravid uterus according to the ultrasonographers performing the procedure.

Table 5.2 Rates of adequate GIUS views per segment across pregnancy

Adequate views obtained, n (%)	**Trimester 1 Weeks 4-13 (n=39)**	**Early trimester 2 Weeks 14-19 (n=28)**	**Late trimester 2 Weeks 20-26 (n=51)**	**Trimester 3 Weeks 27-33 (n=9)**
Sigmoid colon	39/39(100%)	28/28 (100%)	47/51 (92%)	9/9 (100%)
Descending colon	38/39* (97%)	28/28 (100%)	49/51 (96%)	9/9 (100%)
Transverse colon	39/39 (100%)	27/28* (96%)	49/51 (96%)	7/9 (78%)
Ascending colon	37/38*^ (97%)	28/28 (100%)	51/51 (100%)	9/9 (100%)
Terminal ileum	37/39*(95%)	25/28* (89%)	30/51 (59%)	0/9 (0%)

n=number of scans; *inadequate views in the setting of BMI $\geq$ 28kg/m^2

^=one patient with right hemicolectomy

Accuracy of GIUS in the Diagnosis of Disease Activity in Pregnancy and Subsequent Therapy Changes and Pregnancy Outcomes

To assess the accuracy of GIUS in the diagnosis of active disease in pregnancy, FC concentration was compared to disease activity in adequate scans for involved IBD segments. 107/127 (84%) scans were adequate. There were 71 adequate scans among 55 patients with a matched FC available for this analysis, at a median 19 weeks gestation (25 in trimester 1; 42 in trimester 2; 4 in trimester 3) (Figure 5.1).

Figure 5.1: Flow diagram of adequate GIUS scans with matched faecal calprotectin for inclusion in accuracy analysis

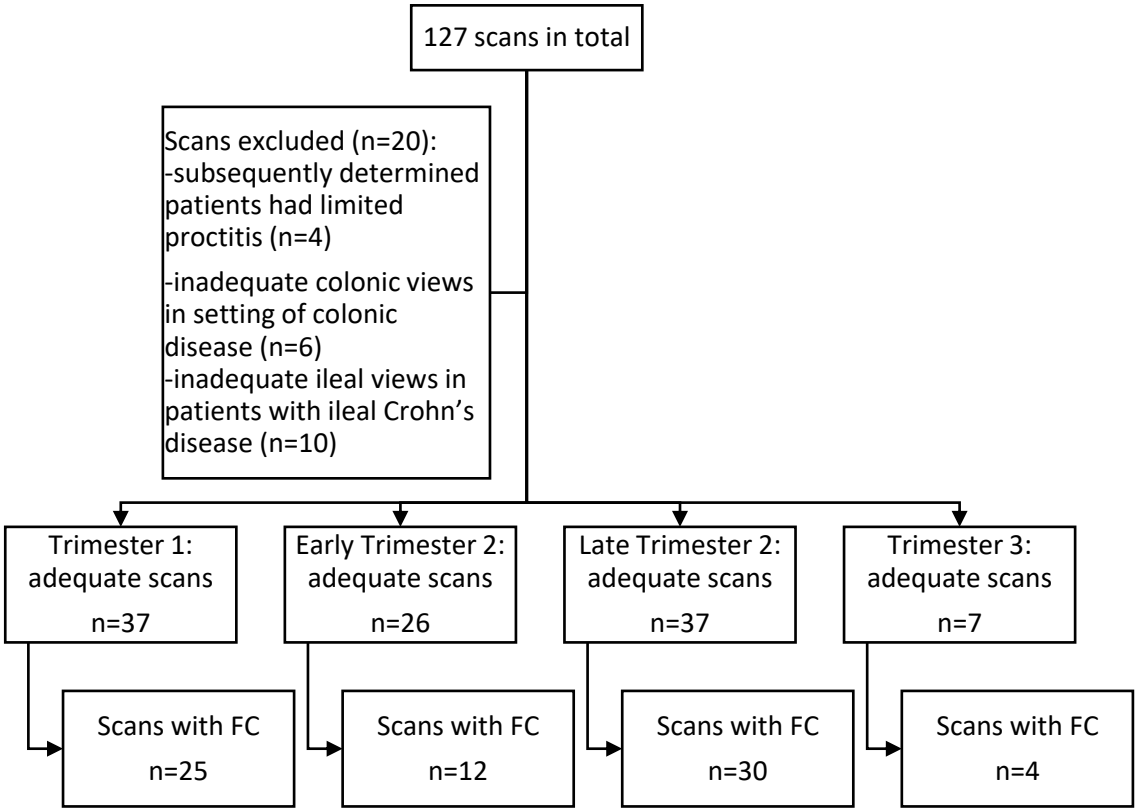

Figure 5.1 Correlation between Faecal Calprotectin and Bowel Wall Thickness

When compared to disease activity according to FC >100μg/g, GIUS in pregnancy delivered a high specificity and sensitivity, of 83% (95% CI 70-92%) and 74% (95% CI 49-91%), respectively, as well as an excellent NPV of 90% **(**95% CI 77-97%) (Table 5.3). In the scans with no sonographic disease activity, the median FC was 20.9μg/g (IQR 9.4-43.8μg/g), compared to a median FC of 186μg/g (IQR 38.2-414.0μg/g) in the scans with disease activity on GIUS (p<0.001). There was a weak but statistically significant correlation between FC and maximal BWT in any affected segment (r=0.26, p= 0.03) (Figure 5.2).

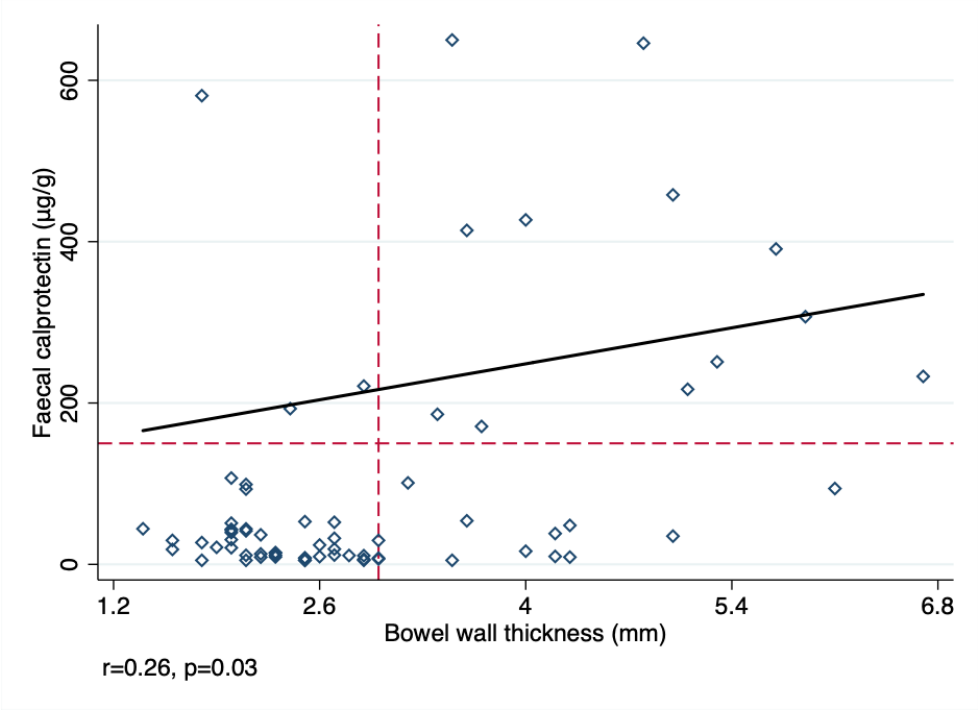

Figure 5.2 Correlation between Faecal Calprotectin and Bowel Wall Thickness

**Outliers (FC of 1680 and 6840) removed for purpose of graphical representation but not from analysis*

Nine scans revealed active sonographic disease in the setting of a FC <100µg/g (Table 5.3). In trimester one, five patients had 'active' GIUS findings with a low FC. Four of these five patients were in clinical remission, had only mildly increased BWT on IUS in one segment (3.6-4.3mm) with no hypervascularity present and these were interpreted to be consistent with chronic disease without active inflammation. One of these five these patients had evidence of disease activity on GIUS located at the ileocolic anastomosis with a corresponding FC of 94µg/g. In trimester two, four patients had 'active' disease detected on GIUS with low FC. In two of these patients, the ultrasound findings were again consistent with chronic disease changes, which were also noted on their first trimester scans. However, in two patients there was stricturing small bowel Crohn's disease seen on GIUS in the setting of a FC<100µg/g. In five scans, no active disease was seen on GIUS with a FC>100µg/g (Table 5.3). For one of these five scans, the patient was in clinical remission at the time and had a FC of 107µg/g, which normalised later in pregnancy. Another four scans had an elevated matched FC with no active disease seen on GIUS, and these results were attributed to active rectal disease in patients with known distal colonic disease. In the third trimester, two patients

had symptoms of active colonic disease and elevated FC, with no active sonographic disease seen beyond the proximal sigmoid colon at 27 and 31 weeks, respectively.

Table 5.3 Comparison of GIUS with FC in pregnant IBD patients

	FC >100μg/g	**FC <100μg/g**
Disease activity on GIUS (BWT>3mm)	14	9
No activity on GIUS (BWT≤3mm)	5	43
Sensitivity (95% CI)	**74% (49-91%)**	
Specificity (95% CI)	**83% (70-92%)**	
Negative predictive value (95% CI)	**90% (77-97%)**	
Positive predictive value (95% CI)	**61% (39-80%)**	
Kappa coefficient	**0.53 (Agreement 80%)**	

GIUS, gastrointestinal ultrasound; FC, faecal calprotectin; CI, confidence interval

Very similar results were obtained when using a FC cut-off of 150μg/g, with a sensitivity of 76% (95% CI 50-93%), specificity of 81% (95% CI 69-91%), PPV of 57% (95% CI 34-77%) and NPV of 92% (95% CI 80-98%); again, there was good agreement between FC and BWT (kappa coefficient 0.52, agreement 80%). For the scans in those patients with a diagnosis of UC, agreement between FC>150μg/g and BWT>3mm on IUS was excellent (kappa coefficient 0.81, agreement 91%).

A flexible sigmoidoscopy was performed during pregnancy in three of these cases. One patient had mildly active disease in the sigmoid colon on GIUS at 10 weeks (Patient B in Table 5.4), then following escalation of her 5-ASA therapy had a normal GIUS and FC at 20 weeks. She subsequently had a severe flare at 28 weeks with sigmoidoscopy showing Mayo 2 colitis to 50cm.

The second patient, who had mildly active UC clinically, had a GIUS at 18 weeks that showed mildly increased BWT of 3-4mm from the sigmoid colon to the transverse colon, then underwent a sigmoidoscopy at 34 weeks, which demonstrated Mayo 1 disease in the transverse colon. Another patient with clinically severely active UC

attended GIUS at 27 weeks and did not have active disease visible on GIUS, including in the proximal sigmoid colon; she had distal colitis to 35cm on sigmoidoscopy.

There was also a significant association between increasing PGA score and BWT on GIUS (OR 4.12, 95% CI 2.09-8.12; p<0.01). The PGA (n=71) was normal in the 45/48(94%) scans with no active disease on GIUS, compared to a normal PGA in 6/23(26%) for those with active disease on GIUS (BWT>3mm) (p<0.001).

HBI scores were available in 42/45 (93%) scans when there was a diagnosis of CD. Although scores were consistent with clinical remission, there was a lower median HBI score of 0 in the 30/42 (71%) with no activity on GIUS, compared to a score of 2 in those with active disease on GIUS (p<0.001). There was no significant difference in the SCCAI scores (available in 24/26 (92%) scans with UC or IBDU) according to disease activity on GIUS (p=0.72).

Active disease on GIUS (BWT>3mm) commonly resulted in changes in therapy during pregnancy. Therapy was changed following the GIUS in 13/23 (57%) of scans with active disease, compared to 1/48 (2%) scans with inactive disease on GIUS (p<0.001).

Pregnancy outcomes were available in 41/55(75%) of these women and there was no significant difference in gestational age at delivery or birthweight according to disease activity based on either GIUS or FC (p>0.05). In 40/41(98%) of these cases, infants were born at term (>37 weeks) with a median gestational age of 39 weeks. 38/41(93%) of these infants had a normal birthweight (>2500g), consistent with the normal population rate of low birthweight infants. The median birthweight was 3340g with a median APGAR score of 9 (normal).

Location of Active Intestinal Inflammation on GIUS (Including Increased Bowel Wall Thickness with Presence of Hypervascularity) and Correlation with Faecal Calprotectin

In 18/127 (14%) of all scans, hypervascularity was detected (Limberg score of 2 or more). Eight patients had increased BWT and hypervascularity in at least one colonic segment on GIUS (Table 5.4). All had elevations in FC (median 217μg/g (IQR 186-646μg/g). Three of these patients were in clinical remission at the time of the scan but escalated topical therapy was initiated following the GIUS findings in two patients, and anti-TNF therapy was dose-escalated in another. The remaining five of these patients

had clinically active disease, three required oral corticosteroids, while two were managed with the addition of topical therapy for left sided colitis seen on GIUS.

Another eight patients had active ileal or anastomotic Crohn's disease with increased BWT and hypervascularity and signs of stenosis detected on GIUS (Table 5.5). The median FC in these patients at the time of these scans was 242μg/g (IQR 94-307μg/g); two of these patients had a FC <100μg/g. Seven of these patients reported abdominal pain in pregnancy. In all eight patients, the GIUS confirmed stricturing disease, resulting in appropriate escalation of therapy including optimisation of a thiopurine, commencement of anti-TNF therapy and/or oral corticosteroids.

Table 5.4 Patients with Active Colonic Inflammation (n=8)

Patient	**GW**	**Maximal BWT**	**Limberg score**	**Bowel wall stratification**	**Mesenteric hyperechogenicity**	**FC μg/g**	**Clinical activity**
A	9	Sigmoid colon 3.4mm	2	Loss of stratification	Yes	186	Yes
B	10	Sigmoid colon 3.9mm	2	Preserved	No	171	**No**
C	17	Sigmoid colon 6.9mm	3	Reduced	Yes	NA	**No**
D	23	Sigmoid colon 4.8mm	2	Preserved	No	646	**No**
E	25	Descending colon 5mm	3	Preserved	No	458	Yes
F	25	Descending colon 5.5mm	2	Preserved	No	1680	Yes
G	25	Sigmoid colon 4.4mm	2	Preserved	No	198	Yes

H	28	Sigmoid colon 5.1mm	3	Loss of stratification	Yes	217	Yes

GW, gestational week; BWT, bowel wall thickness, FC, faecal calprotectin

Table 5.5 Patients with Active Ileal/Anastomotic Inflammation (n=8)

Patient	**GW**	**Maximal BWT**	**Limberg score**	**Bowel wall stratification**	**Mesenteric hyperechogenicity**	**FC μg/g**	**Clinical activity**
1	9 18	TI stricture 5.9mm TI stricture 5.3mm	2 3	Reduced	Yes	307 251	Yes – obstructive pain
2	10 20	Anastomotic stricture 6.1mm Anastomotic stricture 6.1mm	3 2	Reduced	Yes	**94** NA	Yes – obstructive pain
3	10	Neo-TI stricture 6.7mm	2	Reduced	Yes	233	Yes – obstructive pain
4	13	TI stricture 5.7mm	2	Preserved, prominent submucosa	Yes	391	Yes – obstructive pain
5	14	TI stricture 6.1mm	3	Preserved, prominent submucosa	Yes	NA	No obstructive symptoms

6	16	TI stricture 5.3mm	2	Loss of stratification	Yes	NA	Yes – obstructive pain
7	16	Ileal stricture 6.3mm	3	Reduced	Yes	NA	Yes – obstructive pain
8	21	Ileal stricture 5mm	2	Loss of stratification	Yes	**35**	Yes – obstructive pain

GW, gestational week; BWT, bowel wall thickness, FC, faecal calprotectin

5.4 Discussion

GIUS as a safe and non-invasive diagnostic tool that is commonly utilised in the non-pregnant IBD population. There are numerous data confirming its accuracy and efficacy for the detection of disease activity and complications and its utility is now well accepted[8,9]. There is growing enthusiasm about its use in pregnancy given the need for safe, non-invasive and regular monitoring of disease activity during this time to improve outcomes for both mother and infant. However, concerns about the feasibility of GIUS in pregnancy have been raised given the possibility of bowel views becoming obscured by the gravid uterus.

We present the first study assessing the segment-by-segment practicality of GIUS in the evaluation of IBD demonstrating the important role it can play across various stages of pregnancy. We have shown that GIUS is feasible for the assessment of disease activity in both UC and CD during pregnancy with adequate intestinal views obtained in most patients up to the early third trimester. Good views can be obtained throughout the colon and terminal ileum up to 20 weeks gestation. Beyond 20 weeks, colonic views were adequate in almost all cases whereas the ileocaecal valve and terminal ileum itself became difficult to visualise on GIUS, with views possible from 20-33 weeks gestation in only 30/60 (50%) of scans. Additionally, while the terminal ileum specifically may not be adequately assessed, the distal ileum can often still be visualised. Abnormal or actively inflamed bowel is usually prominent and more easily visualised on GIUS when compared to non-inflamed bowel, therefore if there is clinical

suspicion of active or complicated disease, GIUS is likely to remain valuable even in late stages of pregnancy.

Our study has demonstrated that GIUS is accurate in the setting of pregnancy (sensitivity 74%, specificity 83%) when compared to calprotectin. The high specificity of GIUS in pregnancy is clinically very useful and can provide reassurance to the many women with IBD who experience gastrointestinal symptoms during pregnancy, which are not related to active disease[21]. The reduced sensitivity demonstrated in the current study is reflective of GIUS in general, not only during pregnancy, as GIUS has limited sensitivity in assessing rectal and upper GI disease[9,10,22]. Increasing BWT in affected segments correlated with increasing FC concentration. FC was selected as the best available reference standard to objectively establish the presence of disease activity in pregnant IBD patients given the inability to obtain endoscopic or cross-sectional imaging in pregnancy. In addition, FC, unlike clinical disease activity assessments, is not affected by pregnancy[23,24]. Only one other study has examined the use of GIUS in pregnancy and this study did not use FC as an objective marker to correlate the accuracy of sonographic findings[12].

In our study, the accuracy of GIUS in pregnancy is likely to be underestimated by using strict cut-offs for both BWT (3mm) and FC (greater than 100μg/g) to define disease activity. The calprotectin 'cut-off' for determining significant disease activity is controversial, especially in pregnancy. However, we have chosen a FC above 100μg/g to capture relevant disease activity for both UC and CD given that we are aiming for strict disease control in pregnancy. Still, FC can be low in small bowel CD, particularly in fibrotic disease[25]. This makes it difficult to correlate ileal CD activity using GIUS and FC, and hence underestimates the specificity of GIUS. Similarly, for the detection of sonographic disease activity in IBD, a BWT of 3mm is the normal upper limit. In our experience, this measurement can identify chronic as well as active disease changes on GIUS and thus would usually require interpretation by the clinician including assessment of hypervascularity on colour Doppler among other associated findings.

We have shown that GIUS has the capacity to accurately and rapidly determine IBD activity in pregnancy, helping to guide therapy to achieve strict control of inflammation to optimise the health of mother and baby. Moreover, GIUS can provide useful information in relation to the nature of disease activity, its location and extent and the presence or absence of complications, which cannot be obtained from FC or flexible

sigmoidoscopy. In pregnancy, it can be difficult to interpret disease activity clinically due to the effect of pregnancy on clinical symptoms. Whilst obstructive-type pain and inflammatory symptoms are commonly grouped in the global clinical assessment of disease activity, the underlying mechanism is different and a further benefit of GIUS we have highlighted is that it can characterise both fibrotic and inflammatory components of disease. This is significant in pregnancy, when it is especially important to identify active disease and initiate appropriate treatment as soon as possible.

A limitation of our study is the relatively small numbers of patients, particularly in third trimester. Limitations also include the lack of an agreed GIUS scoring system, as there is no validated score that exists currently[9,26]. A second limitation is the inability of GIUS to accurately detect proctitis[9,22,26]. In addition, there is no true gold standard for disease activity. FC may indeed be less accurate than GIUS[27] and can in some cases be low in the setting of active post-operative Crohn's disease[28]. The use of FC as the gold standard is the best available modality given our pregnant patient population, however this may serve to underestimate the utility of GIUS. Lastly, obesity can occasionally limit GIUS views[9]. We observed that several patients had restricted views in early pregnancy due to an elevated BMI, however we noted no difference in adequacy of views overall based on BMI in our cohort. The strengths of our study include its multicentre nature, suggesting these findings are translatable across other GIUS centres, and the well characterised clinical and biochemical data available for these patients.

In women with Crohn's disease affecting the terminal ileum, ultrasound is a valuable imaging tool and can diagnose active IBD and its complications during pregnancy even when FC is normal, particularly up to around 20 weeks gestation. In the setting of a flare of colonic IBD proximal to the rectum, GIUS is a useful, point-of-care, non-invasive alternative to undertaking a flexible sigmoidoscopy throughout pregnancy. This information, when interpreted in a clinical context, allows for informed clinical decision making and prompt treatment modification in pregnancy, in order to optimise disease control and hence pregnancy outcomes for women with IBD.

In summary, GIUS is a feasible and accurate modality for monitoring IBD in pregnancy with the additional benefits of being relatively inexpensive, reproducible and safe. We therefore suggest that GIUS should be performed as part of the routine clinical review for IBD patients in pregnancy in first trimester after confirmation of pregnancy, and again at 20 weeks gestation, when the bowel views are almost universally adequate in

the appropriate patient. GIUS can also be used to characterise disease activity if there is an elevated FC or clinical suspicion of active or complicated disease until late in the second trimester for ileal disease and early in the third trimester for colonic disease.

Further Discussion

The cut-off of 3mm for a normal bowel wall thickness in both terminal ileum and colon was chosen as this is what is accepted in clinical practice for the detection of relevant IBD activity, rather than for assessment of transmural healing. The cut-off of 3mm provides both high specificity and sensitivity for detecting ileal and colonic inflammation.

All three centres used ultrasound machines that were pre-set for abdominal examinations and linear transducers (around 7-14Hz) with similar penetration and resolution for optimised intestinal images.

Adequacy of views was determined by the sonographer performing the examination, according to whether complete bowel wall views could be obtained in a particular segment (adequate) or not (inadequate). All sonographers had undertaken the equivalent specialised, accredited intestinal ultrasound training required, including over 200 supervised examinations; and were all practising members of the same national gastroenterology intestinal ultrasound training body, the Gastroenterology Network of Intestinal Ultrasound (GENIUS).

In addition to the correlation provided between intestinal ultrasound and faecal calprotectin in pregnancy, it would also be useful to include non-pregnant controls in future studies in order to further quantify the loss of accuracy of ultrasound in the third trimester.

There were no study patients included who presented with acute presentations such as suspected ileal obstruction or perforation during pregnancy. Intestinal ultrasound should only be performed as the initial imaging investigation in this setting if it is readily available and may not be diagnostic due to limited views, hence cross-sectional imaging such as non-contrast MRI or CT should be promptly considered.

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6 Maternal Thiopurine Metabolism During Pregnancy in Inflammatory Bowel Disease and Clearance of Thiopurine Metabolites and Outcomes in Exposed Infants

6.1 Introduction

Thiopurine medications, including mercaptopurine and its pro-drug azathioprine, are widely used in inflammatory bowel disease (IBD), both as monotherapy and in combination with anti-TNF agents.

Thiopurines are metabolised to therapeutically active thioguanine nucleotides(6-TGN) and potentially toxic 6-methylmercaptopurine (6-MMP). Measurement of t metabolite levels is important to guide therapy[1, 2]. 6-TGN levels greater than 235 pmol/8x10^8 red blood cells (RBCs) are associated with disease remission in monotherapy, while 6-TGN levels above 450 pmol/8x10^8 RBCs increase the risk of myelosuppression. Hypermethylation or shunting of metabolites can occur, resulting in low 6-TGN levels and high 6-MMP levels. 6-MMP levels above 5700 pmol/8x10^8 RBCs have been associated with hepatotoxicity[2]. Dose escalation in patients who exhibit shunting can increase 6-MMP levels with no increase in 6-TGN levels.

During pregnancy, controlling IBD activity and avoidance of drug toxicities are imperative for both mother and baby. While earlier studies reported concerns regarding adverse pregnancy outcomes in babies exposed to thiopurine medications *in utero*, more recent data have been reassuring[3, 4] and thiopurines are now widely considered to be safe for use in pregnancy[5-8]. There is, however, a paucity of data on the pharmacokinetic effects of pregnancy on thiopurine metabolism and the transfer of thiopurine metabolites across the placenta. Additionally, one study of 30 patients with IBD who were taking thiopurines during pregnancy reported an association between maternal thiopurine use and neonatal anaemia[9]. In this study, 63% (10/16) of newborns were anaemic and 3/12 (25%) infants had an increased alkaline phosphatase (ALP) at birth[9]. They also found maternal 6-TGN levels decreased during pregnancy. Neonatal 6-TGN levels correlated with maternal 6-TGN levels[9]. Thiopurine clearance time and follow up of liver function tests in infants have not been studied.

In this study, we aimed to further characterise the impact of pregnancy on thiopurine metabolism, evaluate neonatal thiopurine metabolite levels, and report neonatal

outcomes including anaemia and liver function.

6.2 Methods

Study design and patient population

This was a prospective observational study to investigate the pharmacokinetics and pharmacodynamics of thiopurines in pregnant women with IBD and their infants. In detail, we aimed to determine how thiopurine metabolism changes during pregnancy, the placental transfer and clearance time of thiopurine metabolites in exposed infants and the impact of *in utero* thiopurine exposure on infant outcomes, including haematology and liver biochemistry to six months.

Patients were recruited through the IBD and Pregnancy service at St Vincent's Hospital Melbourne, Australia. Women with IBD who were taking a thiopurine medication and were pregnant or trying to conceive were enrolled from September 2017 to September 2019.

Study procedures

Maternal thiopurine metabolite levels were measured pre-conception (up to 12 months), in each trimester of pregnancy, at delivery and post-partum (up to six months) when possible. Maternal full blood examination (FBE) and liver function tests (LFTs) were recorded to assess for potential myelotoxicity (maternal white cell count < 4 $x10^9$/L) or hepatotoxicity (alanine aminotransferase (ALT) > 50 IU/L) associated with thiopurine treatment.

Clinical data relevant to pregnancy outcomes and thiopurine metabolite levels were recorded including demographic information, medical and obstetric history, patient weight and medication dose changes. Data regarding disease activity across pregnancy was collected including Physician Global Assessment (PGA) and faecal calprotectin (FC) in each trimester as well as patient weight where possible. Baseline data was collected pre-conception when possible, and in the case of a patient being recruited to the study when already pregnant, baseline and pre-conception data was collected at the time of recruitment.

Thiopurine metabolite levels were included in the statistical analysis if the patient was on stable dosing for at least four weeks prior to the observation. Levels were excluded

from the analysis when a participant was taking an adjusted dose or was non-adherent to the thiopurine.
Participants were offered infant thiopurine metabolite testing along with FBE and LFT at birth, with repeat testing in infants at six weeks, three months, and six months or until undetectable/within normal limits. Samples at birth were collected from the umbilical cord. Repeat testing began at six weeks in order to assess that metabolites were cleared by this time as this is when the first live vaccination is scheduled.

Paediatric review and more frequent blood testing was conducted for infants with abnormal FBE and/or LFTs. Anaemia was defined as haemoglobin (Hb) < 135 g/L from cord blood and Hb < 100 g/L at six weeks of age[10]. Normal range for white cell count was 6.0-18.0 $x10^9$/L with neutropenia defined as <1.0 $x10^9$/L in infants[10]. Normal range for platelets was 150-400 $x10^9$/L[10]. Elevated LFTs in infants were defined as ALT > 42 U/L and ALP > 350 U/L[11].

Pregnancy outcomes including mode of delivery, gestational age, neonatal birth weight, congenital anomalies and APGAR scores were recorded. Infant outcomes were assessed by participant-reported questionnaires at six weeks, three months and six months for those infants who underwent blood testing and included infant growth, infections, chronic medical conditions, allergies and adverse reactions to vaccinations. All babies with abnormal blood tests were reviewed. Paediatric examinations were also reported where performed.

Laboratory methods

A modified Dervieux method including high performance liquid chromatography (HPLC) with mass spectrometry or ultraviolet detection was used to measure 6-TGN and 6-MMP nucleotide concentrations in red blood cells (RBCs) using whole blood. The RBC was determined from an EDTA tube or lithium heparin tube. Metabolite concentrations were reported in pmol/$8x10^8$ RBCs. For the infants who had levels performed, the lower limit of accurate detection reported was 10pmol/$8x10^8$ RBCs for 6-TGN and 50pmol/$8x10^8$ RBCs for 6-MMP. Where maternal 6MMP levels were reported as <250 pmol/$8x10^8$, this was replaced with 249.

Statistical analysis

Data are reported as median [interquartile range (IQR)] or number (%). Between group differences were compared by $\chi 2$ test, Fisher's exact test and Wilcoxon rank-sum test, as appropriate. The Skillings-Mack test, a general Friedman-type statistic, was used to compare results by patient across pregnancy. The Spearman correlation was used to investigate the relationship between continuous variables. Multinomial logistic regression models were fitted to examine 6-TGN and 6-MMP levels across pregnancy at each time point (trimester) in comparison to post-partum, these models were then adjusted for patient weight during pregnancy. Statistical analysis was performed using STATA version 15.1 (STATA LP College Station, TX, USA). A p value < 0.05 was considered statistically significant.

Ethical considerations

Ethical approval for the study was obtained from the Human Research Ethics Committee at St Vincent's Hospital Melbourne, Australia (HREC/17/SVHM/116) and participants provided written informed consent before inclusion.

Patient and Public Involvement statement

It was not appropriate or possible to involve patients or the public in the design, conduct, reporting or dissemination plans of our research.

6.3 Results

40 participants were included with at least two observations (median 3 [IQR 3-4]) from pre-conception to post-partum while on stable dosing for four weeks prior to testing; a further two participants had mother-baby paired levels at delivery but not intrapartum. Patient demographics are shown in Table 6.1.

Table 6.1 Patient demographics (n=42)

Median (IQR) or n (%)		**Total**
Age (years) at beginning of pregnancy		33.0 (30.9-35.2)
Weight (kg) pre-pregnancy		66.0 (58.0-75.0)
Diagnosis	**Crohn's Disease**	27 (64%)
	Ulcerative Colitis	12 (29%)
	IBD Unclassified	3 (7%)

Duration IBD (years) beginning of pregnancy		8.4 (4.3-12.7)
Type of thiopurine medication	**6-mercaptopurine**	19 (45%)
	Azathioprine	23 (55%)
Dose (mg/kg)*	**6-mercaptopurine**	0.9 (0.7-1.2)
	Azathioprine	1.4 (1.0-1.7)
Concomitant medications	**Anti-TNF**	22 (52%)
	5-ASA or sulfasalazine	14 (33%)
	Allopurinol	1 (2%)
	Prednisolone	2 (5%)
	Vedolizumab	1 (2%)
	Ustekinumab	1 (2%)
Crohn's disease location	**Ileal**	11 (26%)
	Colonic	6 (14%)
	Ileocolonic	10 (24%)
Crohn's disease behaviour	**Non-stricturing, non-penetrating**	18 (43%)
	Stricturing	9 (21%)
	Penetrating	0 (0%)
Perianal Crohn's disease	**Yes**	9 (21%)
Upper Gastrointestinal Crohn's disease	**Yes**	1 (2%)
Ulcerative Colitis and IBD Unclassified disease location	**E1 proctitis**	1 (2%)
	E2 left-sided	2 (5%)
	E3 pan-colitis	12 (29%)
Active disease in pregnancy according to Physician Global Assessment		10 (24%)
Patients with levels excluded due to dose change in study period		4 (10%)

**Dose not included for patient on allopurinol combined with low dose thiopurine*

Maternal thiopurine metabolite levels across pregnancy (n=40)

Median 6-TGN levels decreased by the second trimester of pregnancy, with a significant difference in 6-TGN levels observed from trimester one to postpartum

(p<0.001, Skillings-Mack) (Table 6.2, Figure 6.1). The regression model showed that 6-TGN in the second trimester was lower than post-partum (p<0.001), with a decrease also observed in trimester three (p<0.001). Following adjustment for patient weight during pregnancy, the direction and significance of this association was unchanged. Additionally, when only those patients with an available 6-TGN at baseline were included in the model examining 6-TGN levels in relation to pre-conception, 6-TGN in trimester two remained significantly lower (p=0.023).

Table 6.2 Median 6-TGN levels across pregnancy

	Median (IQR) 6-TGN pmol/8x10^8 RBCs	**Number of observations**	**p-value** *(Skillings-Mack test)*
Pre-pregnancy	293.5 (156.5-336.5)	16	
Trimester 1	245.0 (198.0-347.5)	24	**<0.001**
Trimester 2	179.0 (127.0-245.0)	35	
Trimester 3	213.5 (143.0-310.0)	30	
Delivery	221.0 (167.0-320.0)	25	
Post-partum	323.5 (235.0-524.0)	30	

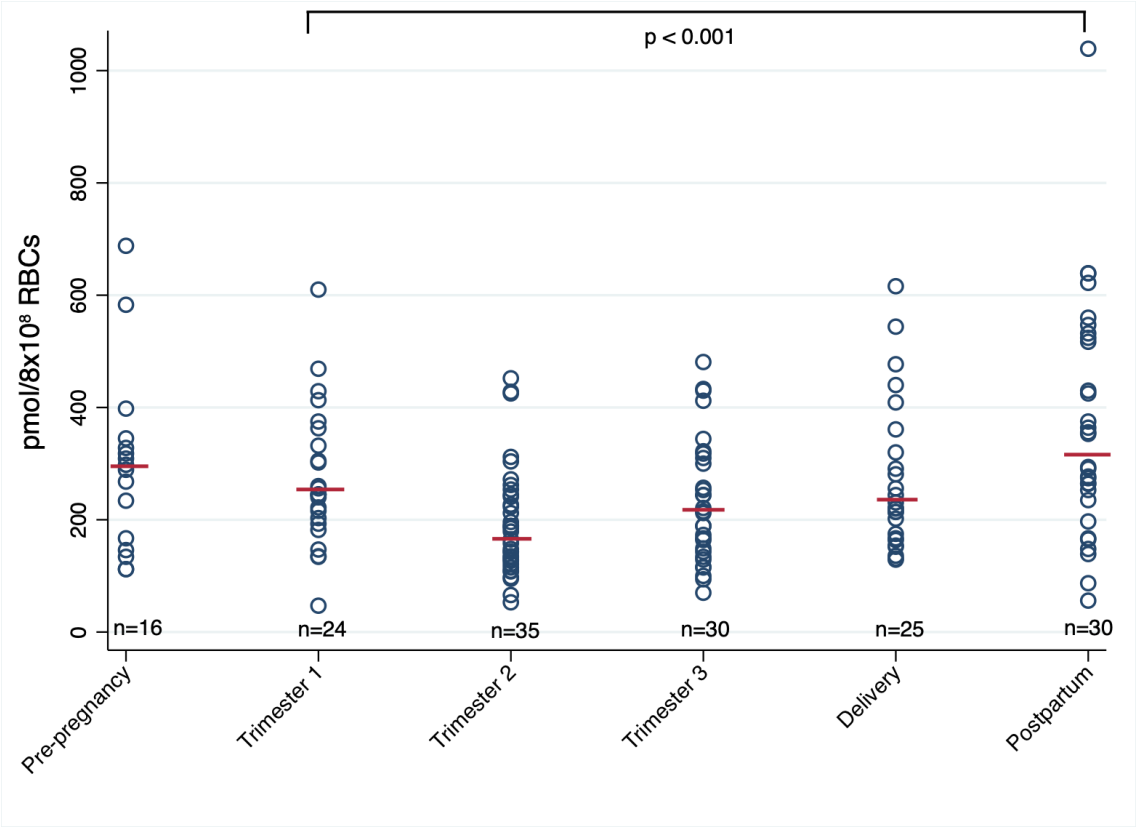

Figure 6.1 Median 6-TGN levels across pregnancy

Median 6-MMP levels increased in the second trimester of pregnancy, with a significant difference in 6-MMP levels observed from trimester one to postpartum (p<0.01, Skillings-Mack) (Table 6.3, Figure 6.2). According to regression modelling a significant increase was observed in pregnancy with the greatest increase in 6-MMP seen in trimester two compared to post-partum (p=0.003). Individual 6-TGN and 6-MMP levels across pregnancy are shown in supplementary Figures 6.7 and 6.8.

Table 6.3 Median 6-MMP levels across pregnancy

	Median (IQR) 6-MMP pmol/8x10^8 RBCs	**Number of observations**	**p-value** *(Skillings-Mack test)*
Pre-pregnancy	529.0 (258.0-2974.5)	16	
Trimester 1	851.0 (255.5-2104.0)	24	**<0.01**
Trimester 2	1103.0 (312.0-2919.0)	35	
Trimester 3	838.0 (236.0-2474.0)	30	
Delivery	747.0 (228.0-2451.0)	25	
Post-partum	329.5 (160.0-854.0)	30	

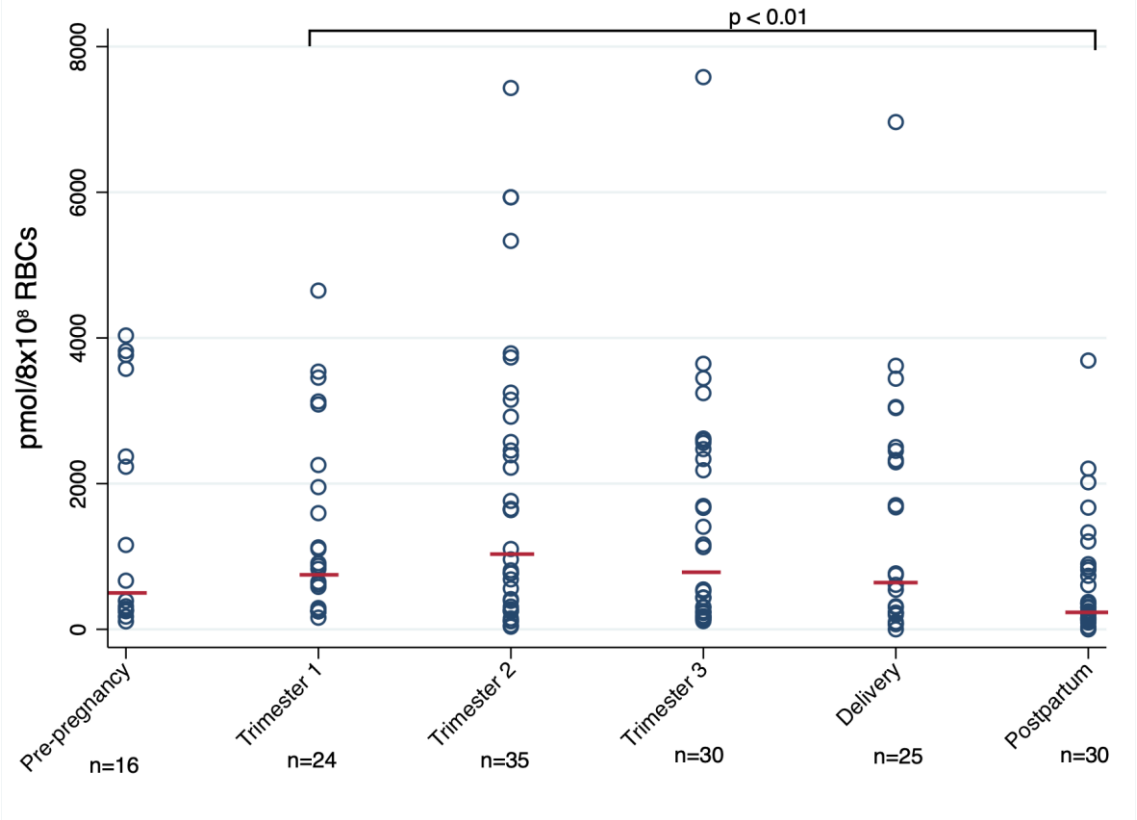

Figure 6.2 Median 6-MMP levels across pregnancy

There was also a significant difference in 6-MMP to 6-TGN ratios across pregnancy from trimester one to post-partum (p<0.001, Skillings-Mack), with the highest ratio observed in trimester two (Table 6.4). Five patients had elevations in 6-MMP to > 5700 pmol/8x10^8 during pregnancy while on stable dosing without any hepatotoxicity related to the thiopurine. Shunting of thiopurine metabolites was evident in these five patients with a median 6-MMP to 6-TGN ratio of 41 (range 19 to 62).

Table 6.4 Median 6-MMP:6-TGN ratios across pregnancy

	Median ratio	**Number of observations**	**p-value** *(Skillings-Mack test)*
Pre-pregnancy	3.4 (1.1-6.5)	16	
Trimester 1	4.0 (1.3-7.6)	24	**<0.001**
Trimester 2	5.7 (2.5-14.9)	35	
Trimester 3	3.7 (1.1-12.4)	30	
Delivery	2.9 (1.2-10.9)	25	
Post-partum	1.3 (0.5-3.1)	30	

Two patients had their thiopurine dose increased in late pregnancy in the setting of active disease and sub-therapeutic metabolites. Substantial shunting of their thiopurine metabolites was subsequently observed (these results were not included in the analysis due to recent dose change). In one of these patients, who had her azathioprine dose increased from 200mg to 225mg in the setting of a sub-therapeutic 6-TGN and ratio of 6, her 6-TGN at delivery was 151 pmol/8x10^8 RBCs with a 6-MMP of 37,326 pmol/8x10^8 RBCs and she presented clinically with jaundice (result sent external to study, not included in results). In the other patient, who had her azathioprine dose increased from 150mg to 200mg, her 6-TGN in the third trimester was 170 pmol/8x10^8 RBCs with a 6-MMP of 13,217 pmol/8x10^8 RBCs.

Pregnancy outcomes

All patients delivered babies at term with normal birth weight and no known congenital anomalies; pregnancy outcomes are shown in Table 6.5. Four (9.5%) mothers were diagnosed with intrahepatic cholestasis of pregnancy (ICP), two of whom had an elevated 6-MMP higher than 5700 pmol/8x10^8 RBCs.

Table 6.5 Pregnancy outcomes (n=42)

		Median (IQR) or n (%)
Gestational age at delivery (weeks) - **Pre-term, n (%)**		39 (38-39) - 0 (0%)
Birth weight (grams) - **Low birth weight, n (%)**		3338 (3150-3520) - 0 (0%)
Birth length (cm)		50 (49.5-51.5)
Sex of baby	**Boy**	20 (48%)
	Girl	22 (52%)
Mode of delivery	**Caesarean section - emergency**	6 (14%)
	Caesarean section - elective	15 (36%)
	Vaginal birth	16 (38%)
	Vaginal birth - instrumental	5 (12%)
APGAR score at 1 minute		9 (8-9)
APGAR score at 5 minutes		9 (9-9)
Infant admitted to Neonatal Intensive Care - **Admitted to Special Care Nursery**		0 (0%) - 2 (5%)
Congenital abnormalities at birth		0 (0%)
Gestational diabetes		2 (5%)
Pre-eclampsia		5 (12%)
Iron infusion during pregnancy		12 (29%)
Smoking during pregnancy		1 (2%)

Patient disease activity during pregnancy

The impact of disease activity on thiopurine metabolites was assessed. When assessing each patient's maximal FC level in trimesters one to three, the median FC level was 62.9 μg/g FC (available in 41/42 patients). Eight/41 (19.5%) patients had biochemical evidence of disease activity with a FC >250 μg/g on at least one occasion in trimesters one to three and a median FC of 497.5 (IQR 340-991.5) μg/g. Meanwhile, 33 patients remained in biochemical remission with a median FC of 32.3 (IQR 14.5-76.8) μg/g at a maximum during pregnancy. There were no significant differences in median 6-TGN levels in those women with biochemical disease activity in pregnancy (FC >250 μg/g) compared to those without ($p>0.05$). Similarly, there were no significant differences in median 6-TGN levels in those women with disease activity in pregnancy according to PGA (n=10) compared to those without active disease ($p>0.05$).

Infant thiopurine metabolites at delivery

25/42 mothers were able to have infant cord blood samples collected at birth. Thiopurine metabolite levels were available in 23 infants. In two infants and two mothers, metabolites were not processed correctly. For two mother-baby pairs, the mother ceased the thiopurine prior to delivery and the infant levels were zero. Therefore, these results were not included in the analysis.

In the remaining 20 mother-baby pairs, the median 6-TGN level in infants at birth was 78.5 (IQR 47.5-107.0) pmol/8x10^8 RBCs, compared to a median maternal level of 217.0 (IQR 165.5-286.0) pmol/8x10^8 RBCs at delivery (p<0.001, Wilcoxon). The median infant: mother 6-TGN ratio in these paired samples was 0.4 (IQR 0.2-0.5). There was a significant positive correlation between infant and maternal 6-TGN levels at delivery (r=0.48, p=0.03) (Figure 6.3).

The median 6-MMP in these mothers at delivery (n=20) was 757.5 (IQR 226.5-2476.5) pmol/8x10^8 RBCs. 6-MMP was detected in 2/20 (10%) infants at birth at low levels (range 70-569 pmol/8x10^8 RBCs) with corresponding maternal 6-MMP levels of and 3052 and 6964 pmol/8x10^8 RBCs, respectively.

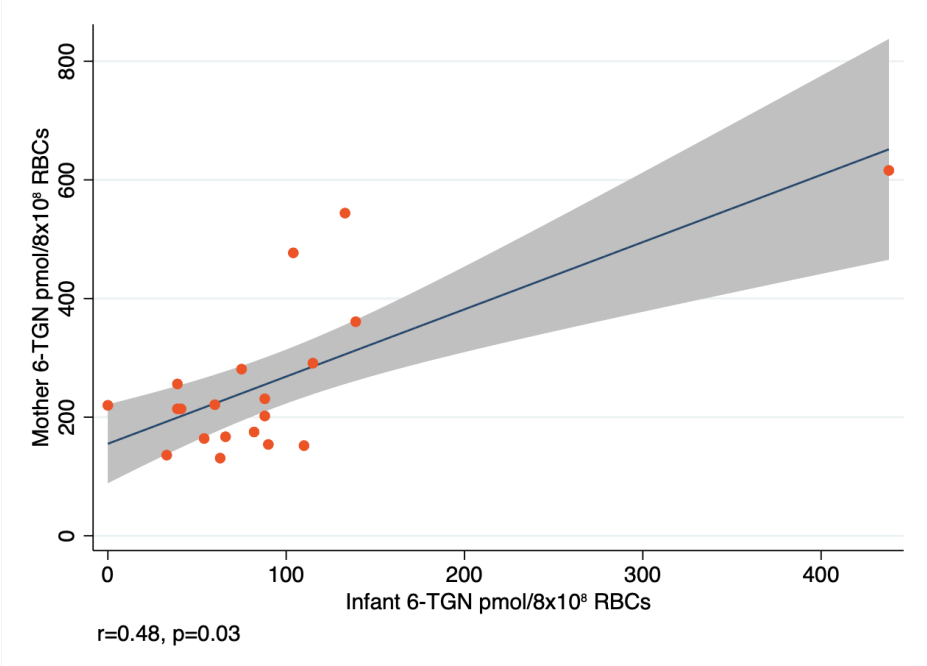

Figure 6.3 Correlation between infant and maternal 6-TGN levels at delivery

Clearance of thiopurine metabolites in infants

18/21 infants had follow-up metabolite testing performed at six weeks. One infant did not have detectable metabolites at birth and in the other two infants an adequate blood sample could not be collected at six weeks. Infant 6-TGN and 6-MMP were undetectable by six weeks in all infants tested (levels performed at ten weeks in two infants).

Infant haematological abnormalities

1/17 (5.9%) infants had a very mild anaemia (Hb 128g/L) and one other infant had a mild thrombocytopenia (platelets 102) at birth, both of which resolved.

Between six weeks and three months of age, three infants had a mild neutropenia detected, which resolved, while 17/19 (89%) infants had thrombocytosis (supplementary data, table 6.7). The median platelet count was 523 [IQR 449-653] $x10^9$/L (n=17) at six weeks of age. There was no significant correlation with infant 6-TGN level at birth and platelet count at six weeks or three months ($p > 0.05$). There was no significant correlation with infant mean cell volume (MCV) at six weeks and infant platelet count at six weeks ($r=0.16$, $p=0.54$).

In the infants with thrombocytosis (n=17), at the six-month follow-up the thrombocytosis had resolved in seven infants and improved in another six (Figure 6.4). The thrombocytosis resolved over a median of six months (range four-twelve months) in the infants who completed follow-up testing until the platelet count was within normal.

At six weeks and three-four months, the median platelet count was significantly higher in those infants who were also exposed to anti-TNF therapy (539 [IQR 491-777] $x10^9$/L vs 401.5 [IQR 332-480]$x10^9$/L, $p=0.021$ at six weeks). When thrombocytosis was examined as a categorical variable, there was a significant association with anti-TNF exposure at six weeks ($p=0.043$), but no significant association at three months or six months between infants with anti-TNF exposure and those without ($p>0.05$). There were no significant associations between infants being breastfed and having thrombocytosis at six weeks, three months or six months ($p>0.05$).

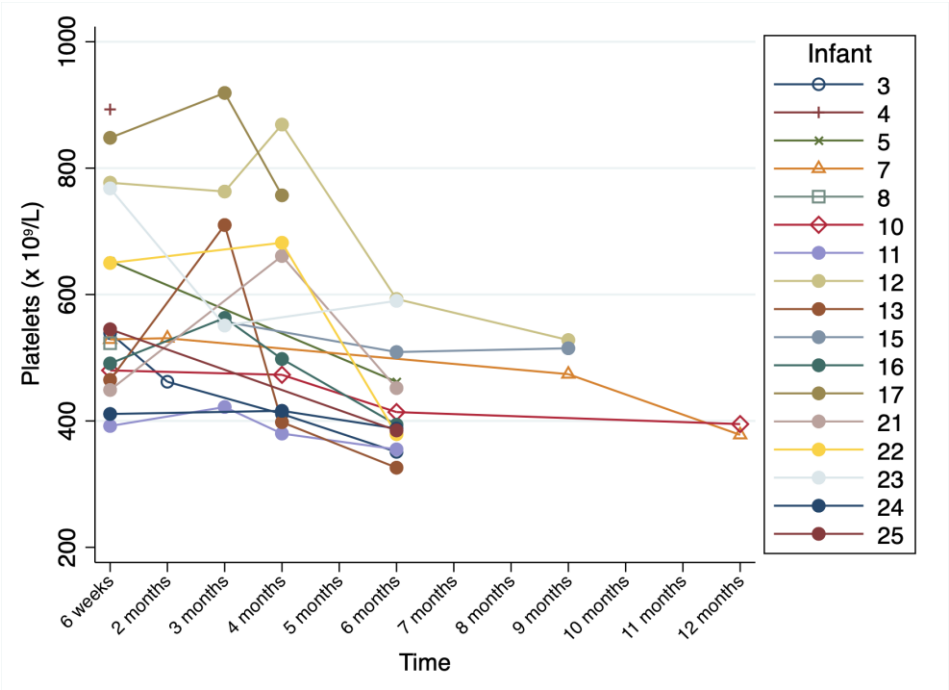

Figure 6.4 Longitudinal measurement of platelet count among infants with platelet elevation

Infant liver biochemistry abnormalities

There were no significant LFT abnormalities detected in infants at birth (n=20). Abnormal LFTs were seen in 15/19 (79%) infants between six weeks and three months (supplementary data, table 6.7).

9/19 (47%) infants had an elevated ALT detected (ALT > 42 U/L). The median ALT was 31 [IQR 24-45] U/L at six weeks (n=19) and 49 [IQR 30-70] U/L at three-four months (in the 15 infants who required follow-up LFT testing). There was no significant correlation with infant 6-TGN level at birth and ALT level at six weeks or three months (p>0.05).

In the infants with an elevated ALT (n=9), this normalised by a median six months of age (range four to twelve months) in 8/9 (89%) infants with complete follow-up testing (Figure 6.5). In three infants, the ALT was normal by four months, in another two infants by around six months and in three infants, the ALT normalised by around twelve months of age. One infant with ALT 70 U/L at four months and 51 U/L at six months has further follow-up pending (Infant 22).

There was no significant difference between median ALT levels at six weeks in babies who were breastfed compared to those who were not (p>0.05). When examined as a

categorical variable, there were no significant associations between infants having an elevated ALT and being breastfed at six weeks or six months (p>0.05). However, at three-four months, median ALT levels were higher in infants who were breastfed (52.5 [IQR 39.5-83.5] U/L vs 25 [IQR 19-32] U/L, p<0.05). When examined as a categorical variable, there was an association between having an elevated ALT and being breastfed at three-four months (p<0.05), although there were only three infants in the non-breastfed group. There were no significant associations between anti-TNF exposure and infants having an elevated ALT at six weeks, three months or six months (p>0.05).

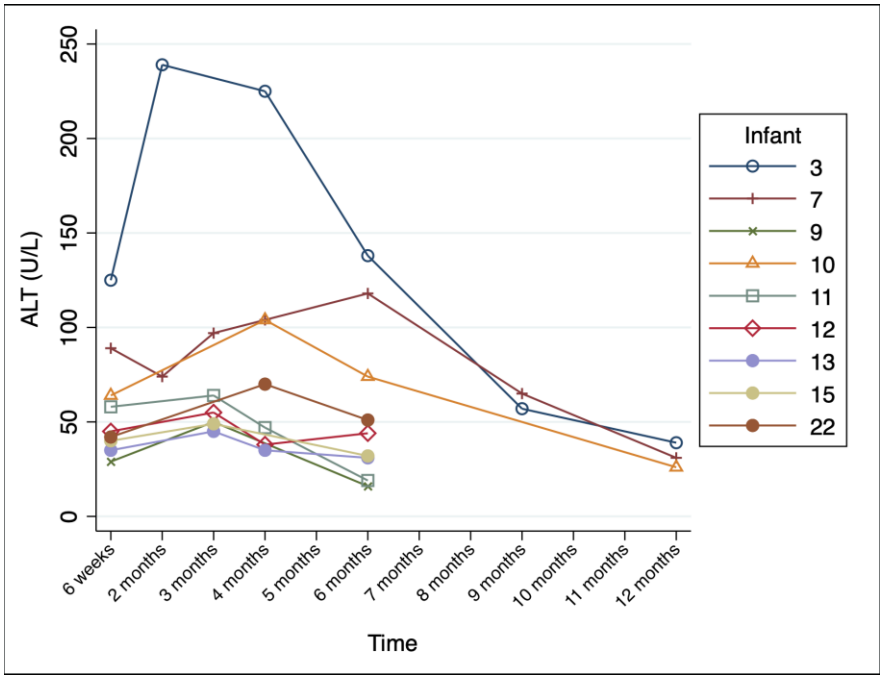

Figure 6.5 Longitudinal measurement of alanine aminotransferase (ALT) among infants with ALT elevation

10/19 (53%) infants had an elevated ALP at six weeks. All 10 infants had completed follow-up testing with a normal ALP seen by a median four months of age (range three to six months) (Figure 6.6). There were no associations between infants having an elevated ALP and being breastfed or exposed to anti-TNF at any time point (p>0.05).

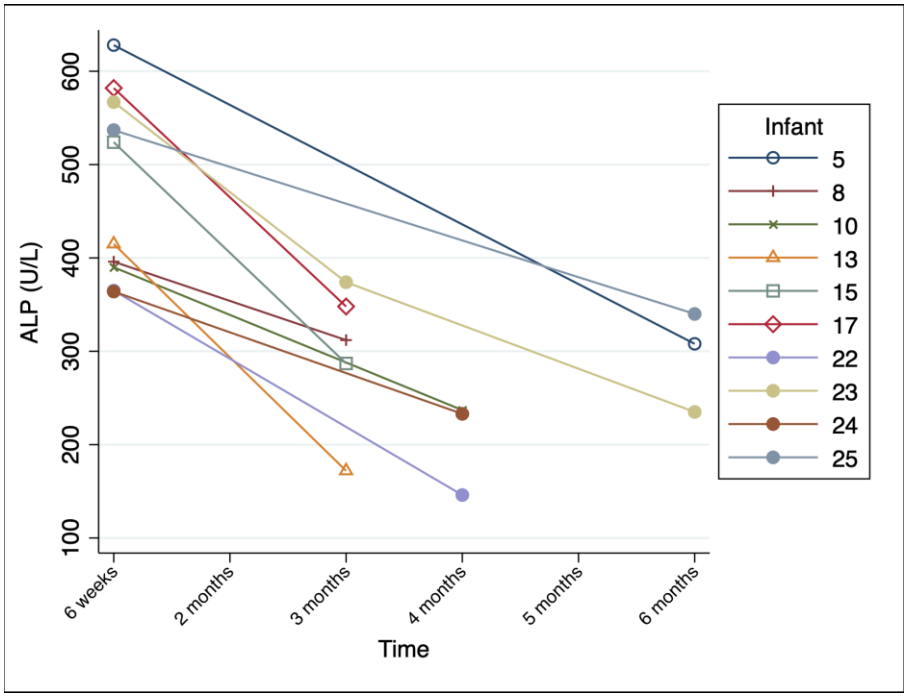

Figure 6.6 Longitudinal measurement of alkaline phosphatase (ALP) among infants with ALP elevation

Infant outcomes up to six months (n=25)

Infant outcomes are available in 23/25 infants to six months of age (Table 6.6 and 6.7). 18/23 (78%) of these infants had no infections reported by their mothers up to six months. Two infants were hospitalised with infection; respiratory syncytial virus at six weeks (Infant 4), and fever of unknown cause at two weeks of age (Infant 11). There were eight other mild infections seen in four infants up to six months of age (upper respiratory tract infection (three), gastroenteritis (two), umbilical site infection (one), toe infection (one) and tonsillitis (one). Infants were clinically well following the detection of haematological and biochemical abnormalities with no intervention required for these findings.

One infant, who had undetectable metabolites at birth and hence no follow up testing, was diagnosed with first-degree atrioventricular block (mother was also on anti-TNF and allopurinol) (Infant 1). One infant had torticollis (Infant 5) and another had a neck mass, thought to be a submandibular gland (Infant 24).

Table 6.6 Infant Outcomes (n=25)

n (%)		**6 weeks n=25**	**3 months n=24**	**6 months n=23**
Infant growth centile for weight	**Above 90th centile**	3 (12%)	2 (8%)	1 (4%)
	Below 10th centile	4 (16%)	3 (13%)	3 (13%)
	10-90th centile	18 (72%)	16 (66%)	16 (70%)
	Unknown	0 (0%)	3 (13%)	3 (13%)
Any infant infection(s) reported	**Yes**	4* (16%)	4* (17%)	5* (22%)
Number of infections	**0**	21 (84%)	20 (83%)	18 (78%)
	1	3 (12%)	2 (8%)	3 (13%)
	2	1 (4%)	2 (8%)	0 (0%)
	3	0 (0%)	0 (0%)	2 (9%)
Hospital admission required for infection	**Yes**	2* (8%)	2* (8%)	2* (9%)
Did not require admission but treated with antibiotics	**Yes**	1* (4%)	1* (4%)	2*(9%)
Any chronic diseases or medical conditions	**Yes**	3 (12%)	2 (8%)	3 (13%)
Adverse reaction to vaccinations	**No**	23 (92%)	24 (100%)	23 (100%)
	Don't know	2 (8%)	0 (0%)	1 (4%)
Allergies	**No**	20 (80%)	22 (92%)	19 (93%)
	Yes	0 (0%)	1** (4%)	2** (9%)
	Don't know	5 (20%)	0 (0%)	2 (9%)
Breastfeeding	**Yes**	19 (76%)	16 (89%)	16 (70%)
	No	6 (24%)	8 (33%)	7(30%)

*these data include the same infant episode/hospital admission(s)

**reported allergy to cow's milk

Note: Two infants (Infants 2 and 20), who did not have metabolites available/detectable from birth and did not have follow-up blood tests, had infant outcomes data up to six weeks and three months, respectively.

6.4 Discussion

This study examined the pharmacokinetics and placental transfer of thiopurine medications during pregnancy in patients with IBD, and thiopurine clearance and safety in neonates. We confirm that 6-TGN levels decrease and 6-MMP levels increase by the second trimester of pregnancy and show that infants of mothers on thiopurines during pregnancy are exposed to both 6-TGN and 6-MMP at low levels.

This is the first study to demonstrate complete clearance of thiopurine metabolites occurs in exposed infants by six weeks of age. Overall neonatal outcomes were excellent, equivalent to the normal population. Unexpectedly, thrombocytosis and abnormal LFTs in well infants were observed at six weeks following intrauterine thiopurine exposure despite undetectable metabolite levels. Unlike a previous study, only one mild neonatal anaemia was seen.

The pharmacodynamics and pharmacokinetics of many drugs are altered in pregnancy. Only one previous study (n=30) has examined thiopurine metabolite levels in pregnancy, and this study found that 6-TGN levels decreased[9]. This study also suggested that 6-MMP levels may increase; however, this was not statistically significant[9]. Our findings, in a similar size group, show that 6-TGN levels decrease and 6-MMP levels increase in the second trimester ($p<0.05$). Possible explanations for the reduced 6-TGN levels in pregnancy may relate to increased plasma volume and increased drug clearance during pregnancy. It is therefore important to consider routine monitoring of metabolite levels and disease activity during pregnancy. We did not demonstrate increased relapse in the setting of lower metabolite levels; however, most patients were in established remission.

Caution should be exercised when considering increased thiopurine dosing in pregnancy, as we observed shunting of metabolites with high levels of 6-MMP, both in those on stable thiopurine dosing and following small dose increases. This was associated with severe liver abnormalities in only one patient, but may create potential difficulties in distinguishing drug-related hepatotoxicity from pregnancy-related liver disease. Nasser *et al* described a recent case of maternal thiopurine hepatotoxicity, which occurred in the setting of pregnancy-related shunting of thiopurine metabolites and also noted that this presentation can mimic intrahepatic cholestasis of pregnancy[12].The development of shunting in pregnancy may be due to inhibition or induction of enzymes in the metabolic pathway of thiopurines. Dose changes of

thiopurines in pregnancy should only be performed if there is concern regarding active disease and with close monitoring because of this possible risk. If dose escalations are implemented during pregnancy due to inadequate disease control, measurement of maternal thiopurine metabolite concentrations should be performed in order to identify any newly developed shunting.

Thiopurine metabolites, including 6-TGN and less commonly 6-MMP, are detected in the umbilical cord blood of infants following intrauterine exposure. Metabolite levels in infants at birth are lower than in mothers, with a median 6-TGN infant:maternal ratio of 0.4. Metabolites were cleared from exposed infants by six weeks of age, unlike other IBD medications such as anti-TNF therapy, where time to complete clearance can be up to twelve months[13]. This information is likely to be reassuring for mothers during pre-pregnancy counselling and also suggests that vaccinations can be safely given according to the standard schedule.

Unlike the previous study, by Jharap et al, we found that thiopurine exposure was not linked to neonatal anaemia. In the current study, neonatal anaemia was defined as a Hb at birth <135 g/L according to age-related reference ranges (established from published reference ranges across a number of newborn cohorts)[10]. We did not detect anaemia by this definition in 16/17 infants at birth in this study, including those with detectable 6-TGN concentrations. The definition of anaemia used by Jharap et al was a Hb <10 mmol/L[9]; this level is equivalent to approximately 161 g/L. These infants would not be classified as anaemic according to known reference ranges established for paediatric cohorts[10].

We did, however, detect a small number (n=3) of cases of mild transient neutropenia or lymphopenia in infants from six weeks (Table 6.7), which appeared unrelated to thiopurine metabolite levels and may have been as a result of an intercurrent infant viral illness. Severe neonatal neutropenia has been previously reported in the setting of supra-therapeutic maternal 6-TGN levels and reduced TPMT activity detected post-partum[14]. Severe neutropenia was not detected in any infants in our cohort. One infant had mild thrombocytopenia at birth, however there is the possibility this reflects a spurious result with platelet clumping from an umbilical cord sample.

A novel finding of this study is that of neonatal thrombocytosis and abnormal liver function beginning at six weeks of age in around 80% of infants exposed to thiopurines *in utero.* All infants with abnormal tests were subsequently reviewed by a paediatrician;

none became unwell. Possible mechanisms behind the changes seen in the current study are unclear. Multiple factors have been known to influence infant blood test parameters, including infection, chronic inflammation and drug exposure. Infant thrombocytosis has been associated with intrauterine exposure to methadone and antipsychotics as well as iron deficiency[15]. One infant with thrombocytosis in the current study (Infant 22) was noted to have microcytosis at six weeks and iron studies are unknown. In our study, platelet counts were higher in babies exposed to combination therapy with anti-TNF. There have been uncommon reports of pancytopenia and thrombocytopenia linked to anti-TNF treatment, but not significant thrombocytosis[16]. Hence, a direct toxic effect from thiopurine and/or anti TNF exposure seems unlikely to cause thrombocytosis. It is possible that subclinical inflammation may be an underlying mechanism for the raised platelet counts observed in this small infant cohort, however further studies are required.

In general, liver enzyme elevations and transient hyperphosphatasemia can be detected in infants in the setting of a viral infection. Some infants in our study did have preceding infections reported, although abnormal liver function tests also appeared to persist or develop without reported intercurrent infection (Table 6.7). The normal reference ranges for paediatric liver function tests are challenging to determine and hence vary somewhat in the literature, with reports of slightly higher ALT levels in infants under one and in breastfed infants[17]. Low concentrations of mercaptopurine have been detected in breastmilk[18]. However, thiopurine metabolites were undetectable in infant blood in breastfed infants in our study as well as in a previous study including four breastfed infants of mothers on azathioprine who had therapeutic metabolite blood concentrations[19]. Although ingested thiopurine metabolites may go to the liver directly, there was no difference in serum ALT levels or platelets at six weeks in infants who were breastfed compared to those were not being breastfed. However, ALT levels were higher at three-four months in breastfed compared to formula-fed infants. This needs to be interpreted with caution given the small sample size of only three infants in the non-breastfed group. Lastly, blood tests normalised in some cases despite ongoing breastfeeding (Table 6.7), suggesting that thiopurine exposure through breastmilk is not an important aetiological mechanism.

In adults on thiopurine medications, it is known that brief and asymptomatic liver enzyme elevations can occur as well as more significant liver injury[20]. Mild idiopathic ALT elevations in the setting of anti-TNF therapy also occur uncommonly and anti-TNF associated autoimmune hepatitis has been rarely reported in adults[21]. Regarding

thiopurine induced-liver injury, both acute hepatocellular hepatitis and cholestatic hepatitis patterns have been reported[20, 22]. In the majority of cases, liver function test abnormalities tend to resolve quickly following cessation of the thiopurine[22]. One other study in older children also found abnormal liver function in relation to thiopurine medications with a 6-MMP:6-TGN ratio above 4[23]. Interestingly, in our study, the two infants with detectable 6-MMP levels at birth had the most pronounced ALT rise. The neonatal liver is physiologically immature at birth in several processes including impaired drug metabolism[24]. It is possible there is delayed minor toxicity on the liver and bone marrow that is manifest by six weeks of age.

Limitations of the study include the small sample size and restricted maternal observations pre-conception where participants were recruited to the study when already pregnant. Accurate determination of RBC and thiopurine metabolite levels is complex, particularly with cord blood, which is prone to clotting. Therefore, we utilised samples from lithium heparin tubes where necessary and it was recommended that samples were shipped at 4°C to maintain stability. We did not include an infant control population as the haematological and LFT abnormalities were reported based on established age-appropriate laboratory reference ranges. Strengths of the study include the prospective design and inclusion of well described clinical data including detailed infant follow up.

In conclusion, thiopurine pharmacokinetics are altered in pregnancy with 6-TGN levels decreasing and 6-MMP levels increasing in the second trimester of pregnancy. Thiopurine metabolite levels, full blood and liver function monitoring should be considered in pregnant women during the second and third trimesters to ensure optimal yet safe metabolite levels; in particular, we recommend assessing for an elevated 6-MMP in the second trimester. Infants of mothers on thiopurines during pregnancy are exposed to both 6-TGN and 6-MMP at levels lower than maternal levels, with metabolite clearance completed before six weeks and no evidence of neonatal anaemia.

This is the first report of thrombocytosis and abnormal LFTs in infants at six weeks following intrauterine thiopurine exposure in the absence of detectable 6-TGN or 6-MMP levels. The cause of these changes is uncertain, however all babies remained clinically well. As we could not ascertain the causative factor in this observational study, we recommend that infants exposed to thiopurines are considered for routine assessment of FBE and LFTs at six weeks of age. However, we do not think these

findings are sufficient to change the current recommendations regarding thiopurines use in pregnancy and breastfeeding in women with IBD. Thiopurines remain an important therapeutic option for women with IBD during a period where tight disease control is paramount.

Further Discussion

Sample size calculation was not performed in this observational study, however the sample size achieved was similar to the previous study by Jharap et al.

The mechanism behind the change in thiopurine metabolism is unclear. Increased plasma volume in pregnancy may explain the reduced 6-TGN levels but not the increased 6-MMP, which may be better explained by a pregnancy-related change in the drug metabolism. There may be inhibition of at least one of the enzymes in the metabolic pathway, or possibly induction of an enzyme in the branch to 6-MMP during pregnancy.

The normal reference ranges for infant liver function tests are defined based on samples from healthy controls. Laboratory reference ranges are usually based on the threshold values between which 95% of the test results from a healthy population would fall. However, liver function tests can also vary due to factors such as age and infection. Future extension studies are planned to further clarify normal liver function tests in infants born to IBD mothers and will be incorporating infants of non-IBD mothers as controls.

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Supplementary data

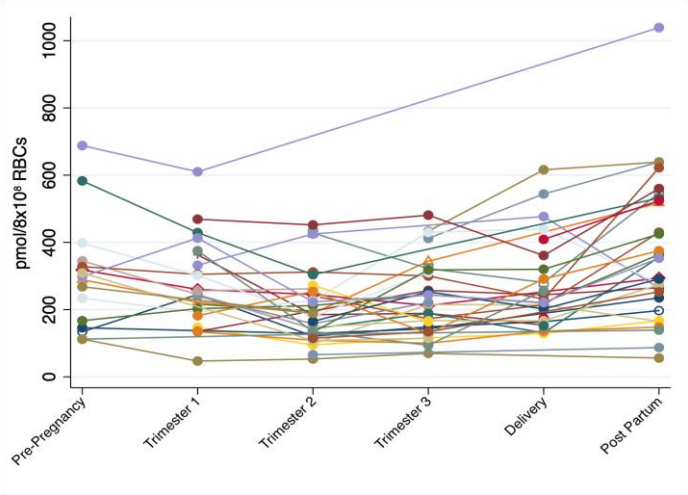

Figure 6.7 Individual 6-TGN levels across pregnancy

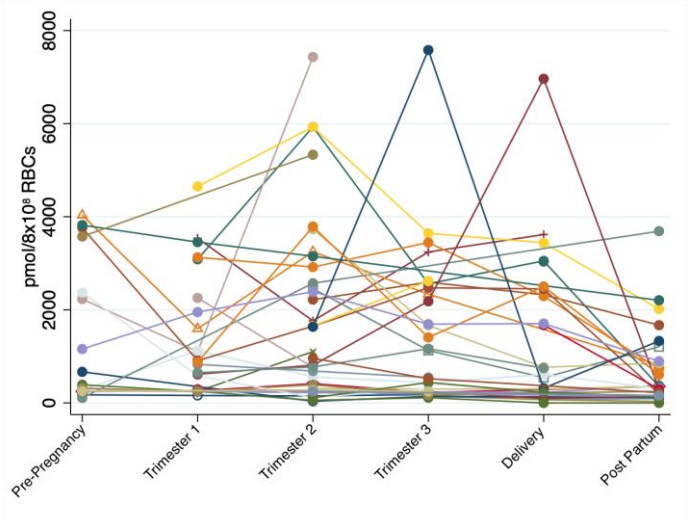

Figure 6.8 Individual 6-MMP levels across pregnancy

Table 6.7 Infants with Cord Blood Test Results (n=25) and Follow-up

Baby	Mother 6-TGN delivery	Mother 6-MMP delivery	Baby TGN delivery	Baby MMP delivery	Mode of delivery	FBE birth (normal Hb>135)	LFT birth	6-TGN/ 6-MMP at 6 weeks	FBE 6 weeks	LFT 6 weeks	FBE 2 months	LFT 2 months	FBE 3 months	LFT 3 months
Infant 1	220	0	0	0	C-section	Clotted	NAD - ALP 90	NA	NA	NA			NA	
Infant 2	Not taken	Not taken	Not sent	Not sent	NVD	NAD Hb 154	NAD	Declined	NA	NA			NA	
Infant 3	131	3052	63	70	NVD	Hb 163, **Plt 102**	NAD	0	**WCC 19.7 lymph 16.3 Plt 539**	**ALT 125**	**Plt 462**	**ALT 239**	See next	See next
Infant 4	477	225	104	0	NVD	NAD Hb 187	Not taken	0*	**Plt 893 lymph 12.3**	NAD- ALT 23			See next	See next
Infant 5	616	70	438	0	NVD	Clotted	Not taken	0	**Hb 91 Plt 653**	**ALP 628 bili 62** ALT 19			See next	See next
Infant 6	26	0	0	0	NVD	NAD Hb 154	NAD - bili 30	NA	NA	NA			NA	NA
Infant 7	361	6964	139	569	NVD	NAD Hb 139	NAD	0	**Hb 99 Plt 529**	**ALT 89**	**Plt 531**	**ALT 74 GGT 47**	See next	**ALT 97** GGT 33
Infant 8	214	302	39	0	C-section	**Hb 128**	NAD	0	Hb 112 **Plt 523**	**ALP 396** ALT 31			Clotted	NAD ALP 312
Infant 9	164	198	54	0	NVD	NAD Hb 160	NAD - bili 38	0	**Neut 0.73** Hb 117	**Bili 68** (conj'd 12) ALT 29			NAD Neut 1.37	Bili 19 **ALT 50 GGT 47**
Infant 10	154	3618	90	0	NVD	NAD Hb 137	NAD	0	**Plt 480**	**ALP 390 ALT 64 Bili 31** (conj'd 12)			See next	See next

Infant 11	221	1705	60	0	NVD	NAD Hb 156	Insufficient sample	0	**Neut 0.8** Plt 392	**ALT 58**			**WCC 5.6** Neut 1.4 **Plt 422**	**ALT 64**
Infant 12	214	2324	41	0	NVD	Hb 149 Plt 457	NAD	0	**Plt 777 lymph 9.6**	ALT 45			**Plt 763**	**ALT 55**
Infant 13	202	317	88	0	NVD	Clotted	Clotted	0	**Plt 465**	ALT 35 **ALP 415 bili 48** (conj'd 12)			**Plt 710 Neut 0.77**	**ALT 45** ALP 172
Infant 14	136	2294	33	0	C-section	Clotted	NAD	Not able to be completed					See next	See next
Infant 15	Not sent	Not sent	165	0	C-section	Clotted	Clotted	0	Clotted	ALT 40 **ALP 524**			**Plt 557**	**ALT 49** ALP 287
Infant 16	231	2451	88	0	C-section	Clotted	NAD - bili 37	0	**Plt 491** Hb 91	NAD ALT 24			**Plt 563**	NAD ALT 19
Infant 17	281	544	75	0	C-section	NAD Hb 146	NAD	0	**Plt 848**	**ALP 582** ALT 24			**Plt 919**	NAD ALP 348
Infant 18	291	2502	115	0	C-section	Clotted	NAD	0	NAD Hb-106, Plat 332	NAD ALT 28			NA	
Infant 19	167	768	66	0	C-section	Clotted	NAD - alb 28, bili 25	Not able to be completed					NA	
Infant 20	0	0	0	0	C-section	NAD Hb 158	NAD	NA					NA	
Infant 21	175	228	82	0	C-section	NAD Hb 142	NAD	0	Plt 449	NAD ALP 336 ALT 31			See next	
Infant 22	256	747	39	0	NVD	NAD Hb 143	NAD	0	**Plt 650**	**ALP 365** ALT 42			See next	

Infant 23	544	79	133	0	C-section	Hb 149 WCC 7.2 Neut 2.3	NAD bili 32	0	**Plat 768**	**ALP 567** ALT 20			**Plt 551**	**ALP 374** ALT 34
Infant 24	152	3038	110	0	C-section	Hb 165, WCC 8.7	NAD - Alb 27	0*	Hb 99 **Plt 411**	**ALP 364**			See next	
Infant 25	<50	5981	Not sent	Not sent	C-section	NAD Hb 171	NAD -ALP 296	0	**Plt 545**	**ALP 537 bili 30** (conj'd 10)			See next	

Table 6.7 *continued*:

Baby	FBC 4 months	LFT 4 months	FBC 6 months	LFT 6 months	FBE 9 months	LFT 9 months	FBE 12 months	LFT 12 months	Breast-feeding to 6 months	Anti-TNF	Paediatric examination	Reported infections / conditions to 6 months
Infant 1			NA	NA					Y	Y	NA	First degree heart block
Infant 2			NA	NA					Y to 6 weeks	Y	NA	Nil to 6 weeks
Infant 3	**Plt 411** Hb 125 **MCV 93**	**ALT 225**	Plt 351 Hb 121 **MCV 91**	**ALT 138**	Plt 375 Hb 118 **MCV 91**	**ALT 57**	Plt 340 Hb 122 **MCV 90**	ALT 39	Y	Y	6 months- no hepatosplenomegaly, thriving	Very mild coryzal illness at 6 weeks
Infant 4			Hb 122, Plt clumped, **lymph 10.3***				Not completed		N	Y	6 months- no hepatosplenomegaly, well	Viral infection (RSV)- hospital admission at 6 weeks
Infant 5			Hb 113 **Plt 462**	NAD-bili 13, ALP 308, ALT 43			NA		Y	Y	2 months- no hepatosplenomegaly, well	Torticollis/ Plagiocephaly
Infant 6			NA	NA					N	Y	NA	Nil
Infant 7		**ALT 104**		**ALT 118**	**Plt 474**	**ALT 65**	Plt 378	ALT 31 (ALP 649 likely due to URTI 12 months)	Y	Y	3 months- no abnormalities; 12 months- liver 1cm below costal margin, no splenomegaly,well	Nil

Infant 8	Not completed	NA							Y	Y	2 months- no reported abnormalities	Nil
Infant 9			NAD	NAD ALT 16, GGT 17					Y	N	6 months- no hepatosplenomegaly, well	Nil
Infant 10	**Plt 473**	**ALT 104**	**Plt 414**	**ALT 74**			Plt 395	ALT 26 ALP 399	Y	N	6 months- no hepatosplenomegaly	Nil
Infant 11	**Neut 0.96** Plt 380	ALT 47	**Neut 0.59** Plt 355	NAD ALT 19	Hb 120 Plt 287 **WCC 5.8*** Neut 1.57	NAD ALT 16			Y	N	3 months- no hepatosplenomegaly; 9 months- previous neutropenia with no obvious infection, no hepatosplenomegaly	At 2 weeks of age febrile illness of unknown cause requiring admission, toe infection; URTI, gastroenteritis
Infant 12	**Plt 869**	NAD ALT 38	**Plt 593 lymph 12.72**	NAD ALT 44	**Plt 528 lymph 10.92**	ALT 35	NA	NA	Y	Y	4 months- mild hepatomegaly 3cm below costal margin; 7 months- well, thriving, platelets improving, no hepatomegaly	Nil
Infant 13	Plt 398	NAD ALT 35	Plt 326	NAD ALT 31					Y	Y	3 months- liver 2cm below costal margin, signs of URTI, cap haemangioma back	Infection of umbilical site, URTI, gastroenteritis
Infant 14			Plt 747	NAD ALT 33			*Pending*		Y	N	NA	Nil
Infant 15			**Plt 509**	NAD ALT 32	**Plt 515**	NAD ALT 29			Y	N	5 months- unremarkable, well	Nil
Infant 16	**Plt 498**	NAD ALT 23	NAD Plt 394	NAD ALT 21					N	Y	4 months- no signs chronic liver disease	Nil

Infant 17	**Plt 757**	NAD ALT 24	Not completed	NA	*Pending*				Y	Y	3 months- well, liver 1cm below costal margin, no splenomegaly	Nil
Infant 18			NA	NA					N	N	NA	Nil
Infant 19			NA	NA					Y	N	NA	Nil
Infant 20			NA	NA					N	Y	NA	Nil to 3 months
Infant 21	Hb 119 **MCV 74** **Plt 661**	NAD ALT 25	Hb 119 **MCV 75** **Pt 452**	NAD ALT 25					N	Y	5 months- no hepatosplenomegaly, recent URTI	Nil
Infant 22	**Plt 682** **MCV 70**	ALP 146 **ALT 70**	Plt 379 MCV 67	ALP 121 **ALT 51**					Y	Y	3 months- telehealth review; 6 months- well, multivitamin for low MCV	Tonsillitis (oral antibiotics) at 5 months
Infant 23			**Plt 590**	ALP 235 ALT 29					Y	N	4 months- well, no hepatosplenomegaly 6 months – no hepatosplenomegaly	Nil
Infant 24	**Plt 416**	ALP 233 ALT 32	Plt 388						N	N	6 months- well, normal examination	Neck mass at 2 weeks of age (submandibular gland)
Infant 25			Plat 385 WCC 18.7	ALP 340 ALT 24	WCC 18.8 Plt 504	ALP 312 ALT 27			Formula from 6 weeks	N	6 months- telehealth review	Nil

NA: not applicable (no metabolites detected/previous blood test normal or improving); NAD: no significant abnormality; NVD: normal vaginal delivery; Plt: platelets; lymph: lymphocytes; Neut: neutrophils; bili: bilirubin; alb: albumin

*taken at 10 weeks

Note: Bold text denotes abnormal according to laboratory reference range

7 Biologic Drug Levels Across Pregnancy and Vedolizumab and Ustekinumab Levels in Infants following Intrauterine Exposure

7.1 Infliximab, Adalimumab and Vedolizumab Concentrations Across Pregnancy and Vedolizumab Concentrations in Infants Following Intrauterine Exposure

7.1.1 Introduction

Infliximab and adalimumab are anti-TNF monoclonal antibodies and vedolizumab is a newer anti-integrin monoclonal antibody. These biologic drugs are used to both induce and maintain remission in inflammatory bowel disease (IBD). During pregnancy, exposure to anti-TNF therapy is not associated with increased rates of adverse pregnancy outcomes[1]. Data relating to vedolizumab during pregnancy are currently more limited, but its risk is also considered low[2,3]. This is in contrast to active disease in pregnancy, which can be associated with adverse outcomes including pre-term birth and low birth weight[4]. Biologic drugs including anti-TNF therapy and more recently vedolizumab therefore form an integral part of IBD treatment during pregnancy.

As immunoglobulin G1 (IgG1) antibodies, anti-TNF agents are actively transferred across the placenta via the Fc receptor in an exponential fashion from the mid second trimester of pregnancy[5]. Vedolizumab, also an IgG1 antibody, is assumed to have the same transfer characteristics. The pharmacodynamics and pharmacokinetics of many drugs are altered during pregnancy. One small study has documented anti-TNF drug levels in pregnant IBD patients. In this study, by Seow et al, including fifteen women who received infliximab and ten women treated with adalimumab, it was observed that infliximab levels increased during pregnancy while adalimumab levels remained stable[6]. Maternal vedolizumab drug levels throughout pregnancy are unknown.

Cord blood concentrations and clearance patterns of anti-TNF agents in infants following intrauterine exposure have previously been studied[7,8]. The infant:maternal ratio of infliximab is higher and the infant clearance time of infliximab is longer than they are for adalimumab[7,8]. The placental transfer and clearance time in vedolizumab-exposed infants has not yet been established.

Although current data suggest there is no need to reduce these medications in pregnancy, the paucity of long-term data results in a commonly expressed desire to minimise infant exposure where possible without compromising maternal disease control. Hence, we aimed to advance our understanding of the pharmacokinetics of infliximab, adalimumab and vedolizumab by measuring these drug levels across pregnancy, in order to inform optimal intrapartum dosing. Secondly, we aimed to evaluate the placental transfer, time to elimination, and short-term infant outcomes following intrauterine exposure to vedolizumab.

7.1.2 Materials and Methods

Study design and population:

A prospective observational study was performed in women with a confirmed diagnosis of IBD who were either planning a pregnancy or were pregnant and on infliximab, adalimumab or vedolizumab. Patients were referred to the IBD and Pregnancy service at St Vincent's Hospital Melbourne, Australia between August 2017 and October 2019, from public hospital IBD clinics and private specialists across Australia.

Study procedures:

Peripheral blood was drawn from patients to measure maternal anti-TNF and vedolizumab levels pre-conception (up to 12 months), in each trimester of pregnancy, at delivery and postpartum (up to six months) where possible. Maternal infliximab and vedolizumab levels were measured at trough and adalimumab levels at steady state[9,10]. Results were excluded from the analysis of maternal levels across pregnancy when observations were not representative of trough or steady state levels, for example if participants had adjusted dosing to facilitate a break in therapy prior to delivery.

For participants treated with vedolizumab, umbilical cord blood and infant peripheral blood samples were taken at birth with further samples at approximately six weeks and three months, or until vedolizumab drug levels were undetectable. Maternal vedolizumab levels were measured at delivery to correlate with infant levels.

Clinical data relevant to pregnancy outcomes were recorded including IBD-related medical history, obstetric history, medication history, disease activity during pregnancy based on Physician Global Assessment (PGA), smoking and alcohol use during pregnancy and pregnancy complications. For participants on anti-TNF therapy, patient

body mass index (BMI), serum albumin, C-reactive protein (CRP) and faecal calprotectin in each trimester were collected where possible and co-therapy with a thiopurine was documented. Baseline data were collected pre-conception when possible, and in the case of a patient being recruited to the study when already pregnant, available baseline and pre-conception data were collected at the time of recruitment. Dosing and timing of anti-TNF and vedolizumab therapy were at the discretion of the treating physician, not based on drug levels. Some participants on infliximab or vedolizumab had two levels measured within one trimester depending on the timing of infusions.

Pregnancy outcomes including mode of delivery, gestational age, neonatal birth weight, congenital anomalies and APGAR scores were recorded for all participants. Infant outcomes were documented by participant-reported questionnaires at six weeks and three months for infants exposed to vedolizumab *in utero*, including infant growth, infections, chronic medical conditions, allergies and adverse reactions to vaccinations.

Laboratory methods:

Serum was extracted from blood samples by centrifugation and frozen in aliquots at -20 ^{o}C until assays were performed at Monash University Department of Gastroenterology, Alfred Health, Australia. Serum adalimumab and infliximab concentrations were measured by enzyme linked immunosorbent assay (ELISA) using the Q-INFLIXI and Q-ADA, Matriks Biotek, Ankara, Turkey kits according to the manufacturer's instructions. Samples were tested in duplicate and the average expressed as µg/mL serum. The coefficient of variation between assay wells was < 10%. In case of very high concentrations, the sample was re-tested in different dilutions. In case of variation between the two results, a third analysis was performed. Serum vedolizumab levels were measured by ELISA using either the Lisa-Tracker (Theradiag, France) or Ridascreen (R-Biopharm AG, Germany). The lower limit of detection was 2 µg/mL for the Lisa-Tracker Vedolizumab kit and 0.25 µg/mL for the Ridascreen kit. In-house testing of the two vedolizumab kits yielded similar results.

A minority of samples were sent to external laboratories for quantitative analysis of anti-TNF drug levels, where other commercially available ELISA (Promonitor (Grifols, Spain)) or Lisa-Tracker (Theradiag, France)) were used, amongst which good correlation has been reported[11-14].

Statistical analysis:

Data are reported as median [interquartile range (IQR)] or number (%). Between group differences were compared by $\chi 2$ test, Fisher's exact test and Wilcoxon rank-sum test, as appropriate and for continuous variables with more than two categories the Kruskal-Wallis test was used. The Wilcoxon sign rank was used to compare drug levels between two time points. The association between biologic drug levels during pregnancy and gestation in weeks was assessed using a generalised estimating equation (GEE) for each drug (infliximab, adalimumab and vedolizumab). A GEE model was selected in order to account for longitudinal within-subject correlations[15]. An exchangeable covariance matrix was specified in order to control for adjustment for dependencies between repeated observations within individual participants. The models also specified robust errors. The effect of clinical parameters including maternal BMI, CRP, serum albumin and combination therapy on anti-TNF levels was also examined, and those that were found to be significantly associated were added to the respective multivariable GEE model. Where CRP or faecal calprotectin were reported as a level below normal such as <5, a fixed number such as 4.9 was used in the analysis. Statistical analysis was performed using STATA version 16.1 (STATA LP College Station, TX, USA). A p value ≤ 0.05 was considered statistically significant.

Ethical considerations:

Ethical approval for the study was obtained from the Human Research Ethics Committees at St Vincent's Hospital Melbourne (HREC/17/SVHM/116) and participants provided written informed consent before inclusion.

7.1.3 Results

50 patients (23 on infliximab, 15 on adalimumab, 12 on vedolizumab) with at least two observations in pregnancy (trimester one to delivery) while on stable dosing were included for analysis of maternal levels. A further five patients on vedolizumab had mother-baby paired samples for vedolizumab levels at delivery (total mother-baby paired levels n=17). Patient demographics are shown in Table 7.1. Patients on vedolizumab more commonly had a diagnosis of ulcerative colitis (UC) and were more likely to have active disease in pregnancy than women on anti-TNF therapy (p<0.02).

Table 7.1 Patient demographics

Median (IQR) or n (%)		Infliximab n=23	Adalimumab n=15	Vedolizumab n=17	p-value
Age at beginning of pregnancy (years)		32.3 (28.8-35.2)	34.0 (30.2-36.7)	30.7 (27.8-33.5)	0.43
Weight prior to pregnancy (kg)		65.0 (58.0-73.0)	70.0 (65.0-86.0)	67.0 (58.0-81.0)	0.20
Diagnosis	**Crohn's disease**	17 (74%)	14 (93%)	5 (29%)	**<0.001**
	Ulcerative colitis	4 (17%)	1 (7%)	12 (71%)	
	IBD Unclassified	2 (9%)	0 (0%)	0 (0%)	
Crohn's disease location	**Ileal**	7 (30%)	4 (27%)	2 (12%)	0.74
	Colonic	5 (22%)	3 (20%)	2 (12%)	
	Ileocolonic	5 (22%)	7 (47%)	1 (6%)	
Crohn's disease behaviour	**Non-stricturing, non-penetrating**	8 (35%)	10 (67%)	3 (18%)	0.59
	Stricturing	8 (35%)	4 (27%)	2(12%)	
	Penetrating	1 (4%)	0 (0%)	0 (0%)	
Perianal Crohn's disease	**Yes**	6 (26%)	7 (47%)	4 (19%)	0.23
Upper gastrointestinal Crohn's disease	**Yes**	1 (4%)	2 (13%)	1 (6%)	0.47
Ulcerative colitis location	**E2 left-sided**	1 (4%)	0 (0%)	5 (31%)	0.73
	E3 pan-colitis	5 (22%)	1 (7%)	7 (44%)	
Disease duration at start of pregnancy (years)		8.0 (6.9-14.1)	8.6 (4.1-12.6)	11.6 (7.9-14.2)	0.30
Duration anti-TNF at start of pregnancy (years)		2.2 (1.6-4.5)	1.4 (0.8-3.8)	-	0.24
Duration vedolizumab at start of pregnancy (years)†		-	-	1.4 (0.7-2.9)	
Anti-TNF therapy prior to vedolizumab		-	-	12 (71%)	

Active disease during pregnancy according to PGA	**Yes**	2 (9%)	0 (0%)	6 (35%)	**0.012**
Thiopurine during pregnancy	**Yes**	14 (61%)	9 (60%)	4 (24%)	**0.044**

†In patients with intrapartum maternal vedolizumab levels (n=12)

IBD: inflammatory bowel disease; PGA: Physician global assessment

Infliximab cohort (n=23):

Infliximab was administered 6-8 weekly at a dose of 5 mg/kg in 21 patients, while one received 4-weekly dosing and another patient 10 mg/kg. The last intrapartum dose was given at a median 31 (IQR 29-33) weeks. Individual trough infliximab levels including delivery levels (if representative of trough levels) are shown in Figure 7.1.

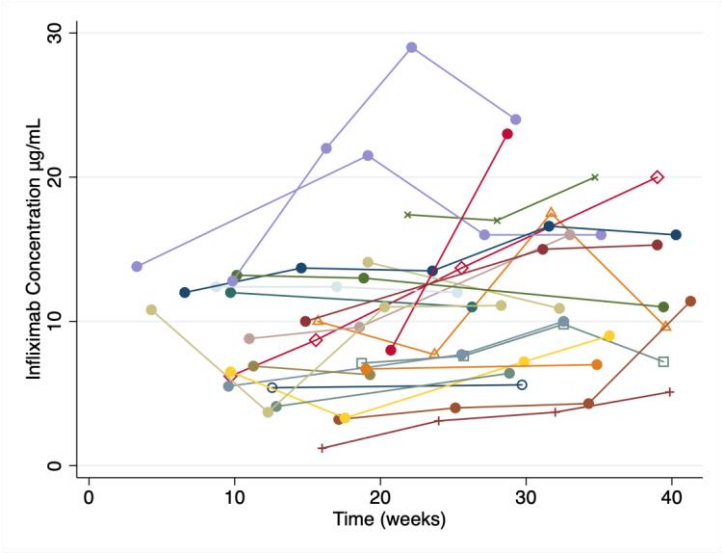

Figure 7.1 Individual trough infliximab levels during pregnancy

All participants on infliximab were in remission according to the Physician Global Assessment at the time of trough level measurements except for one. This participant, on 4-weekly infliximab, had persistently elevated faecal calprotectin from pre-conception to postpartum, with a faecal calprotectin up to 1400 µg/g in the third trimester. Another participant, on 6-weekly dosing, had mildly active disease in the first trimester, prior to inclusion in the study. One other participant, who elected to cease her infliximab at 24 weeks gestation, experienced recurrence of her perianal fistulising Crohn's disease postpartum (infliximab levels following adjusted therapy not included).

For the patients on infliximab, the median available BMI, CRP and faecal calprotectin levels showed no significant difference between trimesters one to three (p>0.05), although there was a numerical increase in BMI. Median albumin levels decreased from 36.0 g/L (n=17) in trimester one, to 30.5 g/L (n=26) in trimester two and fell to 28.0 g/L (n=21) in trimester three (p<0.001).

The median number of trough levels per patient was 4 (range 2-6). Median infliximab trough levels were stable overall (Table 7.2, Figure 7.2). There were no significant differences in paired levels in trimester one (median 8.8, IQR 5.5-12.4 μg/mL) compared to trimester two (median 10.0, IQR 7.1-13.7 μg/mL), trimester two compared to trimester three (median 11.0, IQR 7.1-16.8 μg/mL) or trimester one compared to trimester three (all p>0.05, Wilcoxon). There was no significant difference in the median number of weeks between infusions (eight weeks) at each trimester (p=0.77).

There was, however, a small but statistically significant increase observed in infliximab level by gestational week when modelled using a generalised estimating equation, with a univariate regression coefficient of 0.16 (95% CI 0.08-0.24, p<0.001). This positive association between infliximab levels and gestational week remained significant in multivariable models following the individual addition of BMI, albumin, CRP or concomitant thiopurine therapy.

Table 7.2 Median infliximab levels across pregnancy (n=23)

	Number of observations	**Median (IQR) infliximab level (μg/mL)**
Pre-pregnancy	6	7.9 (6.3-11.0)
Trimester 1	15†	8.8 (5.5-12.4)
Trimester 2	30‡	10.0 (7.1-13.7)
Trimester 3	20§	11.0 (7.1-16.8)
Delivery	8	11.2 (8.4-15.7)
Postpartum	12	10.3 (4.3-13.8)

† *1 participant had 2 levels within trimester 1;* ‡ *9 participants had two levels within trimester 2;* § *2 participants had two levels within trimester 3*

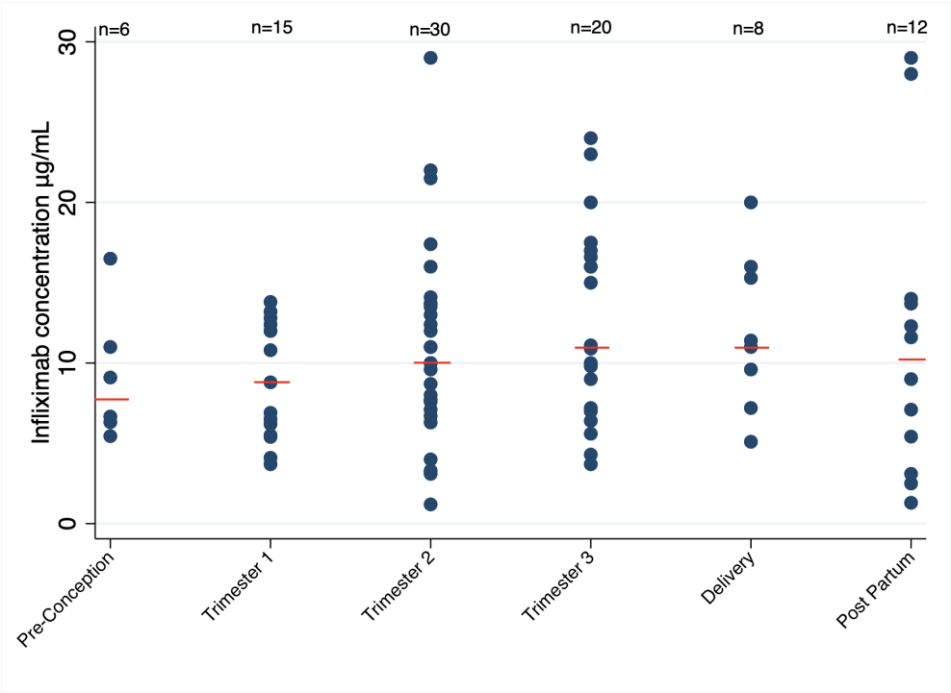

Figure 7.2 Median trough infliximab levels across pregnancy

Adalimumab cohort (n=15):

Thirteen patients were on adalimumab fortnightly and two were on weekly dosing. Two patients were commenced on adalimumab in pregnancy at least 12 weeks before the earliest adalimumab level. Ten patients continued adalimumab throughout pregnancy and five stopped at 30-33 weeks. The last intrapartum dose was given at a median 37 (IQR 31-38) weeks.

All patients on adalimumab were in remission according to PGA at the time of included drug levels. One patient had a faecal calprotectin of 453 µg/g in trimester one, which subsequently normalised and she remained clinically well. Another patient, who was switched from infliximab to adalimumab in the second trimester due to anti-drug antibodies, had a severe postpartum flare in the setting of a postpartum adalimumab level of 0.73 µg/mL (postpartum result excluded in the setting of loss of response to anti-TNF; the participant previously had therapeutic adalimumab levels and was well throughout pregnancy).

For the patients on adalimumab, the median available BMI, CRP and faecal calprotectin levels showed no significant difference across trimesters one to three ($p>0.05$), although there was a numerical increase in BMI. Median albumin levels

decreased from 33.5 g/L (n=8) in trimester one, to 30.0 g/L (n=12) in trimester two and fell to 27.0 g/L (n=15) in trimester three (p=<0.001).

Individual adalimumab levels including delivery levels that were reflective of steady-state (with no break in therapy prior to delivery) are shown in Figure 7.3. The median number of adalimumab levels per patient was 3 (range 2-6). Median adalimumab levels were stable across pregnancy (Table 7.3, Figure 7.4). There were no significant differences in paired levels in trimester one (median 5.7, IQR 4.8-10.2 μg/mL) compared to trimester two (median 5.2, IQR 4.0-6.8 μg/mL), trimester two compared to trimester three (median 5.8, IQR 4.8-8.0 μg/mL) or trimester one compared to trimester three (all p>0.05, Wilcoxon).

No association was found between adalimumab levels and gestational weeks when modelled using a generalised estimating equation, with a regression coefficient of -0.01 (95% CI: -0.10, 0.09, p=0.90).

Table 7.3 Median adalimumab levels across pregnancy (n=15)

	Number of observations	**Median (IQR) adalimumab level (μg/mL)**
Pre-pregnancy	2	10.4 (10.0-10.8)
Trimester 1	9	5.7 (4.8-10.2)
Trimester 2	12	5.2 (4.0-6.8)
Trimester 3	14	5.8 (4.8-8.0)
Delivery	8	6.7 (5.1-8.0)
Postpartum	8	7.2 (4.3-9.7)

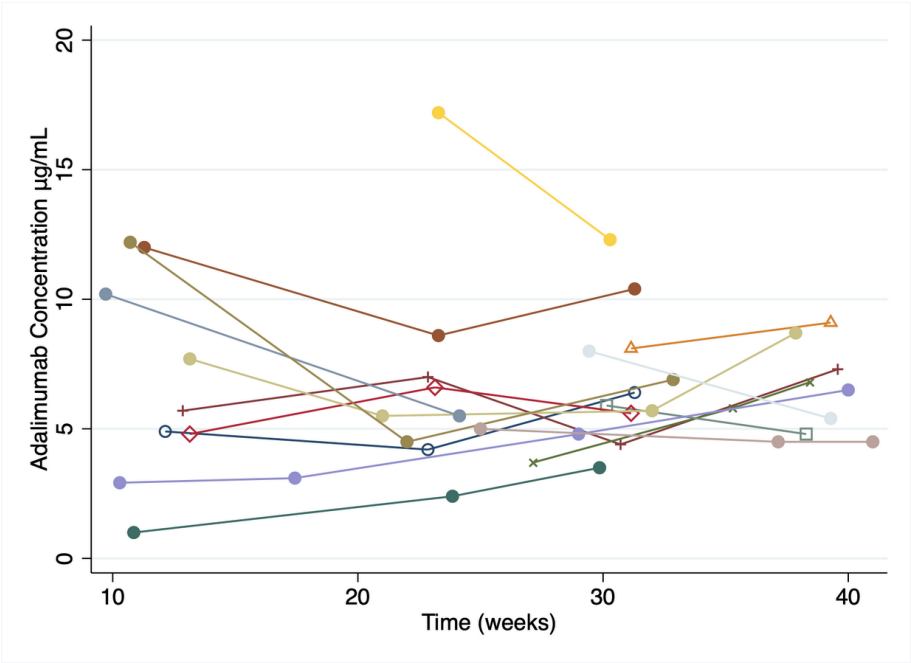

Figure 7.3 Individual adalimumab levels during pregnancy

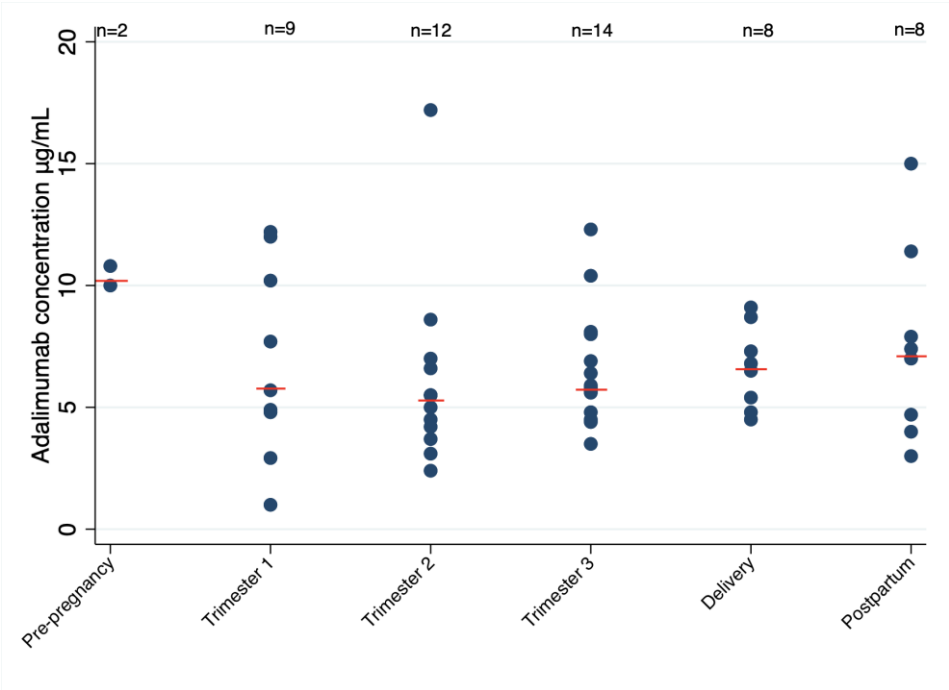

Figure 7.4 Median adalimumab levels across pregnancy

Vedolizumab cohort (n=17):

Vedolizumab was administered at a dose of 300 mg, 8-weekly in fourteen patients and 4-weekly in three patients. The last intrapartum dose was given at a median 30 weeks.

Of the 17 patients on vedolizumab, six experienced active disease during pregnancy, reflecting a more refractory and biologic-experienced cohort. One had active disease in early pregnancy while on 4-weekly dosing, two patients required prednisolone, one required antibiotics for perianal disease and another continued vedolizumab to 35 weeks gestation. Another patient had a severe flare requiring hospital admission for intravenous steroids and was subsequently re-commenced on vedolizumab at 14 weeks gestation; her vedolizumab trough levels were not included throughout pregnancy (only mother-baby paired samples at delivery).

In the 12 patients with at least two observations in pregnancy, maternal trough vedolizumab levels are shown in Table 7.4 and Figures 7.5 and 7.6. The median number of intrapartum levels per patient (n=12) was 3 (range 2-4). In one of the patients on 4-weekly dosing, vedolizumab was de-escalated to 8-weekly for the third trimester (following an atypical lower respiratory tract infection) and hence the subsequent trough levels were not included in the analysis of maternal levels across pregnancy for this patient. One other patient was commenced on vedolizumab at around three weeks' gestation, with steady state trough levels included from late in her second trimester of pregnancy. Vedolizumab levels were not representative of trough levels in the majority of participants at delivery and postpartum due to timing of the dose around delivery.

Table 7.4 Trough vedolizumab levels during pregnancy (n=12)

	Number of observations	**Median (IQR) vedolizumab level (μg/mL)**
Trimester 1	5	19.0 (13.0-23.0)
Trimester 2	16†	15.1 (8.6-21.7)
Trimester 3	9	9.5 (3.7-20.0)
Delivery	2‡	5.5 (1.1-9.9)

† *5 participants had two levels within trimester 2;* ‡ *other delivery levels not trough*

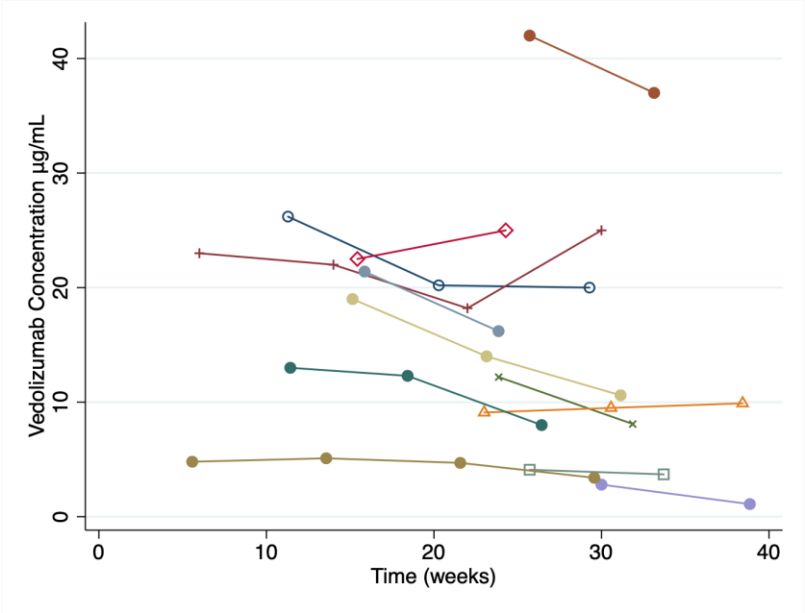

Figure 7.5 Individual trough vedolizumab levels during pregnancy

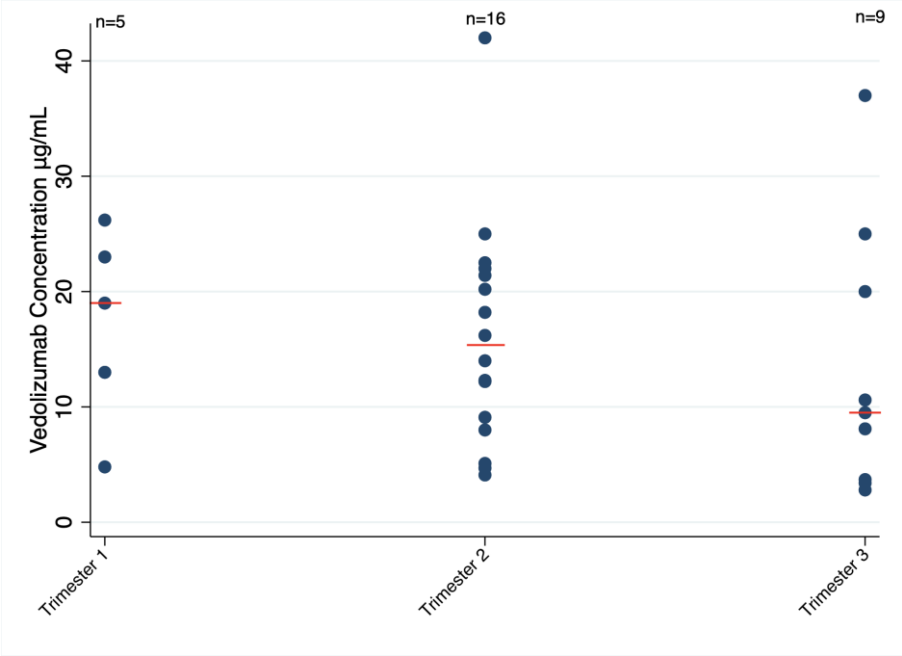

Figure 7.6 Median trough vedolizumab levels in pregnancy

There were no significant differences in paired levels between trimester one (median 19.0, IQR 13.0-23.0) µg/mL) and trimester two (median 15.1, IQR 8.6-21.7µg/mL), trimester two and trimester three (median 9.5, IQR 3.7-20.0 µg/mL) or trimester one and trimester three (all p>0.05, Wilcoxon).

However, there was a small but statistically significant decrease observed in vedolizumab level by gestational week when modelled using the generalised estimating equation, with a univariate regression coefficient of -0.18 (95% CI: -0.33 – -0.02, p=0.03).

Placental transfer of vedolizumab (n=17):

The median infant vedolizumab level was 5.0 (IQR 2.5-7.1) μg/mL, which was lower than the median level in their mothers at delivery, 9.5 (IQR 3.0-13.0) μg/mL) (p<0.05). The median infant to maternal vedolizumab ratio was 0.7 (IQR 0.5-0.9). There was a strongly positive correlation between infant vedolizumab levels and maternal vedolizumab levels at delivery (r=0.91, p<0.001) (Figure 7.7). The time since last intrapartum dose inversely correlated with infant vedolizumab levels at delivery (r= -0.79, p<0.001) (Figure 7.8).

Individual infant vedolizumab levels at birth were all lower than their mother's, except in two infants with low cord blood levels; one infant had vedolizumab level of 2.5 μg/mL when the mother's delivery level was also low at 1.6 μg/mL and another infant had a vedolizumab level of 1.9 μg/mL when the maternal level was 1.6 μg/mL).

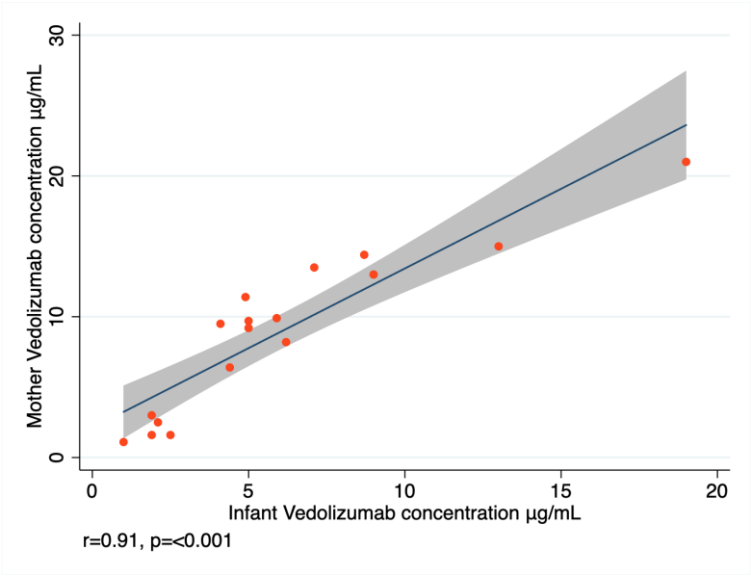

Figure 7.7 Correlation between maternal and infant vedolizumab levels

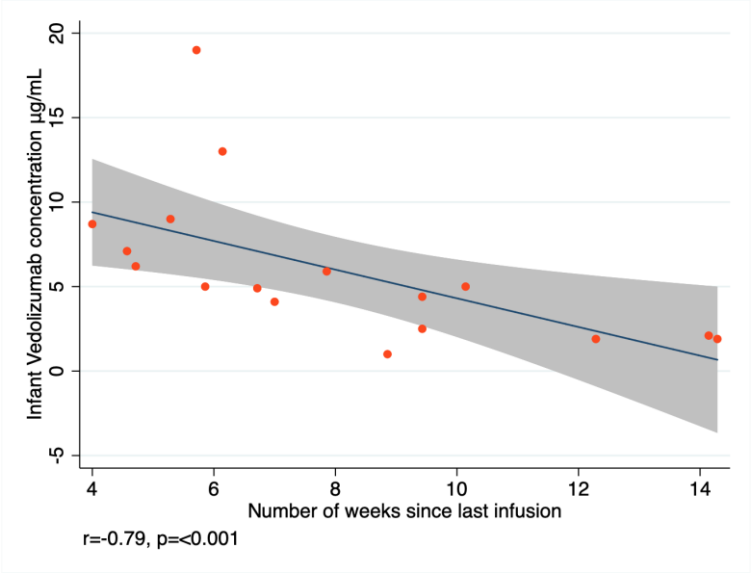

Figure 7.8 Correlation between infant vedolizumab level and weeks since last intrapartum infusion

Vedolizumab time to clearance in infants:

Vedolizumab was undetectable at 6-8 weeks of age in four infants, and at 10-15 weeks of age in another seven infants (Table 7.5). One infant, who was exposed to 4-weekly vedolizumab to 33 weeks gestation, had a vedolizumab level of 1.9 µg/mL at 12 weeks and an undetectable level at 16 weeks (Patient 12). Three infants had very low levels at 6-8 weeks of age and further blood testing was declined (Table 7.5). One participant declined all follow-up blood testing after birth (Patient 13) and one infant remains in follow-up testing (Patient 17).

Table 7.5 Infant vedolizumab levels

Infant	**Vedolizumab level at delivery (µg/mL)**	**Vedolizumab level at 6-9 weeks (µg/mL)**	**Vedolizumab level at 10-15 weeks (µg/mL)**
Patient 1	2.1	0.20	**0.0**
Patient 2	4.9	0.70	*Declined*
Patient 3	5.9	0.86	*Declined*
Patient 4	8.7	**0.0**	NA
Patient 5	1.0	**0.0**	NA
Patient 6	19.0	-	**0.0**
Patient 7	5.0	**0.0**	NA
Patient 8	4.1†	-	**0.0**

Patient 9	2.5	-	**0.0**
Patient 10	4.4	0.50	**0.0**
Patient 11	9.0	0.65	*Declined*
Patient 12	13.0	4.40	1.9 (12 weeks)
Patient 13	6.2	*Declined*	*Declined*
Patient 14	7.1	-	**0.0**
Patient 15	5.0†	-	**0.0**
Patient 16	1.9	**0.0**	NA
Patient 17	1.9	*Pending*	

† *venous sample collected (not cord blood)*

Overall Pregnancy Outcomes:

The majority of babies were delivered at full term with normal birthweight, showing rates similar to the population norms in Australia. Pregnancy outcomes are shown in Table 7.6. One infant exposed to vedolizumab was diagnosed with hip dysplasia at birth.

One participant on 6-weekly infliximab who had active UC in early pregnancy and placenta praevia underwent an elective caesarean at 36 weeks + 5 days. One participant who was induced with vedolizumab in the second trimester due to active UC in pregnancy delivered at 34 weeks gestation following preterm premature rupture of membranes. Another participant on 4-weekly vedolizumab with chronic active colitis delivered at 35 weeks gestation after preterm premature rupture of membranes.

Table 7.6 Pregnancy outcomes

Median (IQR) or n (%)		**Anti-TNF n=38**	**Vedolizumab n=17**	**p-value**
Gestation at delivery (weeks)		39 (38-39)	38.5 (38-39)	0.34
Pre-term (<37 weeks)	Yes	1 (3%)	2 (12%)	0.17
Birth weight (g)		3295 (3010-3650)	3390 (2896-3470)	0.67
Low birth weight (<2500g)	Yes	3 (8%)	2 (12%)	0.64
Birth length (cm)		50.25 (49-52)	50 (48-51)	0.48

Sex of baby	Boy	18 (47%)	8 (47%)	0.98
	Girl	20 (53%)	9 (53%)	
Mode of delivery	Caesarean section-emergency	9 (24%)	2 (12%)	0.42
	Caesarean section-elective	12 (32%)	9 (53%)	
	Vaginal birth	12 (32%)	5 (29%)	
	Vaginal birth-instrumental	5 (13%)	1 (6%)	
APGAR score at 1 minute		9 (9-9)	9 (9-9)	0.23
APGAR score at 5 minutes		9 (9-9)	9 (9-9)	1.00
Infant admitted to neonatal intensive care	Yes	4 (11%)	3 (18%)	0.46
Congenital abnormality at birth	Yes	0 (0%)	1 (6%)	0.26
Gestational diabetes	Yes	4 (11%)	3 (18%)	0.59
Pre-eclampsia	Yes	3 (8%)	1 (6%)	0.78
Iron infusion during pregnancy	Yes	10 (26%)	13 (76%)	**<0.001**
Smoking history	Yes, daily	1 (3%)	0 (0%)	0.38
	Yes, but not every day	0 (0%)	1 (6%)	
Alcohol during pregnancy	Yes	4 (11%)	0 (0%)	0.19

Infant outcomes following intrauterine vedolizumab exposure up to three months of age (n=14):

16 infants have completed follow up of infant outcomes to three months of age, while one baby remains in follow-up testing (Table 7.7). All babies were reported to be well at three months of age. Two infants had hip dysplasia; one diagnosed at birth (reported above), which resolved, and another diagnosed at three months in the setting of breech positioning and pre-term delivery. Another infant was diagnosed with a neck mass at around two weeks of age, which was improving and thought to be a submandibular gland on imaging; the infant was otherwise well. Two infants had a possible allergy to cow's milk-based formula.

Table 7.7 Infant outcomes following intrauterine vedolizumab exposure up to three months of age

Median (IQR) or n (%)		**6 weeks** ***n=16***	**3 months** ***n=16***
Infant growth – centile according to weight	**Below 10th centile**	2 (12%)	1 (6%)
	Between 10th-90th centile	13 (79%)	11 (69%)
	Above 90th centile	1 (6%)	1 (6%)
	Unknown	0 (0%)	3 (19%)
Any reported infections	**No**	16 (100%)	16 (100%)
Chronic diseases or medical conditions	**Yes**	2 (12%)	1 (6%)
Adverse reactions to vaccinations	**Yes**	0 (0%)	0 (0%)
Allergies	**Yes**	0 (0%)	2 (12%)
Breastfeeding	**Yes**	9 (56%)	9 (56%)

7.1.4 Discussion

Therapeutic drug monitoring of biologic levels is increasingly used to optimise and guide therapy when clinical response is inadequate. Given the importance of maintaining an adequate clinical response during pregnancy, it is important to understand whether pregnancy impacts drug levels. In this prospective observational study, the effect of pregnancy was determined by longitudinal measurements of drug levels with utilisation of GEE modelling to gain an accurate understanding of the association between maternal levels and gestational week of pregnancy. For

adalimumab, levels are stable in pregnancy whether examined by the median levels in each trimester or by modelling. In contrast, modelling indicates that infliximab levels can display a small increase, while maternal vedolizumab levels decreased through pregnancy. Additionally, this study examined the placental transfer and clearance time of vedolizumab following intrauterine exposure, showing that median vedolizumab levels in infants are lower than maternal levels and are cleared by sixteen weeks or earlier. Pregnancy and infant outcomes in this cohort, although small, appeared consistent with the background population.

The elimination of anti-TNF monoclonal antibodies, while predominantly linear, is subject to multiple physiological, drug-specific and disease-related factors that include changes in body weight and serum albumin concentrations, the development of anti-drug antibodies, the type of anti-TNF drug[7], and more severe disease activity[16,17]. The marked physiological changes that occur in association with pregnancy might be anticipated to change the clearance of these drugs. The clearance of many drugs is known to be increased during pregnancy[18], therefore lower drug levels may be expected. It is also possible that TNFα itself may be reduced during pregnancy[19], resulting in less binding with anti-TNF antibodies and therefore increased levels of free drug might be seen.

Clearance of adalimumab in pregnancy, however, appears unchanged. Both the current study and that by Seow et al have shown that adalimumab levels are stable in pregnancy[6]. Meanwhile, infliximab levels increased in pregnancy, suggesting clearance appears mildly reduced for infliximab. Given the similarities between the two anti-TNF antibodies, this is somewhat unexpected. However, the data from Seow et al also supports our findings. In the previous report, median infliximab trough levels increased from 8.5 μg/mL in trimester one (5 included observations) to 21.0 μg/mL in trimester three (16 included observations), and logistic regression modelling suggested that, after adjusting for albumin, CRP and BMI, maternal infliximab levels increased by 4.2 μg/mL each trimester[6]. In contrast, in the present study that reports on a larger cohort with more complete longitudinal drug levels, no significant differences between median infliximab levels were observed in trimester one through trimester three. However, our modelling has shown a small but significant increase in infliximab levels of 0.16 μg/mL per gestational week, which is equivalent to an estimate of 4.8 (95% CI 2.4-7.2) μg/mL over 30 weeks from the first measurement towards the end of the first trimester, assuming a constant linear rise in infliximab in pregnancy. This was not influenced by

changes in albumin, CRP, BMI or concomitant thiopurine. The effect of a 4-5 μg/mL increase in levels is unknown, but is unlikely to be associated with adverse effects[20]. While the direction of change seems similar, the more than two-fold greater increase in maternal infliximab levels found in the previous study compared with that in the current cohort may have reflected the lower numbers of observations in the earlier report.

In contrast to infliximab, median maternal vedolizumab levels tended to fall across pregnancy and modelling indicated a small but statistically significant decrease in vedolizumab levels per gestational week. This amounted to about the same rate of fall as the increase for infliximab. Evidence regarding an exposure-efficacy relationship is weaker with vedolizumab than infliximab[21,22], therefore a small drop across pregnancy may not be clinically significant. As an IgG monoclonal antibody, pharmacokinetic properties of vedolizumab should be expected to be similar to the anti-TNF agents[17]. Vedolizumab exhibits a slower, linear elimination at levels above 10 μg/mL, but rapid, saturable, non-linear elimination at lower concentrations[23]. Clearance also appears increased with higher body weight and low albumin[21,23]. Although distribution is slower for adalimumab as it is subcutaneously injected, the distribution of monoclonal antibodies remains mainly within the plasma and extracellular fluid due to their large molecular size, with a relatively small volume of distribution ranging from approximately 3-6 L for infliximab, adalimumab and vedolizumab[23,24]. During pregnancy, plasma volume increases by around 40-50%, but, with their limited volume of distribution, the pharmacokinetics of monoclonal antibodies are not considered likely to be substantially altered[24], despite other physiological adaptations in pregnancy such as the reduced albumin concentrations later in pregnancy. However, the current study suggests there may be pregnancy-related changes that marginally increase vedolizumab clearance in pregnancy. In contrast to the changes seen with infliximab and adalimumab, the increased clearance of vedolizumab during pregnancy observed in the current study appears more consistent with what might be the typical expectation of drug clearance change in pregnancy.

Our data show that median infant levels of vedolizumab at birth are lower than maternal levels. The median infant:maternal vedolizumab level ratio in 17 mother-baby pairs at delivery was 0.7 (IQR 0.5-0.9). Along with a possible decrease in maternal vedolizumab levels in pregnancy, this study suggests placental transfer of vedolizumab is less than with infliximab and adalimumab, for which the median infant:maternal ratios from the ERA study were 1.97 and 1.21, respectively[7]. Preliminary findings from our

study were presented in a letter to the editor reporting the first five of these mother-baby pairs and time to clearance in three infants[25]. Our results relating to placental transfer of vedolizumab are consistent with two other smaller studies, including preliminary data from the ongoing Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry (n=7) and another small case series from Denmark (n=2), where infant vedolizumab levels at birth were also reported as lower than maternal levels[26,27]. Given that vedolizumab is also an IgG1 molecule, which is thought to be actively transported across the placenta in a similar way to infliximab and adalimumab, it is unclear why infant vedolizumab levels are lower than maternal levels. The expression of integrin receptors in the placenta is unknown but it is possible that vedolizumab remains bound within the placenta rather than transferring to the neonate.

A novel finding of our study is that vedolizumab levels are undetectable by sixteen weeks of age in exposed infants (median time to undetectable concentrations of 10.5 weeks, range 8-16 weeks). The only previous report was of one baby from the Danish case series with a very low vedolizumab level of 0.10 μg/mL at six months of age[26]. Infant clearance time for anti-TNF medications has previously been established, with a mean clearance time of 7.3 months for infliximab and 4.0 months following intrauterine adalimumab exposure[7]. In contrast, the current study has shown that vedolizumab was cleared at a median of 2.5 months (Table 7.5). Although vedolizumab has a longer half-life than infliximab and adalimumab, the rapid clearance in neonates may be in keeping with the known vedolizumab pharmacokinetic property of increased clearance at lower concentrations.

There is some uncertainty regarding the safety of the live rotavirus vaccine following antenatal vedolizumab exposure, particularly given its gut-specific mode of action. In a small subset from the PIANO registry data, there were no serious adverse events reported in infants administered the rotavirus vaccine (n=40)[28]. However, these data do not include vedolizumab-exposed infants[28]. Reassuringly, from our study to date it appears that in over 90% of babies vedolizumab is cleared by the recommended age limit at which the rotavirus vaccine can be given in Australia (fifteen weeks). Until further data regarding infant clearance time are available, if the rotavirus vaccine is to be given to vedolizumab-exposed infants we advocate for consideration of one serum vedolizumab level assessment prior to vaccine administration.

Limitations of the study include the potential variance in drug levels due to the use of ELISA kits from different sources for maternal infliximab and adalimumab levels.

Previous studies[11-14] and our own in-house evaluation (unpublished) show similar levels across the different assay kits. Small differences would be unlikely to significantly influence the results as the majority of intrapartum levels were measured using the Q-INFLIXI and Q-ADA assays, respectively. Paired mother and infant vedolizumab samples were performed using the same assay. Additionally, adalimumab levels were defined as steady-state rather than documented trough levels, as is widely practiced (including in the previous study by Seow et al)[6,9]. Nonetheless, we routinely advised trough adalimumab levels to be performed and the majority of intrapartum adalimumab levels were measured at trough; thus the effect of potential intra-patient variability in adalimumab levels was deemed to be minimal[10,29]. Another limitation of the study includes the small sample size, particularly for intrapartum vedolizumab levels and vedolizumab-exposed infants, although this is the largest study in the field to date and we have included more serial observations in each participant across pregnancy than previously described.

In conclusion, this longitudinal study indicates that biological drugs used in patients with IBD differ in their altered clearance profiles during pregnancy. Adalimumab levels remain stable in pregnancy, while there can be a small increase in infliximab levels and decrease in vedolizumab levels during pregnancy. However, the alterations in concentrations predicted are small and unlikely to be of clinical significance regarding efficacy or toxicity. Hence, routine therapeutic drug monitoring and intrapartum dosing adjustment are not indicated. Unlike anti-TNF monoclonal antibodies, infant vedolizumab levels are lower in cord blood than in mothers and are likely to be fully eliminated by sixteen weeks of age in infants following intrauterine exposure.

Further Discussion

It is unclear why vedolizumab clearance increased in pregnancy whereas infliximab clearance appeared mildly reduced. This may be related to vedolizumab binding to lymphocytes within the circulation, whereas infliximab and adalimumab are mostly bound in the tissues.

We recommend considering one serum vedolizumab measurement in infants to check if the drug level is undetectable just prior to administering the live rotavirus vaccine. The rotavirus vaccine is administered orally, and it is unclear whether the presence of vedolizumab impairs the delivery of antigen to the mucosal immune system, therefore potentially influencing vaccine efficacy.

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7.2 Ustekinumab Concentrations During Pregnancy and in Infants Following Intrauterine Exposure

7.2.1 Background

There remains a paucity of data in the literature regarding maternal ustekinumab levels during pregnancy and infant ustekinumab levels following intrauterine exposure. Ustekinumab is an IgG1 therapeutic antibody, therefore placental transfer is expected to begin in the second trimester and increase exponentially throughout pregnancy[1]. We hypothesised that neonatal ustekinumab levels would be higher than maternal levels, similar to infliximab and adalimumab.

Exposure to ustekinumab during pregnancy remains rare in Australia currently. As the PICCOLO study offered testing to women on vedolizumab, this was extended to those on ustekinumab as a clinical and research service. This small pilot is continuing to recruit participants beyond the PhD. Preliminary data will be presented in relation to the first six patients enrolled in this study who were treated with ustekinumab during pregnancy.

7.2.2 Methods

The methodology for this pilot study was the same as that employed for vedolizumab (see above). Maternal trough ustekinumab levels during pregnancy were measured when possible and maternal levels at the time of delivery were measured in all patients to date. At the time of delivery, blood samples were also taken from the umbilical cord to measure ustekinumab levels. Infant levels are then repeated between six and eight weeks, and at approximately three months of age to measure time to clearance. Serum ustekinumab concentrations were determined by ELISA (Theradiag LISA TRACKER Ustekinumab, Marne La Vallee, France) according to manufacturer's instructions. Pregnancy outcomes were reported as outlined in the methods for Section 7.1.

7.2.3 Results

Patient cohort:

Six women with Crohn's disease aged 24-39 years were included (Table 7.8). Patient 4, who had a history of stricturing ileocolonic Crohn's disease and previous ileocaecal resection, had ceased adalimumab pre-conception due to anti-TNF induced psoriasis. She developed evidence of disease recurrence in the first trimester of pregnancy and was subsequently commenced on ustekinumab at 17 weeks gestation. The other five

patients were on ustekinumab prior to pregnancy and in clinical remission (according to Physician Global Assessment) during the study period.

Pregnancy and neonatal outcomes:

Five mother-baby paired ustekinumab levels were available at delivery. All five patients delivered healthy babies at term (37-40 weeks) with normal birthweight, normal Apgar scores and no congenital anomalies (Table 7.8).

Maternal and neonatal ustekinumab levels:

Four patients to date had two intrapartum ustekinumab levels performed (Figure 7.9). Patient 1, on 6-weekly dosing, had her last ustekinumab dose at 32 weeks gestation. Patients 2 and 3, on standard 8-weekly ustekinumab, had their final intrapartum doses at 25 and 33 weeks, respectively. Patient 5, on 4-weekly dosing, remains pregnant currently. Patients 4 and 6 had only mother-baby paired levels at delivery included.

Maternal delivery levels ranged from 0.35-4.4 μg/mL (median 1.57 μg/mL). The maternal level at delivery inversely correlated with the duration since last intrapartum dose (Spearman correlation r= -0.90, p=0.04). Cord blood ustekinumab levels were higher than maternal levels (median 5 μg/mL, range 0.61-11.2 μg/mL), with a median infant:maternal ratio of 1.7 (range 1.3-7.1). The cord blood level did not correlate with the maternal level or the time since last dose (p>0.05).

One infant to date has had follow-up testing performed, this infant had a level of 11.2 μg/mL at birth and a much lower ustekinumab level of 1.6 μg/mL at seven weeks of age (86% reduction). One participant declined follow-up infant blood testing, and in another infant an adequate sample could not be collected at six weeks. The remaining follow-up infant levels are pending.

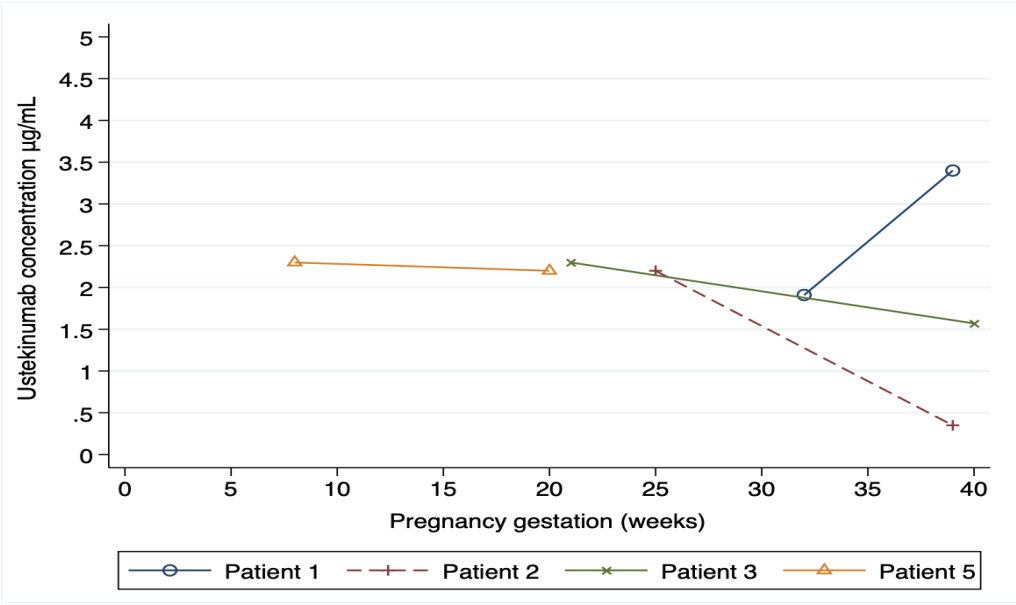

Figure 7.9 Maternal intrapartum trough and delivery ustekinumab levels in pregnancy

Note: Patient 2 had her last intrapartum ustekinumab dose at 25 weeks gestation

7.2.4 Discussion

Our preliminary results show good pregnancy and neonatal outcomes in this small cohort of women with IBD who achieved disease remission on ustekinumab. Ustekinumab has a relatively long half-life in adult non-pregnant patients of approximately three weeks[2].Our preliminary data suggest maternal ustekinumab levels are likely to remain relatively stable in pregnancy but larger number of women and more frequent testing are required to confirm this.

Neonatal ustekinumab levels at birth are higher than levels in mothers., as has been reported with infliximab and adalimumab exposure[3]. Interestingly, in one infant the ustekinumab level at birth was markedly higher than the mother's level (Patient 3), while in the other infants the level was up to two-fold higher. This apparent variation in placental transfer is in keeping with the two available case reports of Crohn's disease patients treated with ustekinumab in pregnancy with drug levels reported at delivery. In one of these cases, where ustekinumab was last administered at 30 weeks gestation, the cord blood ustekinumab level was 4.1 µg/mL compared to a maternal serum level of 0.3 µg/mL[4]. In the other reported case, the cord blood level was 8.0 µg/mL while the maternal ustekinumab level was 4.3 µg/ml at the time of delivery[5]. More data are currently being collected to determine the placental transfer and clearance time of ustekinumab in infants.

This study remains ongoing in order to increase the sample size. Further follow up of the cohort is underway to document longer term infant outcomes following *in utero* exposure to ustekinumab.

Table 7.8 Mother-baby characteristics and ustekinumab drug levels (n=6)

	Patient and Infant 1	**Patient and Infant 2**	**Patient and Infant 3**	**Patient and Infant 4**	**Patient and Infant 5**	**Patient and Infant 6**
Maternal characteristics						
Age at start of pregnancy (years)	26	24	33	25	32	39
Diagnosis	CD	CD	CD	CD	CD	CD
Disease phenotype	Stricturing ileocolonic, perianal	Inflammatory ileocolonic, upper GI	Stricturing colonic	Stricturing ileocolonic	Stricturing ileal, perianal	Inflammatory colonic, perianal
Disease duration (at start of pregnancy, years)	4	12	5	9	18	22
Biologic medications prior to ustekinumab	Infliximab Adalimumab Vedolizumab	Infliximab Adalimumab	-	Adalimumab	Infliximab Adalimumab	Infliximab Adalimumab
Concomitant medications	-	-	Azathioprine	Azathioprine	-	-
Duration of ustekinumab therapy (at start of pregnancy, years)	0.5	0.5	0.5	Commenced in pregnancy at 17 weeks gestation	1.8	2.4
Ustekinumab dosing	6-weekly	8-weekly	8-weekly	8-weekly	4-weekly	8-weekly
Pregnancy and neonatal outcomes						
IBD state during pregnancy	Remission	Remission	Remission	Mild activity in first trimester	*Pending*	Remission
Gestational age at delivery (weeks)	39	39	40	40	*Pending*	37
Delivery mode	CS	CS	NVD	NVD	*Pending*	NVD
Neonatal birth weight (g)	3230	3415	3130	4167	*Pending*	2640
Neonatal Apgar scores	9,9	9,9	8,9	9,9	*Pending*	8,9

at 1 and 5 minutes						
Congenital anomalies	Nil	Nil	Nil	Nil	*Pending*	Nil
Maternal and neonatal ustekinumab levels *(µg/mL)*						
Maternal at delivery	**3.4**	**0.35**	**1.57**	**0.73**	*Pending*	**4.4**
Infant at delivery	**5.0**	**0.61**	**11.2**	**0.92**	*Pending*	**8.2**
Days since last intra-partum dose	46	98	47	100	*Pending*	40
Infant: maternal ratio	1.5	1.7	7.1	1.3	*Pending*	1.9
Infant at 6-8 weeks	NA*	NA*	1.3	*Pending*	*Pending*	*Pending*
Infant at 3 months	-	-	*Pending*	*Pending*	*Pending*	*Pending*

CD, Crohn's disease; CS, caesarean section; NVD, normal vaginal delivery

*NA not available, further testing declined or sample not able to be collected

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8 Summary and Future Directions

8.1 Summary

IBD can have profound physiological and psychosocial implications on a patient's life, and these may be more pronounced throughout the pregnancy journey. Women with IBD face unique concerns in relation to reproduction, which have remained largely unexplored within the current treatment paradigm. This thesis presents the first qualitative study to assess the impact of IBD on pregnancy from the patient perspective through in-depth interviewing. The study delivered comprehensive insights into specific fears related to pregnancy in the setting of enduring IBD. It has highlighted anxieties regarding a perceived incompatibility between pregnancy and IBD, as well as concern, distrust and uncertainty regarding IBD medication safety in pregnancy. These maternal worries can persist throughout pregnancy and beyond, despite specialised IBD care, and are often concealed from the treating team.

The next part of the thesis aimed to address the deficits in pregnancy-related counselling and education for women with IBD that had been identified. As part of this work, a model for delivering pregnancy-related education was developed, consisting of an individualised intervention dedicated to evidenced-based discussion and addressing patient concerns. In a cohort of 100 women with IBD, half of whom were pregnant and half wishing to conceive, the study has shown that this targeted educational intervention significantly improves pregnancy-related knowledge. Notably, women who were already pregnant or had previously received counselling from their treating specialist still had shortcomings in baseline knowledge, and important gains could be made with this dedicated information session. This cohort was under the care of other IBD specialists, highlighting a deficit in pregnancy-related education within IBD healthcare. Additionally, knowledge levels may be poorer and gains even greater in a more general IBD population. The work has also demonstrated considerable anxiety amongst this patient group, which persisted following the intervention. However, overall emotional wellbeing improved and patient satisfaction rates were over 90% following the educational intervention.

The third study of this thesis evaluated the utility of gastrointestinal ultrasonography as a novel tool for disease activity monitoring during pregnancy. With the recent evolution of 'treating to target' in IBD, aiming for resolution of objective markers of inflammation to improve patient outcomes, gastrointestinal ultrasound has gained increasing

recognition as a useful non-invasive tool. During pregnancy, the disease course can be particularly challenging to predict, while the potential negative ramifications of active disease for maternofoetal outcomes are well recognised. In this setting, where clinical symptoms can be unreliable and other objective disease markers may be affected by pregnancy (e.g. albumin, CRP) or pose potential safety concerns (e.g. CT, endoscopy), the use of ultrasound presents an attractive modality for monitoring of IBD. I therefore performed the first study to determine the accuracy and feasibility of gastrointestinal ultrasonography for the assessment of IBD during pregnancy. This work has defined the role of intestinal ultrasound as an accurate tool for monitoring IBD during pregnancy, with adequate intestinal views in the majority of patients to the end of the second trimester. Adequate views of the colon and terminal ileum were obtained in over 90% of patients up to 20 weeks gestation. The test was acceptable to pregnant mothers and well-tolerated with no safety signals. Beyond 20 weeks, ultrasound continued to provide adequate views of the colon, with adequate views of the terminal ileum possible in approximately 60% of patients up to 27 weeks gestation. Gastrointestinal ultrasound delivered a high sensitivity and specificity for active IBD compared to faecal calprotectin and provides a valuable, non-invasive test that can inform prompt treatment modification in pregnancy.

There has also been a growing emphasis on the role of monitoring and optimisation of drug therapies in the management of IBD. Pregnancy can alter the pharmacokinetics of many medications, yet data are lacking regarding the metabolism of thiopurine medications during pregnancy and the pharmacodynamic consequences for mothers and infants. My next study therefore evaluated thiopurine metabolite levels in pregnant mothers with IBD over time. This study described the altered metabolism of thiopurines in pregnancy, showing that 6-TGN levels decrease by the second trimester of trimester while 6-MMP levels increase. Significant shunting of thiopurine metabolites may occur and therefore thiopurine metabolite levels are recommended for pregnant women in order to ensure optimal yet safe levels. Additionally, maternal thiopurine hepatotoxicity in the setting of pregnancy-related shunting can be difficult to distinguish from intrahepatic cholestasis of pregnancy. Unlike a previous study, this work has shown that there is no association with neonatal anaemia. Infants of mothers on thiopurines during pregnancy are exposed to both 6-TGN and 6-MMP at low levels. This study has shown for the first time that complete clearance of thiopurine metabolites occurs in exposed infants by six weeks of age. This research has also identified the novel findings of thrombocytosis and abnormal liver function tests in exposed infants from six

weeks of age, in the absence of detectable metabolite levels; the underlying pathophysiology contributing to these findings remains uncertain.

The final part of this thesis examined the impact of pregnancy on the levels of biologic drugs used to control IBD during pregnancy, an area in which there has also been a paucity of evidence in the literature. This work has demonstrated that adalimumab levels remain stable and infliximab levels display a small increase in pregnancy. This study described the first data regarding vedolizumab levels in pregnancy and clearance time in infants exposed to vedolizumab. These data show that vedolizumab levels may show a small decrease in pregnancy, while the placental transfer is less than with infliximab and adalimumab and clearance time in vedolizumab-exposed infants is faster, with all infants having undetectable vedolizumab levels by sixteen weeks of age. This research also presented preliminary data regarding another newer biologic agent, ustekinumab, including maternal levels in pregnancy and placental transfer. Infant cord blood levels of ustekinumab were found to be higher than maternal levels in the small cohort to date. Findings from this work suggest that routine therapeutic drug monitoring and adjustment of biologic dosing in pregnancy are not currently indicated.

8.2 Future directions

The knowledge gained from this thesis can be applied to change future international practice and enhance the care of patients with IBD during the significant pre-conception, pregnancy and post-partum stages, in order to help optimise health outcomes for these women and their babies.

Pregnancy-related counselling can be enriched by recognising and discussing individual patient circumstances, beliefs and preferences and incorporating a more personal and less clinical approach. Our findings emphasise the importance of employing open questioning for patients to express their concerns and offering psychological support when indicated to address anxiety. The most appropriate management for the continued patient anxiety in this population needs to be further explored.

Widespread uptake of the simple, accessible and repeatable educational intervention model developed as part of this study has the potential to not only improve pregnancy-related knowledge but also emotional health in women with IBD. The content covered was defined, and there was also an opportunity to focus on areas of specific concern to

increase patient satisfaction and engagement. It would be suitable as a template to guide this important discussion for English-speaking women with IBD and could be validated in other cohorts.

The educational intervention does require time, a valuable commodity. Evaluating whether part of the education can be delivered in an even more widely applicable way will be useful. It is possible that the model may be enhanced by additional means of education delivery such as an online decision aid or educational video. Further research is required to determine the benefits of a combined approach, integrating an introductory package relating to IBD and pregnancy that is delivered online or by an IBD nurse, followed by a shortened personalised medical education session focusing on medications and concerns emerging from the initial session. Reaching patients via the websites of patient support organisations such as Crohn's & Colitis Australia may further expand the benefits of education programs to patients beyond the care of tertiary hospitals and IBD specialists. As part of this PhD, information leaflets on IBD and pregnancy were developed for gastroenterologists, general practitioners, midwives and obstetricians (Appendix VI). These currently reside on the Gastroenterology Society of Australia website, but could be taken to other speciality training organisations such as the colleges of general practice and obstetrics for endorsement and promotion to increase their impact.

During pregnancy, incorporation of non-invasive monitoring of IBD is paramount, and we have demonstrated the utility of gastrointestinal ultrasound along with faecal calprotectin in this setting. These findings provide the recommendation for routine gastrointestinal ultrasound to form part of the clinical review of patients with IBD prior to the end of the second trimester in order to accurately assess disease activity. Additionally, in the setting of a flare of IBD proximal to the rectum, intestinal ultrasound offers a safe, point-of-care alternative to undertaking a flexible sigmoidoscopy during pregnancy. While the accuracy of ultrasonography and faecal calprotectin for assessing the disease during pregnancy have been established, we have not investigated how to best predict disease activity during pregnancy. Further studies planned by our group aim to examine whether these non-invasive disease markers can allow for prediction of the disease course in pregnancy, in order to facilitate early intervention to further optimise maternal and infant outcomes.

The thesis has provided new data on the pharmacokinetics and safety of IBD medications in pregnancy, including identifying a potential association between *in utero* thiopurine exposure and delayed infant thrombocytosis and liver function test

abnormalities. However, this aspect requires further exploration in a larger infant cohort, along with investigation of possible additional contributing or causative mechanisms. Our planned study extension aims to establish whether an association exists and to assess other underlying causes. This will involve the inclusion of a control group of women with IBD who are not prescribed a thiopurine or anti-TNF drug. The future study will seek to elicit the potential influence of other factors on infant blood test parameters, such as underlying inflammation related to maternal IBD and/or iron deficiency, and to better characterise the normal ranges in this infant cohort.

This research reports some of the earliest data worldwide regarding drug levels of the newer biologic agents, vedolizumab and ustekinumab, during pregnancy and in exposed neonates. The number of women exposed to these agents in pregnancy remains small and hence this emerging data will continue to be collected in order to further define the pharmacokinetics in pregnancy, placental transfer and infant clearance of vedolizumab and ustekinumab in an ongoing cohort.

The potential effects of pregnancy in the setting of IBD on the maternal and foetal immune systems present further avenues to be pursued in this sphere that have not been explored in this thesis. It will be useful to integrate the investigation of maternal and foetal immune system changes in association with clinical factors, measures of maternal disease activity and any relationship with antenatal drug therapy exposure. The overarching aim in this field is to continue to enrich our understanding of the interplay between IBD and pregnancy in order to accurately predict and optimise the pregnancy disease course, therapeutic strategies and, in turn, maternofoetal outcomes.

In conclusion, it is clear there are unique challenges facing pregnant women with IBD. With the continuing increase in IBD patients treated with immunosuppressive and biologic drugs, there is ongoing demand for data regarding use of these medications in pregnancy and the ensuing immunological profiles and outcomes of IBD mothers and their children. Confirmation of drug safety in pregnancy cannot be captured through clinical trials or drug development programs. Prospective observational datasets and well-characterised real-world cohorts such as ours therefore play a key role and offer vital opportunities to address these issues.

Appendix I Qualitative Interview Schedule

Background history/IBD history:

1. Can you tell me about when and how you were diagnosed with IBD?
2. Can you describe what treatments you have had in the past for your IBD?
    a. Probe - tell me more about your IBD, do you know which part/s of bowel affected, any surgeries (if the participant doesn't begin to tell the story of their disease)
3. What medications are you currently taking for your IBD?
4. What physical symptoms have you had from your IBD? Do you have any of these at the moment? Do you feel like your IBD is well controlled?
5. Who lives at home with you at the moment?
    a. If children-How old are they? Do they have any current health problems? How were your pregnancies with them? (If IBD flare during pregnancy, tell me more...)
    b. If partner-How long have you been together? Do they have any health problems?

IBD and fertility/reproduction:

6. Can you tell me if you are currently pregnant or planning a pregnancy? (Expand e.g. how many weeks/how long have you been trying?)
7. Are/were you worried about getting pregnant? Can you tell me why that is?
8. What are your feelings about your IBD in relation to falling pregnant/being pregnant? Can you tell me why you think you feel this way?
9. How do you feel about having children? What are your main concerns?
    a. Probe – if not offered, do you worry that your child may get IBD? Do you worry about being able to care for your child during flares?
10. What impact has your IBD had on falling pregnant/being pregnant? Tell me about anything you found difficult in getting pregnant/being pregnant with IBD?
11. Probe – if not covered, has IBD affected the timing of your pregnancy? Have you had any negative comments about your chances of getting pregnant? From whom.

IBD medications:

12. Have you/are you planning to make any changes to your medications during pregnancy? Can you tell me why that is? Does taking the medications worry you?
13. What are your feelings/experiences regarding breastfeeding?

14. How does/did your partner/family feel about your IBD and IBD medications when you are/were pregnant or trying to fall pregnant?
15. Have you had any negative comments about using IBD medications in pregnancy? From whom?

Information/support:

16. Do you feel like you have/had enough information about IBD and pregnancy/delivery? Have you tried to find information and how successful have you been? Where did you get information from?
17. Is there any other support/information you can think of that would be helpful for women with IBD who want to get pregnant/are pregnant?
18. Are there any other thoughts you would like to share in relation to your IBD or pregnancy?

Appendix II Pro-forma for Educational Intervention

Introduction:

- Trying to conceive and being pregnant can be an emotional time
- For most patients with IBD, medication is required during pregnancy to control the disease and it is common to be worried about the effect of medication on your baby
- It is important to know that the greatest threat to a successful pregnancy is having active disease; we recommend controlling disease by medication before trying for a baby
- We would like to help make sure you are fully informed and also give you the opportunity to discuss any issues or concerns you have around fertility, pregnancy and breastfeeding in relation to your disease
- **What are the Top 3 questions you would like answered?**

Clinical and Objective Assessment:

- Previous medical, surgical, obstetric history
- Current medications
- Clinical disease activity scores
- Objective assessment – endoscopy, imaging, CRP, nutritional markers, calprotectin

General pre-conception health:

- Discontinue teratogenic medications e.g. methotrexate
- Folic acid, iron supplementation
- Immunisation status
    - Pre-pregnancy – advise patient to see GP re vaccination status including chickenpox, influenza, MMR, diphtheria, tetanus, whooping cough
    - Wait to fall pregnant for at least one month after receiving live vaccines e.g. MMR
    - During pregnancy – influenza, whooping cough vaccines
- Substance use: advise cessation

Effect of IBD on fertility:

- Men and women with IBD generally have normal fertility
- There is no evidence that UC itself affects fertility
- However, studies have shown a reduction in fertility in patients who have had pouch surgery
- Women with Crohn's can have reduced fertility if they have active disease
- IBD does not affect fertility in men, but some medications including sulfasalazine and methotrexate may cause reduced sperm count

Passing on IBD to children:

- A child is more likely to have IBD if one of their parents has IBD
- The chance of your child developing IBD is around 5-9% (if one affected parent)

Effect of IBD on pregnancy:

- You will have the best chance of a healthy pregnancy if your disease is under control when you conceive
- If you conceive at time when your disease is under control, the risk of a flare during pregnancy is about 1/3, which is similar to the risk in non-pregnant patients
- However, if conception occurs at a time of active disease, about two-thirds of patients will have active disease during pregnancy
- It has been shown that mothers with IBD have a higher risk of their baby being born early/prematurely (before 37 weeks) and with low birth weight, and this risk is greater in women who have active disease during pregnancy; and active disease also increases the risk of a miscarriage
- A small number of studies have revealed slightly more birth defects in babies of mothers with IBD
- The chances of having a healthy baby are very good, particularly if your disease is under control when you conceive and during pregnancy

Effect of pregnancy on IBD:

- Pregnancy may have an effect on IBD due to changes in the immune system
- Pregnancy can be associated with a reduced number of flares in the following year

Disease monitoring during pregnancy:

- Endoscopy should only be done when there is a strong indication and should be performed in the second trimester whenever possible
- Exposure to radiation should be kept to a minimum, ultrasound is safe

Medication safety in pregnancy:

- Most IBD medications are considered of low risk to the baby, except for methotrexate
- Methotrexate is contraindicated in pregnancy; to avoid exposure to methotrexate it should be stopped at least for 3–6 months before trying to conceive
- 5-ASAs are considered safe
- Thiopurines e.g. azathioprine (Imuran), mercaptopurine are considered safe
    - Studies have shown no increased risk of birth defects or infections in babies
- Anti-TNF agents are considered safe
    - Studies have shown no increased risk of birth defects or infections in babies
    - Long term side effects of these drugs are unknown e.g. effect on developing immune system
    - These drugs do cross the placenta in the 2nd and 3rd trimesters and research has shown that levels in the babies can be higher than in their mothers and can stay detectable in the babies for up to 12 months
    - The European guidelines recommend that anti-TNF drugs should be discontinued at the end of the 2nd trimester to minimize this transfer across the placenta
    - However, in the US and Canada the recommendation is to continue anti-TNF medications throughout pregnancy due to the risk of disease flare and also the drug may not remain effective if stopped and restarted
    - Infection risk in babies may be increased if exposed to both anti-TNF and a thiopurine
    - If you chose to continue an anti-TNF during pregnancy, live vaccines should be avoided in your baby until they are 12 months of age
- Vedolizumab
    - Available data pertaining to vedolizumab use during pregnancy is limited
    - Vedolizumab is a large protein, similar to the anti TNF agents and

therefore likely to cross the placenta later in pregnancy and thought likely to have a similar safety profile

- Allopurinol
    - Potential safety concerns with use in early pregnancy
    - Stop pre-conception if possible and change to BD dose of thiopurine with monitoring of levels

Mode of delivery:

- The mode of delivery is mostly guided by your obstetrician, most women with IBD can have a vaginal delivery
- A planned caesarean section in patients with perianal Crohn's disease or a history of ileoanal pouch surgery is generally recommended
- Perianal disease after a vaginal delivery is more likely in women who have had perianal disease in the past

Breastfeeding:

- Benefits to newborn
- 5-ASAs, thiopurines and anti-TNFs considered safe while breastfeeding, low levels can be found in breastmilk

Appendix III Article: Abdominal Imaging in Pregnancy (maternal and foetal risks)

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Abdominal Imaging in pregnancy (maternal and foetal risks)

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ABSTRACT

Imaging studies are useful in the diagnostic evaluation of inflammatory bowel diseases. However, concern often exists about the safety of imaging for pregnant and lactating women and their infants, leading to unwarranted avoidance of beneficial diagnostic tests or disruption of breastfeeding. Ultrasonography and magnetic resonance imaging (MRI) are not associated with ionizing radiation and are the imaging techniques of choice for pregnant patients. Safety of MRI contrast agent gadolinium in pregnancy is uncertain, therefore MRI without gadolinium should be performed. Intestinal ultrasound where available and MRI without gadolinium can be used to characterise disease complications such as bowel obstruction or intra-abdominal collections. Ionising radiation exposure through computed tomography (CT) is usually at much lower doses than those associated with foetal harm, however CT should be reserved for the rare clinical situations in which ultrasound and MRI are either unavailable or unable to provide the required diagnostic information.

Introduction

Caring for a woman with inflammatory bowel disease (IBD) during her pregnancy presents a challenging and unique circumstance, as it requires consideration of the wellbeing of both mother and foetus in all of our clinical decision making. It is now known that active IBD or its complications can indeed lead to adverse pregnancy outcomes including foetal growth restriction and pre-term birth, and therefore prompt diagnosis and management during pregnancy is paramount [1].

Imaging studies are useful in the diagnostic evaluation of IBD. However, concern often exists about the safety of imaging for pregnant and lactating women and their infants, leading to unwarranted avoidance of beneficial diagnostic tests or disruption of breastfeeding. When we consider foetal and maternal risks relating to imaging being undertaken during pregnancy, the 'safety' of an imaging technique must appreciate the clinical benefit of obtaining the diagnosis. Our perspective on the benefit of imaging must also respect the potentially harmful consequences of neglecting to achieve the clinical information that can be provided by various imaging modalities.

Several guidelines including from the American College of Radiology and the American College of Obstetricians and Gynaecologists provide general recommendations for abdominal imaging in pregnancy, but current practice is not always in line with such guidelines and some controversies remain [2]. Furthermore, available evidence in the field is largely retrospective in nature, given the ethical limitations of including pregnant women in randomised controlled trials.

The safety and utility of standard imaging modalities used in IBD are impacted by pregnancy. During pregnancy, ultrasonography is considered the safest mode of imaging. However, where ultrasound is inadequate or unavailable, magnetic reasonance imaging (MRI) is generally preferred over computed tomography (CT) due to the lack of exposure to ionising radiation. The current evidence and consequent recommendations for abdominal imaging in the context of IBD during pregnancy will be discussed in this review.

Intestinal ultrasonography in pregnancy

Indications for intestinal ultrasonography in pregnancy

Intestinal ultrasonography can provide a useful adjunctive, non-invasive assessment to evaluate disease activity and is particularly important when investigating suspected disease complications in patients with IBD. In non-pregnant patients with IBD, it is widely established that ultrasound can accurately assess luminal disease activity of the small and large bowel as well extra-luminal complications and stricturing disease, particularly in patients with Crohn's disease [3]. Intestinal ultrasonography has been shown to have similar diagnostic accuracy for imaging in IBD compared with MRI and CT [4,5].

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Intestinal ultrasonography is a non-invasive imaging modality that does not require radiation and is therefore an ideal imaging modality in pregnancy [6]. However, views of the bowel can be impeded by the foetus in late pregnancy, and hence intestinal ultrasonography is most useful for assessing IBD during the first two trimesters of pregnancy.

In our experience, it is possible to obtain adequate assessment of the colon and terminal ileum with intestinal ultrasound up to around 26 weeks gestation, although the terminal ileum becomes more difficult to assess beyond 20 weeks gestation due to the gravid uterus [7]. Intestinal ultrasound provides good views of the colon in the majority of patients until early in the third trimester [7]. In patients with Crohn's disease affecting the ileum, ultrasound can be a valuable imaging tool up to around 26 weeks gestation. In the setting of a flare of colonic IBD during pregnancy, bowel ultrasonography may be a useful, non-invasive alternative to undertaking a flexible sigmoidoscopy, except in the case of a severe flare when biopsies are required.

Similarly, it has also been shown that ultrasound can be used for the diagnosis of appendicitis in pregnancy. Although it has a higher rate of failure to visualise the appendix than cross-sectional imaging techniques such as MRI, ultrasound generally remains first line for suspected appendicitis in pregnancy followed by MRI without intravenous contrast [8].

Foetal and maternal risks associated with ultrasound

Intestinal ultrasonography is the preferred imaging modality in pregnancy as it can be rapidly and safely performed where available.

Ultrasonography involves the use of sound waves and is not associated with any ionising radiation exposure for mother and foetus [9]. There have been no reports of documented adverse foetal effects for diagnostic ultrasonography procedures, including with Doppler imaging [9].

It is important to be aware that given the inherent limitations of ultrasound, adequate views may not possible, for example due to body habitus or anatomical changes in pregnancy. Hence, for the benefit of both mother and baby, further diagnostic evaluation should then proceed to consideration of alternative imaging in order to obtain the diagnosis and ensure appropriate management in pregnancy.

Recommendations for intestinal ultrasound in pregnancy

Intestinal ultrasound is the recommended first-line imaging modality in pregnancy for the assessment of luminal disease activity in both colonic and ileal IBD. It is also the preferred initial investigation for suspected extra-luminal complications or progressive stricturing disease where available. Ultrasonography, however, may not be diagnostic due to limited views and hence subsequent imaging such as MRI should be considered.

MRI in pregnancy

Indications for MRI in pregnancy

MRI of the small bowel is helpful in Crohn's disease in order to measure small bowel disease extent and activity, as well as assess for the presence of strictures, small bowel obstruction, intra-abdominal fistulae and abscesses when there is clinical suspicion. MRI is less useful in the assessment of ulcerative colitis where the disease can be accessed with endoscopy.

The advantage of MRI over ultrasound is the ability to image deep intra-abdominal and pelvic structures. MRI is indicated if there is suspected extra-luminal disease complications or progressive stricturing Crohn's disease and ultrasound is inadequate or unavailable. MRI should be performed in pregnancy if the diagnosis of these complications following MRI would alter patient management in pregnancy.

Foetal and maternal risks associated with MRI in pregnancy

MRI does not involve any ionising radiation exposure, however there have been theoretical concerns regarding foetal exposure to the electromagnetic fields such as potential effects from tissue heating and damage to foetal hearing due to the loud noise in an MRI [10].

Still, there have been no documented adverse effects on the human foetus linked to MRI exposure including cases reported since the 1980's [8,10]. Non-contrast MRI is considered safe during pregnancy by the American College of Radiology and the American College of Obstetricians and Gynecologists [9,11].

The usual small bowel MRI protocol includes administration of the contrast medium gadolinium. However, there is uncertainty regarding the use of gadolinium in pregnancy. Gadolinium is water-soluble and can cross the placenta into the foetal circulation and amniotic fluid [12]. Free gadolinium is toxic and is therefore given in a chelated (bound) form [9]. Gadolinium has been found to be teratogenic in animal studies in high and repeated doses [10] . This is thought to be due to dissociation from the chelation agent and prolonged exposure because the contrast remains in the amniotic fluid and is swallowed by the foetus and then re-enters the foetal circulation [9]. The longer the gadolinium-chelate molecule is present in the amniotic fluid, the greater potential for dissociation of the gadolinium from its ligand and the higher the potential risk of harm to the foetus from free gadolinium ions [12].

A recent large, retrospective study from Canada, identified all births of more than 20 weeks gestation from 2003 to 2015 and compared first-trimester MRI (n = 1737) to no MRI exposure (n = 1,418,451) [13]. There was no significant increase in the risk of stillbirth, neonatal death, congenital anomalies, neoplasm or hearing loss following first trimester MRI [13]. However, higher rates of rheumatologic, inflammatory, or infiltrative skin conditions up to 4 years of age were seen in gadolinium MRI exposed infants (n = 397) compared with no MRI (adjusted hazard ratio, 1.36) [13]. Stillbirths and neonatal deaths also occurred more frequently among 7 gadolinium MRI-exposed pregnancies compared to 9844 MRI unexposed pregnancies, however this could also relate to the condition necessitating the MRI in pregnancy [13,14]. The limitations of the study included using a control group who did not undergo MRI for comparison (rather than patients who underwent MRI without gadolinium) and the rarity of the outcomes [13].

Hence, given these concerns regarding gadolinium, contrast-enhanced MRI in pregnant women is only performed when considered crucial for the diagnosis [15]. MRI should be performed without gadolinium, or delayed until post-partum if clinically appropriate. In the lactating patient, MRI can then be performed with gadolinium as the water solubility of gadolinium limits the excretion into breast milk. Less than 0.04% of standard dose of gadolinium is excreted into the breast milk within the first 24 h and of this amount, the infant will absorb less than 1% from the gastrointestinal tract [9]. Hence, breastfeeding can be safely continued where applicable [16].

Recommendations for MRI in pregnancy

Data regarding gadolinium exposure in pregnancy are extremely limited but it has been associated with adverse outcomes, and as such contrast-enhanced MRI is not recommended. Although the usual MR enterography protocol includes administration of gadolinium, MR enterography can be accurately performed without gadolinium. MR enterography can assess Crohn's disease activity by incorporating a number of other parameters such as bowel wall thickness, hyperintense signal on T2-weighted images and extra-luminal complications [17].

In a small case series including nine pregnant patients with known or suspected Crohn's disease, MR enterography utilising a modified protocol without gadolinium demonstrated reliable diagnostic information and impacted clinical management [18]).

MRI without gadolinium in pregnancy is recommended to assess complications of small bowel Crohn's disease if ultrasound is not feasible

and the MRI result will inform management during pregnancy.

Abdominal and pelvic CT in pregnancy

Indications for CT in pregnancy

Cross-sectional imaging may be indicated in pregnancy to investigate for possible extra-intestinal complications of Crohn's disease. MRI without gadolinium or intestinal ultrasonography are preferred when available. Abdominal and pelvic CT is associated with significant ionizing radiation and therefore should only be performed when the possible risk of misdiagnosis is greater than the potential risks associated with radiation exposure, such as suspected intra-abdominal sepsis.

Foetal and maternal risks of CT in pregnancy

The potential effects of ionizing radiation exposure for the foetus include an increased risk of malformations, neurodevelopmental abnormalities and carcinogenesis.

The risk of malformations, developmental abnormalities or growth restriction is dependent on the timing and dose of the ionizing radiation exposure (Table 1) [11,19]. The foetus is most susceptible during the period of major organogenesis and early foetal development (2–15weeks gestation). It is thought that doses above 100 mGy of radiation may induce malformations based on animal data [19]. Foetal risk of malformations, growth restriction, or abortion have not been reported with radiation exposure of less than 50 mGy [20].

Similarly, for neurodevelopmental effects the most sensitive period is 8–15 weeks gestation and in association with radiation doses of at least 100 mGy [19]. The risk for intellectual disability may be a minimum exposure of 60–310 mGy between 8 and 15 weeks of gestation [8].

Abdominal and pelvic CT scans are associated with increased ionizing radiation exposure compared with head or chest scans, however the foetal dose exposure from an abdominal and pelvic CT is significantly less than these levels. The foetal ionizing radiation doses for common procedures are approximately 0.01 mGy for a chest x-ray, 0.66 mGy for a chest CT, 3.0 mGy for abdominal x-ray, up to 35 mGy for abdominal CT and up to 50 mGy for a pelvic CT [21]. Radiation exposure from CT procedures also varies depending on the number and spacing of adjacent image sections, for example pelvic CT pelvis exposure can be reduced to approximately 13 mGy by using dose-reduction techniques if that is adequate for diagnosis [9,22]. By comparison, it is estimated that any foetus is exposed to approximately 1 mGy of background radiation throughout a normal pregnancy [8].

There is no dose threshold relating to risk of childhood cancer, for which the risk is thought to increase with increasing doses of radiation but remains low overall [21]. However, the relationship between cancer risk and low dose radiation exposure is controversial and epidemiological data is inconsistent [14]. A 10–20 mGy foetal exposure may increase the risk of leukaemia by a factor of 1.5–2.0 over a background rate of approximately 1 in 3000 [9]. Another reported excess cancer incidence following a 50 mGy dose exposure in utero is 1.1–3.0 events per 1000 exposures [22]. It is not currently recommended that children exposed to radiation from CT in utero undergo longer-term follow up.

High-dose exposure (in excess of 1000 mGy or 1Gy) during early embryogenesis is likely to be lethal to the embryo [11]. However, these dose levels are not used in diagnostic imaging. In humans, growth restriction, microcephaly, and intellectual disability are the most common adverse effects from high-dose radiation exposure, including data from atomic bomb survivors [8,9]. Termination is not required on the basis of exposure to diagnostic radiation. If multiple imaging studies using ionizing radiation have been conducted, the total dose received by the foetus should be calculated by a medical physicist to assist in risk counselling [9,11].

Contrast can be administered if required for additional diagnostic information with CT. Oral contrast agents are not absorbed by the patient and do not cause harm [9]. Intravenous iodinated contrast media can cross the placenta and either enter the foetal circulation or pass directly into the amniotic fluid [15]. However, animal studies have not reported any teratogenic effects from its use [23] nor have there been any reports of thyroid disease in infants exposed to water soluble iodinated contrast [24]. For lactating patients, only a very small percentage of iodinated contrast is excreted into the breast milk and absorbed by the infant, therefore it is considered safe to continue breast-feeding after receiving such an iodinated contrast agent [15]. There is no risk to breastmilk from external sources of ionizing radiation.

Regarding maternal risks of ionising radiation exposure, the main area of concern is regarding breast tissue in pregnant women, which relates more to CT imaging of the chest [14]. Nonetheless, the choice of abdominal imaging modality in pregnancy should ideally be in the form of non-ionizing radiation techniques, in order to limit exposure and lifetime risk overall given that patients with IBD often require multiple imaging studies over their disease course [25].

Recommendations for CT in pregnancy

Exposure to radiation through CT should be avoided in pregnancy if possible and should only be performed during pregnancy in the rare instance when the possible risk of misdiagnosis is greater than the potential risks associated with radiation exposure. For example, CT should be considered in cases of significant intra-abdominal sepsis where intestinal ultrasound and MR are not available. When a CT is justified, it can be performed with contrast if necessary and should be tailored to the lowest possible dose.

Summary

Like in our non-pregnant IBD patients, the choice of imaging modality is dependent on clinical urgency and accessibility, and overall, ultrasound and/or MRI remain the first-line imaging choice over CT due to the lack of ionising radiation exposure. Intestinal ultrasound, where available, is the imaging modality of choice and is most useful in the first and second trimesters. If ultrasound does not provide adequate images or is unavailable, MRI without gadolinium can be performed to investigate suspected severe complications of IBD where the results would affect management during pregnancy. CT should be avoided in pregnancy where possible, but should be performed in cases of suspected significant intra-abdominal sepsis when intestinal ultrasound and MRI either do not

Table 1
Suspected induced deterministic effects of radiation in utero according to conception age and estimated dose[a] (modified from Amercican College of Radiology) [11].

Conception age	<50 mGy	50–100 mGy	>100 mGy
Prior to conception	None	None	None
1st–2nd weeks	None	Probably none	Possible spontaneous abortion
3rd–8th weeks	None	Potential effects uncertain and likely too subtle to be clinically detectable	Possible malformations (increasing in likelihood with increasing dose)
9th–15th weeks	None	Potential effects uncertain and likely too subtle to be clinically detectable	Risk of reduced IQ or of mental retardation (increasing in severity and frequency with increasing dose)
16th–25th weeks	None	None	IQ deficits not detectable at diagnostic doses
>25 weeks	None	None	None applicable to diagnostic medicine

[a] Deterministic effects include gross malformations, growth retardation or developmental abnormalities; they are dose related and are only seen above a threshold dose, the higher the dose the greater the effects [11].

provide adequate images or are not readily available. Appropriate patient counselling should be provided when imaging is required in pregnancy, including discussion of any relevant maternal and foetal risks as well the consequences of not performing or delaying investigations.

Practice points

- *Intestinal ultrasound is the first line imaging investigation where readily available*
- *MRI without gadolinium can be performed during pregnancy to investigate severe complications of IBD*
- *CT should be avoided in pregnancy, except in cases of suspected significant intra-abdominal sepsis when intestinal ultrasound and MRI are inadequate or unavailable*
- *Abdominal and pelvic CT involves foetal dose exposure below the* 50 mGy *threshold and should not be withheld when indicated during pregnancy*

Research agenda

- *Ongoing studies are required to define the role of intestinal ultrasonography in pregnancy*
- *Further epidemiological data are required relating to health risks of low dose radiation exposure from prenatal CT*
- *Future data relating to gadolinium exposure with MRI* in utero *are necessary to define any potential association with foetal harm*

Declaration of competing interest

None.

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Appendix IV Book Chapter: Pregnancy and IBD

Pregnancy and IBD

17

Emma Flanagan and Sally Bell

Abstract

This chapter examines the role of biomarkers in the assessment of inflammatory bowel disease (IBD) during pregnancy. The pregnant state is unique as it requires consideration of the wellbeing of both mother and foetus. It is now established through multiple studies that active IBD can lead to adverse pregnancy outcomes. Hence, accurate monitoring of disease activity during pregnancy is imperative. However, evaluating disease activity during pregnancy is complicated as the physiological adaptations that occur during pregnancy may affect gastrointestinal symptoms and interpretation of available biomarkers. In addition, several methods of assessing IBD bring safety concerns regarding potential risks to the foetus, including endoscopy and computed tomography (CT) imaging.

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17.1 Introduction

Inflammatory bowel disease (IBD) is a chronic disease that commonly affects women in their peak childbearing years. The majority of women with IBD who are taking maintenance therapy will require medication throughout pregnancy, and most IBD medications are thought to be less harmful to pregnancy outcome than the risk of disease flare during pregnancy [1].

IBD, particularly if active, can lead to adverse pregnancy outcomes including spontaneous abortion, preterm birth and low birth weight [2–4]. Women with IBD who become pregnant when their disease is active are more likely to experience ongoing active disease during pregnancy than those who become pregnant when their disease is in remission [5].

A prospective European cohort study among pregnant women with IBD who were mostly in remission at conception showed that women with Crohn's disease (CD) had a similar disease course during pregnancy when compared to their respective age- and disease-matched non-pregnant cohorts, whereas pregnant women with ulcerative colitis (UC) had a higher risk of relapse during the first and second trimesters of their pregnancy than non-pregnant women with UC [6]. Similar data for larger cohorts of women with active disease during pregnancy have not been reported.

In light of the potential variability in disease activity during pregnancy and the known adverse

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impact of active disease on pregnancy outcomes, pre-pregnancy disease activity status should be measured, ideally to confirm established remission, but importantly to serve as a baseline from which to monitor individual disease activity throughout pregnancy. Once pregnant, monitoring of disease activity in each trimester is essential. However, evaluating disease activity during pregnancy can be challenging, as the available methods are either precluded due to possible risk to the foetus or are not validated during pregnancy [7].

Endoscopy is considered to be the gold standard for the diagnosis of IBD; however, it is not without significant risk [8]. This becomes even more meaningful during pregnancy when the wellbeing of both the patient and the developing foetus must be considered. Hence, a combination of available biomarkers including serological, faecal and radiological methods should also be used to best assess disease activity in IBD. The interpretation, utility and safety of standard markers of inflammation used in IBD are impacted by pregnancy; the evidence for this and consequent recommendations will be discussed in this chapter.

17.2 Serum Biomarkers in Pregnancy

17.2.1 Physiology of Serum Biomarkers in IBD

Serum biomarkers of inflammation such as C-reactive protein (CRP) are often used to aid in monitoring the disease course in IBD [9]. CRP is an acute phase-reactant protein that is produced by hepatocytes primarily in response to the inflammatory cytokine interleukin-6 (IL-6).

CRP has been shown to correlate with endoscopic disease activity in both CD and UC; however, there is a stronger association with histologic findings in CD [10]. It must be noted, however, that CRP is not specific to inflammation of the bowel and levels can indeed be raised in the setting of alternative inflammatory states. Moreover, when using CRP as a serologic biomarker of inflammation in IBD, it is important to consider that active IBD does not always manifest with biochemical evidence in the form of an elevated CRP [11].

17.2.2 Physiology of Serum Biomarkers During Pregnancy

The values of serum biomarkers such as CRP may be altered in healthy pregnant women compared to non-pregnant women secondary to the physiological changes that take place in pregnancy.

During normal pregnancy, there are complex shifts in maternal inflammatory responses [12, 13]. Some studies have shown increased levels of cytokines such as IL-6 in pregnancy, and likewise, CRP can be elevated slightly during normal pregnancy [14, 15]. Moreover, elevated CRP levels have also been associated with maternal obesity and obstetric complications such as pre-eclampsia and preterm labour [16–18].

Laboratory blood tests were measured during pregnancy in a study by Klajnbard et al., including 391 healthy Caucasian women with uncomplicated pregnancies [19]. Suggested reference intervals during pregnancy are reported based upon results on the 2.5–97.5 percentiles. In this study, the CRP concentrations were largely stable throughout pregnancy but were higher than the standard non-pregnant reference range; the suggested reference interval for CRP at 35–42 weeks gestation was 10–210 nmol/L (1.05–22.05 mg/L) [19].

Similarly, other serological biomarkers used to monitor IBD can be affected by physiological changes in normal pregnancy. Albumin may be low in normal pregnancy and mild anaemia is normal in the pregnant state.

In the same study by Klajnbard et al., haemoglobin (Hb) values were stable during pregnancy but were slightly lower than the standard reference range. The suggested reference interval for Hb in iron replete pregnant women at 35–42 weeks gestation was 110–147 g/L [19].

Additionally, this study demonstrated that albumin levels were lower during pregnancy than non-pregnant reference intervals and decreased slightly as pregnancy progressed, with reference intervals for albumin at 35–42 weeks gestation being 30.0–

39.8 g/L [19]. Another study measuring laboratory markers in 52 normal pregnancies showed that albumin levels can decrease further during pregnancy, with reference intervals calculated as 23.1–33.8 g/L at 34–38 weeks gestation [20].

17.2.3 Interpreting Biomarkers During Pregnancy

Serum biomarkers including CRP can be useful for monitoring IBD in the non-pregnant patient. However, particular care needs to be taken when interpreting serum biomarkers during pregnancy due to physiological adaptations, which can simultaneously affect these markers.

In addition, serum levels of biomarkers of inflammation such as CRP may be affected by other pertinent factors such as maternal body mass index or pregnancy complications. Consideration given to these limitations is necessary during pregnancy when using serum biomarkers to monitor disease activity and ideally such biomarkers should be combined with other non-invasive markers to improve accuracy.

While it is important not to rely solely on serum biomarkers during pregnancy for assessment of disease activity in IBD, blood laboratory tests are readily available. Serial measurements of Hb, albumin and CRP should be performed at preconception and throughout pregnancy and integrated with other parameters to monitor disease activity over time on an individual patient basis.

17.3 Faecal Biomarkers

17.3.1 Faecal Calprotectin

Faecal calprotectin is a protein produced by neutrophils and is a useful non-invasive faecal biomarker for monitoring disease activity in IBD. An elevated faecal calprotectin level has consistently been shown to correlate with endoscopic disease activity in IBD and can be predictive of relapse, while a normal faecal calprotectin reflects mucosal healing [21].

Data related to the use of faecal calprotectin in pregnancy are somewhat limited. A number of small studies have demonstrated that, unlike serum biomarkers such as CRP, faecal calprotectin can be useful to detect disease relapse and does not appear to be affected by physiological changes during pregnancy.

In the prospective multicentre ERA study, it was demonstrated in a subset of 46 pregnant patients with IBD that an elevated faecal calprotectin (above 250 mg/g) correlated with active disease according to the Physicians Global Assessment during pregnancy [22]. In another study including 75 pregnant patients with IBD, faecal calprotectin had an overall specificity of 80.7% for detecting disease activity, but an elevated faecal calprotectin did not accurately predict disease relapse [23].

More information is needed regarding faecal calprotectin levels in pregnancy and further studies are ongoing; however, it represents a simple, repeatable biomarker that can be followed during pregnancy and the peri-partum period.

17.3.2 Faecal Lactoferrin

Faecal lactoferrin is also a protein produced by neutrophils that has been shown to reflect endoscopic disease activity in IBD [24].

Data related to the use of faecal lactoferrin in pregnancy are very limited. Recent evidence from the MECONIUM (Exploring MEChanisms Of disease traNsmission In Utero through the Microbiome) study has shown that it may be useful in monitoring disease activity in IBD during pregnancy. These data include faecal lactoferrin concentrations during pregnancy from 76 patients with IBD and 175 controls showing that faecal lactoferrin was higher in patients with IBD than controls during each trimester of pregnancy [25].

17.3.3 Use of Faecal Inflammatory Markers in Pregnancy

Faecal calprotectin appears to be accurate in detecting relapse during pregnancy. Faecal cal-

protectin is a non-invasive biomarker that can be utilised as a monitoring tool for disease activity and can be performed preconception and then in each trimester or when there is a suspected flare in pregnant patients with IBD. It is likely that faecal lactoferrin will be similarly helpful in monitoring individual disease activity in pregnancy.

17.4 Imaging Considerations in IBD During Pregnancy

17.4.1 Indications for Imaging in IBD

Cross-sectional imaging including magnetic resonance imaging (MRI), computed tomography (CT) imaging and bowel ultrasonography may be necessary as non-invasive markers to evaluate disease activity and in particular to investigate extra-luminal complications in patients with IBD. Imaging in IBD is especially useful in Crohn's disease in order to measure small bowel disease extent and activity, as well as assess for the presence of strictures, intra-abdominal fistulae and abscesses when there is clinical suspicion. Traditionally, cross-sectional imaging is less useful in the assessment of ulcerative colitis where the disease can be accessed with colonoscopy.

Bowel ultrasonography, magnetic resonance imaging (MRI) and computed tomography (CT) have been shown to have similar diagnostic accuracy for imaging in IBD [26, 27]. The choice of imaging modality in non-pregnant patients is dependent on clinical urgency and accessibility, but MRI or ultrasound is preferred over CT for assessment of IBD due to the lack of radiation exposure.

17.4.2 Efficacy and Safety Considerations of Imaging Options in Pregnancy

17.4.2.1 Computed Tomography (CT)

Abdominal and pelvic CT is associated with significant ionising radiation and thus should only be performed during pregnancy in the rare circumstance when the possible risk of misdiagnosis is greater than the potential risks associated with radiation exposure.

The potential effects of radiation exposure on the foetus include an increased risk of malformations, neurodevelopmental abnormalities and carcinogenesis. The risk of malformations is dependent on the timing and dose of radiation exposure, with the foetus being most susceptible during the period of major organogenesis and early foetal development (2–15 weeks gestation), while it is thought that doses above 100 mGy of radiation may induce malformations based on animal data [28, 29]. Similarly, for neurodevelopmental effects the most sensitive period is 8–15 weeks gestation and associated with radiation doses of at least 100 mGy [28, 29]. The foetal dose exposure from abdominal and pelvic CT is less than this threshold. In the setting of foetal exposure to radiation from CT scanning, termination of pregnancy is not indicated; closer ultrasound monitoring is undertaken for congenital anomalies. There is no dose threshold relating to risk of childhood cancer, for which the risk increases with increasing doses of radiation but remains low overall [30]. It is not currently recommended that neonates exposed to radiation from CT in utero undergo longer-term follow-up.

17.4.2.2 Magnetic Resonance Imaging (MRI)

The safety of MR enterography in pregnancy has not been definitively established. In particular, there is uncertainty regarding the contrast medium gadolinium.

While MR imaging does not involve any radiation exposure, there have been theoretical concerns regarding the exposure to the electromagnetic fields such as potential effects on cell proliferation or foetal hearing. However, there have not been any reported adverse effects on the human foetus linked to MRI exposure, and MRI is considered safe during pregnancy [30]. Studies involving gadolinium exposure in pregnancy are extremely limited, and as such contrast-enhanced MR imaging is only recommended when considered crucial for the diagnosis [30].

Although the optimal MR enterography protocol includes administration of gadolinium, MR enterography can be accurately performed without gadolinium. Typically, MR enterography is used to assess Crohn's disease activity by incorporating a number of findings including contrast enhancement. However, other parameters are evaluated such as bowel wall thickness and hyperintense signal on T2-weighted images as well as extra-luminal complications [31].

In a small case series including nine pregnant patients with known or suspected Crohn's disease, MR enterography utilising a modified protocol without gadolinium demonstrated reliable diagnostic information and impacted clinical management [32].

17.4.2.3 Bowel Ultrasonography

In non-pregnant patients with IBD, ultrasound is increasingly being recognised as an accurate method to assess luminal disease activity of the small and large bowel as well extra-luminal complications, particularly in patients with Crohn's disease. The precise role of bowel ultrasonography for monitoring of IBD in pregnancy has not yet been substantiated; however, this is an emerging area of investigation.

Bowel ultrasonography is a non-invasive imaging modality that does not require radiation and is notionally an ideal imaging modality in pregnancy [33]. However, views of the bowel can be impeded by the foetus in late pregnancy, and thus, currently, bowel ultrasonography is thought to be useful for assessing IBD during the first two trimesters of pregnancy.

In our experience, adequate assessment of the colon and terminal ileum can generally be obtained with ultrasound up to 24 weeks gestation [34]. Beyond 24 weeks, bowel ultrasound provides good views of the left colon, but the remainder of the colon and terminal ileum can be difficult to assess with confidence [34]. In the setting of a flare of left-sided colonic IBD during pregnancy, bowel ultrasonography may be a useful, non-invasive alternative to undertaking a flexible sigmoidoscopy. In patients with Crohn's disease affecting the terminal ileum, ultrasound is a valuable imaging tool up to around 24 weeks gestation.

17.4.3 Imaging Recommendations During Pregnancy

Cross-sectional imaging may be indicated in pregnancy to investigate a suspected flare of IBD or possible extra-intestinal complications of disease. Imaging results should be used to complement other biomarkers of disease activity in pregnancy. During pregnancy, MRI without gadolinium or bowel ultrasonography are preferred if available.

17.5 Endoscopy for IBD in Pregnancy

17.5.1 Indications for Endoscopy for IBD in Pregnancy

Colonoscopy is generally considered the gold standard for assessing luminal disease activity in patients with IBD. Hence, endoscopy may be indicated if the findings will alter the management of IBD during pregnancy.

For instance, endoscopy is indicated if there is suspected severe disease activity or if after initiating therapy for a disease flare, there is ongoing clinical and biomarker evidence of disease activity.

17.5.2 Safety Considerations in Pregnancy

Potential foetal safety concerns include adverse effects of anaesthetic medications and risk of hypotension or hypoxia. However, limited data exists regarding the safety of endoscopy in pregnant women and in particular in pregnant women with IBD, and much of the published data is retrospective or case series in nature.

Procedural precautions must be observed when performing endoscopy during pregnancy

to minimise risk to the patient and foetus. This includes using the minimum dose of sedating medication possible and standard monitoring, including pulse oximetry and positioning to avoid maternal hypotension [35]. For patients in the second or third trimesters, endoscopic procedures should be performed with the patient in the left lateral position to prevent vascular compression.

On the basis of limited human data, the latest American Society for Gastrointestinal Endoscopy guidelines for endoscopy during pregnancy recommend sedation with narcotic analgesia such as low-dose fentanyl [35], and if this is inadequate, small doses of midazolam may be used [36]. If deeper sedation is required, propofol may be administered by a trained specialist in anaesthesia [36].

A recent Swedish population-based cohort study reported no increased risk of stillbirth or congenital malformation associated with any endoscopy during pregnancy, but did report an increased risk of preterm birth or small for gestational age [37]. However, although the risk of adverse pregnancy outcomes associated with endoscopy remained rare overall, this study was based on registry data and was not able to take into account indication for endoscopy or disease activity, which can affect pregnancy outcome [37].

In relation to endoscopy in pregnant patients with IBD specifically, a systematic review and small prospective cohort study by De Lima et al. concluded that lower gastrointestinal endoscopy appears to be of low risk based on the limited available data in this field [38, 39]. The prospective study, including 42 pregnant patients with IBD, demonstrated no increase in adverse outcomes for the mother or the newborn relating to endoscopy when compared to controls matched based on age, medication and disease activity [38]. In this study, 42 patients underwent 47 lower gastrointestinal endoscopies (35 sigmoidoscopies, 12 colonoscopies) during pregnancy; in 48.9% of these patients, no sedation was used, in 19.1% fentanyl only was used, in 6.4% midazolam only and midazolam was not used as sedation in the first trimester [38].

17.5.3 Recommendations

Endoscopy for IBD can be performed during pregnancy if there is a strong indication such as acute severe UC or failure to respond to escalation of therapy. If clinically indicated, endoscopy should not be delayed in pregnant patients. Whenever possible, endoscopy during pregnancy should be in the form of flexible sigmoidoscopy (for patients with distal colitis) and can be performed without sedation, rather than colonoscopy (which is generally reserved for patients in whom the terminal ileum cannot be otherwise satisfactorily assessed).

17.6 Tools Predictive for Disease Flare and Future Directions

Currently, we advocate for the utilisation of serological biomarkers during pregnancy with cautious interpretation and in combination with faecal calprotectin, which is able to detect disease relapse during pregnancy.

It is likely that faecal calprotectin may be useful not only in accurately detecting disease flare during pregnancy but also in predicting disease flare during pregnancy and the post-partum period. This has not yet been demonstrated in available studies to date.

One small study has suggested that another faecal biomarker, faecal lactoferrin, may also be useful in the future to monitor disease activity during pregnancy. We await further data regarding correlation of faecal lactoferrin with disease activity during each trimester of pregnancy.

Bowel ultrasonography is likely to be effective in detecting and predicting disease relapse in pregnancy, but there is a paucity of data relating to bowel ultrasonography in IBD during pregnancy. Practically, it is likely that views of the bowel may be obscured after week 24 of gestation. A number of studies are currently being conducted to monitor the usefulness and accuracy of bowel ultrasonography for IBD during pregnancy.

Further prospective data relating to endoscopy in IBD patients during pregnancy will help to inform the potential risk associated with endoscopic procedures in the future.

17.7 Case Studies

Case 1

A 29-year-old female presents to outpatient IBD clinic currently 18 weeks pregnant with recently diagnosed Crohn's disease of the terminal ileum

- *Background*: Diagnosed with Crohn's disease 2 months prior to pregnancy with colonoscopy demonstrating severe ulceration of the ileocaecal valve, terminal ileum unable to be intubated due to stenosis; MR enterography at diagnosis showed thickening of the terminal ileum over 15 cm with mild proximal small bowel distension. Had declined to commence a thiopurine at diagnosis due to concerns regarding medication in future pregnancy.
- *Presentation*: On review in clinic at 18 weeks gestation, reports colicky abdominal pain, bloating, occasional nausea and vomiting.
- *Assessment of disease activity performed with available biomarkers*:
  - Serum biomarkers: Hb 127 g/L, albumin 34 g/L, CRP 10 mg/L
  - Faecal calprotectin: 310ug/g
  - Intestinal ultrasound: moderately active inflammation of the terminal ileum over 10 cm with associated luminal narrowing and proximal small bowel distension of 2 cm
- *Outcome*: Active Crohn's disease treated with course of weaning prednisolone with improvement in biomarkers (repeat CRP <5 mg/L; faecal calprotectin 90 ug/g; no active inflammation of terminal ileum on intestinal ultrasound).
- *Learning point: A suite of objective, non-invasive tests including intestinal ultrasonography is useful to identify active disease in pregnancy.*

Case 2

A 25-year-old female currently 22 weeks pregnant with left-sided UC admitted to hospital with severe disease flare

- *Background*: Chronic active left-sided UC. Colonoscopy 4 months prior to (unplanned) pregnancy showed moderate colitis to descending colon. Maintenance therapy 5 mg/kg infliximab 8-weekly and maximal dose of 5-ASA, previously intolerant to thiopurine. Had trialed 1 week of high-dose oral prednisolone prior to admission without resolution of colitis symptoms.
- *Presentation*: On admission reports increased bowel frequency up to 10 bowel actions daily with blood, associated urgency.
- *Assessment of disease activity performed with available biomarkers*:
  - Serum biomarkers: Hb 87 g/L, albumin 24 g/L, CRP 28 mg/L
  - Faecal calprotectin: 2700ug/g (culture negative)
  - Flexible sigmoidoscopy performed: Mayo 2 colitis to descending colon (CMV negative)
- *Outcome*: Obstetric ultrasound as inpatient showed normal foetal appearance. Active colitis treated with IV hydrocortisone and additional dose of 10 mg/kg infliximab then weaning course of prednisolone and infliximab increased to 10 mg/kg dose 6-weekly.
- *Learning point: Flexible sigmoidoscopy is indicated during pregnancy in cases where there is clinical or biomarker evidence of severe disease activity that has not responded to escalation of therapy in order to perform direct evaluation of mucosal inflammation and exclude CMV infection.*

Case 3

A 34-year-old female with pan-UC reviewed regularly in outpatient IBD clinic during pregnancy

- *Background*: Diagnosed age 14 with pan-colitis on colonoscopy, treated initially with oral steroids then remained in remission on maintenance dose 5-ASA therapy.
- *Preconception disease assessment*:
  - Serum biomarkers normal (CRP <5 mg/L)
  - Faecal calprotectin normal (<50ug/g)
  - Colonoscopy: no active inflammation
- *Trimester 1 review in IBD clinic* – remains clinically well:
  - 11 weeks pregnant, no symptoms of colitis
  - Serum biomarkers: normal (CRP <5 mg/L)
  - Faecal calprotectin: 193ug/g
  - 5-ASA increased to maximal dose due to calprotectin result, which was elevated compared to patient's previous level
- *Trimester 2 review in IBD clinic* – moderate flare of colitis:
  - 23 weeks pregnant, increased frequency with up to 8 bowel actions daily with blood, associated urgency
  - Serum biomarkers: Hb 129, albumin 29 g/L, CRP 12 mg/L
  - Faecal calprotectin: 458ug/g (culture negative)
  - Intestinal ultrasound performed: moderately active colitis from sigmoid to mid-transverse colon
  - Disease flare managed with addition of weaning course of oral steroids and topical 5-ASA/steroid therapy with clinical improvement
- *Trimester 3 review in IBD clinic* – improved:
  - 31 weeks pregnant, no symptoms of colitis
  - Serum biomarkers: Hb 124, albumin 29 g/L, CRP 10 mg/L
  - Faecal calprotectin: 221ug/g
  - Intestinal ultrasound performed: adequate views of left colon from proximal sigmoid with no active colitis seen
  - Maximal dose 5-ASA oral and topical therapy continued throughout pregnancy
- *Normal vaginal delivery at term*, healthy baby; reviewed concurrently in high-risk obstetric clinic due to active disease.
- *Planned for review at 6 weeks post-partum* with repeat biomarkers.
- *Learning point: Preconception disease activity status should be measured with a combination of available biomarkers to confirm established remission and to serve as a baseline from which to monitor individual disease activity in each trimester of pregnancy and post-partum.*

17.8 Therapeutic Drug Monitoring in Pregnancy and Exposed Infants

Infliximab and adalimumab are immunoglobulin G1 (IgG1) anti-TNF monoclonal antibodies, which are used both to induce and maintain remission in IBD. Available data has shown that IBD patients exposed to anti-TNF therapy during pregnancy do not have increased rates of adverse pregnancy outcomes [40–42]. Infliximab and adalimumab are transferred across the placenta in the second and third trimesters of pregnancy [43].

Our group has shown in the ERA study, which measured drug levels in infants following intrauterine exposure to anti-TNF medications, that infant drug levels at birth were inversely related to the time from last intrapartum dose of anti-TNF therapy [44]. Clearance

occurred by 6 months in all adalimumab-exposed neonates and by 12 months in infliximab-exposed babies [44]. The presence of anti-TNF antibodies may allow replication of live vaccines, with a death from disseminated BCG reported in an infliximab-exposed infant [45]. Hence, infants exposed to anti-TNF medications in utero should not be administered any live vaccinations until 12 months of age. Routine therapeutic drug monitoring at birth in exposed infants is not currently indicated as a predictive biomarker to assess the timing of live vaccinations as the most important live vaccinations are not administered until 12 months in most countries (such as the vaccine against measles, mumps and rubella). Similarly, breastfeeding is considered safe with anti-TNF agents, and while very low levels of anti-TNF medication may be detected in the breast milk, this does not alter neonatal levels. Therefore, monitoring of levels in breast milk or infants is not required.

17.9 Summary

Due to the increased risk of adverse pregnancy outcomes associated with active IBD, safe and reliable biomarkers are necessary in order to accurately guide management and ensure optimal pregnancy outcomes. During pregnancy, there is no single ideal biomarker for both detecting and predicting disease activity, and thus we need to use a number of tools and interpret blood biomarker results in the context of the normal ranges for each trimester of pregnancy in IBD (Table 17.1).

Effective monitoring of IBD during pregnancy should integrate all available non-invasive biomarkers of disease activity, and this includes establishment of disease activity preconception using the same tools so that serial measurement during pregnancy is meaningful. Pregnant patients with IBD should undergo assessment of serological biomarkers (CRP, Hb, albumin) and faecal calprotectin at least once per trimester and more regularly if they have active disease during pregnancy. If imaging is required, this should ideally be in the form of bowel ultrasonography or MR enterography without gadolinium. Exposure to radiation through CT should be avoided if possible but could be considered in cases of significant intra-abdominal sepsis where bowel ultrasound and MR are not available, as an alternative to surgery. Endoscopy should only be performed if clinically necessary such as acute severe UC and is generally considered safe in pregnancy with appropriate monitoring and precautions regarding patient positioning and minimal anaesthetic.

Table 17.1 Summary of available biomarkers for IBD in pregnancy

Biomarker	Considerations and recommendations
Serum inflammatory markers	Values altered in normal pregnancy; interpret with caution
Faecal calprotectin	Limited data; helpful to detect relapse
Radiographic imaging	Radiation risk with CT; avoid if possible Limited data regarding gadolinium; MRI without contrast recommended Bowel ultrasound safe; views restricted in late pregnancy
Endoscopy	Limited safety data in pregnancy; perform if strong indication

Summary Points

- IBD commonly affects women in their peak childbearing years.
- Active IBD can lead to adverse pregnancy outcomes.
- Assessing disease activity during pregnancy is challenging as available methods may present potential risks to the foetus or are not substantiated during pregnancy.
- Serum biomarkers such as CRP are affected by normal physiological adaptations during pregnancy.
- Faecal biomarkers including calprotectin are useful for detecting disease relapse in pregnancy but data are limited.

- There are foetal safety concerns regarding the use of both CT and MRI in pregnancy due to radiation exposure associated with CT and the contrast medium gadolinium used in the standard small bowel MRI protocol.
- Bowel ultrasonography is safe in pregnancy; however, views of the bowel can be impeded by the foetus in late pregnancy.
- Safety data concerning endoscopy for IBD during pregnancy are limited.

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Appendix V Medical Journal of Australia Review Article: Updates in the management of inflammatory bowel disease in pregnancy

Updates in the management of inflammatory bowel disease during pregnancy

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Summary

- The best pregnancy outcomes for women with inflammatory bowel disease (IBD) occur when their disease is in remission at conception and remains in remission throughout pregnancy.
- Active IBD can lead to adverse pregnancy outcomes, including spontaneous abortion, pre-term birth and low birthweight.
- The majority of women with IBD who are taking maintenance medication will require medication throughout the pregnancy to prevent disease relapse.
- Most IBD medications are considered safe in pregnancy and breastfeeding, except for methotrexate.
- Pre-conception counselling should be arranged with the patient's IBD specialist and should include discussions regarding the importance of optimising disease control before and during pregnancy as well as the medication management plan for pregnancy.
- Patients with IBD should be reassured that their fertility is normal when the disease is quiescent, with the exception of women who have had pelvic surgery.
- IBD activity should be carefully monitored during pregnancy using non-invasive techniques, and disease flares during pregnancy should be treated promptly with escalation of therapy in consultation with the patient's IBD specialist.
- Mode of delivery should be determined by obstetric need; however, caesarean delivery is preferred for women with a history of ileal pouch anal anastomosis surgery or active perianal Crohn's disease.

Inflammatory bowel disease (IBD) is a chronic disease that affects women in their childbearing years. It is known that the best pregnancy outcomes for women with IBD occur when their disease is in remission at conception and remains in remission throughout the pregnancy. The majority of women with IBD who are taking maintenance medication will require medication throughout the pregnancy to prevent relapse. Most IBD medications are thought to be safe in pregnancy, with disease flare during pregnancy being the major risk to the developing child.[1]

Non-compliance with maintenance therapy during pregnancy occurs frequently and a common reason for this is the fear of medication adverse effects on the baby.[2,3] While fear of adverse effects of medication on pregnancy and non-compliance are common among women with IBD, patients often have insufficient knowledge of the adverse effect of active disease on pregnancy outcomes.[4] Likewise, medical practitioners may have inadequate pregnancy-related knowledge in IBD, including use of IBD medications.[5] Patients with IBD require tailored education and pre-conception counselling regarding the impact of disease activity on pregnancy and potential risks and benefits of medication use in pregnancy.

In this Narrative Review, we present the current evidence-based and expert recommendations regarding the management of IBD in pregnancy — a 2018 Australian article provided a general review of the current management of IBD.[6]

Methods

We performed a PubMed review of original and review articles as well as specialist society guidelines (the Toronto consensus statements[7] and the European Crohn's and Colitis Organisation guidelines[8]), from the late 1970s to the present, to formulate an evidence-based overview of the topics as applied to clinical practice for the management of IBD in pregnancy.

Effect of inflammatory bowel disease on fertility

A significant proportion of Australian women with IBD have a fear of infertility and thoughts of voluntary childlessness.[9,10] However, fertility is in fact not affected in patients with quiescent IBD, with the exception of women who have had pelvic surgery.[11–13]

Patients with IBD should be reassured that their fertility is normal when the disease is quiescent. There is no evidence that IBD medications are associated with reduced fertility in females. However, in males, sulfasalazine and methotrexate can be associated with oligospermia.[14,15] Hence, sulfasalazine should be switched instead to a 5-aminosalicylic acid (5-ASA) agent and methotrexate should be stopped 3 months before conception in males. Methotrexate should be stopped 6 months before conception in females, as it is teratogenic.

Surgery to control active IBD has a greater beneficial effect on fertility than uncontrolled disease. For the minority of women who require colectomy for ulcerative colitis, open ileal pouch anal anastomosis surgery is associated with a two- to three-fold increased rate of infertility.[16] This is thought to be related to pelvic adhesions from open pouch surgery causing reduced fallopian tube motility and patency.[17] However, the newer laparoscopic pouch surgery approach is associated with lower rates of infertility.[18,19] Therefore, a minimally invasive approach for pouch surgery is preferable.

Success rates of in vitro fertilisation are similar in women after pouch surgery to women without a history of IBD and surgery.[20] Early referral to a fertility specialist should be considered for patients who have had ileal pouch anal anastomosis surgery.

Effect of inflammatory bowel disease on pregnancy

IBD, especially when active, can lead to adverse pregnancy outcomes, including spontaneous abortion, pre-term birth and low birthweight.[21–23] A meta-analysis assessing the risk of adverse pregnancy outcomes in women with IBD reported a 1.87-fold increase in the incidence of pre-term birth (< 37 weeks gestation) and, similarly, the incidence of low birthweight (< 2500 g) was over twice that of normal controls.[21]

Disease activity before conception and during pregnancy is the main driver of adverse pregnancy outcomes in patients with IBD. In a large Swedish cohort study, there was an increased risk of

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pre-term birth and low birthweight for patients with ulcerative colitis or Crohn's disease, and these risks were greater in women with disease flares during pregnancy.[24] Another Scandinavian study showed that women with ulcerative colitis had an increased risk of adverse pregnancy outcomes compared with the general population and this was associated with disease activity at pre-conception.[23]

Effect of pregnancy on inflammatory bowel disease

The effect of pregnancy on IBD remains uncertain. Disease activity at the time of conception is likely to have an impact on disease activity during pregnancy.

Historically, pregnancy was thought to be a state of immune suppression in order to tolerate the fetus and was hence thought to improve inflammatory disease. However, this notion has been challenged by more recent data demonstrating that women with IBD who become pregnant when their disease is active are more likely to experience ongoing active disease during pregnancy than those who become pregnant when their disease is in clinical remission.[25]

Disease relapse may be seen more commonly in pregnant patients with ulcerative colitis. A prospective European cohort study among pregnant women with IBD who were mostly in remission at conception showed that women with Crohn's disease had a similar disease course during pregnancy to their respective age and disease matched non-pregnant cohort, whereas pregnant women with ulcerative colitis had a higher risk of relapse during the first and second trimesters of their pregnancy than non-pregnant women with ulcerative colitis.[26]

Pre-conception counselling and disease assessment

Opportunities exist when primary care doctors are reviewing patients with IBD to establish their wishes and beliefs regarding pregnancy and to provide subsequent education and encourage specialist review for pre-conception counselling, as often patients do not initiate this discussion. Patients should be counselled to continue their IBD medication until review, with the exception of methotrexate, which must be stopped.

The chance of a successful pregnancy for patients with IBD is excellent if the pregnancy is planned and if women conceive when their disease is in remission. It is known that pre-conception counselling improves pregnancy outcomes in IBD.[27] In a recent prospective cohort study in the Netherlands, it was shown that a pre-conception care clinic for patients with IBD reduced disease relapse rates during pregnancy and risk for babies with low birthweight.[27]

Pre-conception counselling should be arranged with the patient's IBD specialist and will include discussions regarding the importance of optimising disease control before and during pregnancy as well as the medication management plan for pregnancy. The patient's specialist will perform a pre-conception IBD assessment to ensure the patient is in remission. Patients should ideally undergo pre-conception counselling and disease assessment 6 months before conception to ensure that the disease is in remission and that patients have a clear understanding of the recommendations for the management of their IBD in pregnancy.

Preparation for pregnancy should include standard health recommendations such as folate supplementation. Folate supplementation (400 µg/day) should be commenced at least one month before conception to help prevent neural tube defects; women taking sulfasalazine should start taking 2 mg folate daily, as sulfasalazine affects folate absorption, and women with a history of malabsorption (small bowel Crohn's disease) should take 5 mg folate daily.[8,28]

Patients often worry about heritability of IBD and, thus, should be informed that the chance of a child developing IBD is low if one parent is affected (3–8%), but higher with two affected parents (25–30%).[29–31]

Monitoring of inflammatory bowel disease during pregnancy

Monitoring of disease activity throughout pregnancy is imperative. Communication between primary care doctors, gastroenterologists and the obstetric team during pregnancy is essential. Patients should be reviewed at least once per trimester by their gastroenterologist and more regularly if they have active disease. Clinical assessment can be particularly unreliable in the setting of pregnancy-related symptoms; therefore, IBD activity should be monitored during pregnancy using objective, non-invasive techniques.

Serial assessment of serum markers, including haemoglobin, albumin and C-reactive protein (CRP) should be performed pre-conception and in each trimester, along with faecal calprotectin, to monitor disease activity. It is important to note that laboratory markers are altered in pregnancy. During normal pregnancy, CRP can be elevated up to about 22 mg/L, albumin can be as low as 30 g/L, and mild anaemia with a haemoglobin level of 110 g/L is normal in pregnancy.[32] An elevated faecal calprotectin above 250 µg/g correlates with active disease in pregnancy.[33] Effective monitoring of IBD during pregnancy should integrate these non-invasive biomarkers, which should be interpreted over time on an individual patient basis.

Exposure to radiation should be avoided, and imaging, when required, should be done with intestinal ultrasound or magnetic resonance imaging without gadolinium.[34] Limited endoscopy may be performed in patients with severe disease flares during pregnancy.[35]

Standard pregnancy monitoring should be undertaken with careful monitoring of fetal growth to identify early intrauterine growth restriction. Women with a history of previously severe IBD, including patients taking biological therapy, or with perianal Crohn's disease should be managed in a high risk obstetric clinic with more intensive monitoring of fetal growth during pregnancy.

Management of a flare during pregnancy

A flare of IBD during pregnancy poses a greater risk of harm to mother and baby than IBD therapies.

Flares in ulcerative colitis are characterised by increased frequency of loose stools, abdominal pain, rectal bleeding, urgency and, when severe, incontinence.[36] Patients with colonic Crohn's disease will have similar symptoms.[37] Patients with terminal ileal Crohn's disease should be asked about symptoms of subacute small bowel obstruction such as nausea, vomiting, postprandial colicky abdominal pain, weight loss or failure to gain weight appropriate to stage of pregnancy.[37] If morning sickness does not settle by the expected time in pregnancy (usually, Week 16) or is associated with pain, this should raise the suspicion of obstruction.

If a patient has a suspected flare of IBD during pregnancy, standard investigations such as faecal microscopy, faecal calprotectin, full blood examination and CRP should be performed. Patients with ulcerative colitis treated with 5-ASA drugs should be taking full dose therapy (4–4.8 g daily). Rectal 5-ASA or rectal steroid therapy can be safely used in pregnancy. Patients with moderately severe disease (more than four to six bowel movements daily or nocturnal symptoms) should start a course of prednisolone, and the gastroenterologist should be promptly notified and a review arranged. Patients with obstructive symptoms should commence steroids and a low fibre diet and they should obtain an urgent review.

Disease flares that fail to settle on steroids (prednisolone 40–50 mg daily and tapered over 6–8 weeks) may require the introduction of thiopurines (azathioprine or 6-mercaptopurine) and anti-tumour necrosis factor-α (anti-TNF-α) antibodies by the patient's gastroenterologist. These drugs are safe in pregnancy and breastfeeding (see below). Patients with active disease during pregnancy require obstetric follow-up in a high risk clinic, including additional antenatal scans to monitor for intrauterine growth restriction.

Medication safety in pregnancy and lactation

Most IBD medications are safe to continue during pregnancy and breastfeeding.[1] Stopping IBD medications before or during pregnancy may result in higher rates of spontaneous abortion, intrauterine growth restriction and prematurity due to active disease.[24] Women should be encouraged to continue their maintenance IBD medications in order to maintain disease remission.

Patients should be educated regarding the risk of birth defects in the general population, which is around 3%,[38] and informed that current evidence does not suggest an increase in birth defects from IBD medications (with the exception of methotrexate and thalidomide, which are teratogenic).

Electronic prescribing programs may show warnings when IBD medications are prescribed. These pop-up warnings are based on outdated data and do not take into consideration the negative effect of disease activity during pregnancy. The categorisation system for prescribing medications in pregnancy of the Australian Therapeutic Goods Administration, while simple and accessible, can be misleading. The alphabetical structure of the system implies that it is hierarchical. However, a "Category B" medication, for example, does not mean a medication is of lower risk than a "Category C" medication. The categories system is not able to take into account the clinical indication for the medication and the labelling is often not updated when new evidence emerges regarding the safety of medications in pregnancy. In the United States, the Food and Drug Administration is no longer using categories A, B, C, D and X in product labelling in recognition of this problem.

All patients should have an agreed IBD medication plan for the pregnancy from their gastroenterologist and this plan should be communicated to the treating team, including primary care physicians, obstetricians and midwives. Primary care physicians are encouraged to liaise with the gastroenterologist if there are any queries regarding a patient's medication plan in pregnancy in order to ensure a clear and consistent message for the patient.

5-Aminosalicylic acid drugs

Sulfasalazine and 5-aminosalicylates, including mesalasine, are considered safe in pregnancy. A meta-analysis demonstrated no significant increase in risk of congenital anomalies, spontaneous abortion, pre-term delivery or low birthweight.[39] Women taking sulfasalazine should take high dose folate supplementation (2 mg daily).[8]

Corticosteroids

Short courses of corticosteroids may be required to treat disease flares during pregnancy. Hence, in available studies regarding corticosteroid use in pregnancy, it is difficult to interpret the confounding effect of active disease. An older meta-analysis showed a small increased risk of oral cleft with first trimester corticosteroid exposure.[40] However, a recent large Danish cohort study showed no increased risk of cleft lip or palate with exposure to corticosteroids in the first trimester.[41] The data from the ongoing prospective multicentre Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry, which have been adjusted for disease activity, indicated that corticosteroids were associated with gestational diabetes and low birthweight.[42] Thus, steroids must not be an alternative to maintenance therapy for IBD during pregnancy, but should be prescribed as a weaning course when necessary to treat active disease.

Thiopurines

Thiopurines comprising 6-mercaptopurine and its pro-drug azathioprine are widely used as maintenance therapy for IBD and have been shown to be safe during pregnancy in a number of studies, including a recent meta-analysis incorporating some prospective cohort studies.[43–45] The large PIANO registry has not shown an association between thiopurine use and congenital anomalies or pregnancy complications.[45] A recent prospective study found no association between maternal thiopurine use and adverse birth outcomes or number of infections in infants out to 12 months.[46]

Anti-tumour necrosis factor-α agents: infliximab and adalimumab

Infliximab and adalimumab are anti-TNF-α monoclonal antibodies, which are used both to induce and maintain remission in IBD. Available data, including a recent meta-analysis, have shown that patients with IBD who are exposed to anti-TNF-α therapy during pregnancy do not have increased rates of adverse pregnancy outcomes or congenital anomalies.[45,47,48] These agents are transferred across the placenta in the second and third trimesters.[49] Levels in infants at birth usually exceed maternal levels and can take between 3 and 12 months to clear.[50] Therefore, infants exposed to anti-TNF-α agents in utero should not be administered live vaccinations, including rotavirus, until 12 months of age.[50] A systematic review did not reveal an increased risk of infections in the first year of life in infants exposed to anti-TNF-α agents in utero.[51] Babies exposed to both thiopurines and anti-TNF-α agents in utero have been shown to have a higher risk of childhood infections (eg, chickenpox) out to 12 months, but there is no link to serious infections or need for antibiotics.[50] There is no current evidence of harm from continuing anti-TNF-α therapy into the third trimester and in women whose disease has been recently active, anti-TNF-α agents should continue throughout pregnancy.[1,7] For women in remission, dosing may be adjusted in the third trimester to both reduce placental transfer and also minimise the break in therapy, with the last anti-TNF-α dose administered at around 32–34 weeks' gestation.

Vedolizumab

Vedolizumab is a monoclonal antibody that modulates gut lymphocyte trafficking and is increasingly used for moderate to severely active IBD.[52] Initial data relating to vedolizumab in

Drug classes and recommendations for pregnancy and breastfeeding[1,8]

Medication	Use in pregnancy	Use in breastfeeding
Sulfasalazine and 5-ASA	Low risk	Low risk
Steroids (prednisolone and budesonide)	Low risk	Low risk
Thiopurines (azathioprine and 6-mercaptopurine)	Low risk	Low risk
Anti-TNF-α antibodies		
Infliximab	Low risk	Low risk
Adalimumab	Low risk	Low risk
Ustekinumab	Limited data	Limited data
Vedolizumab	Limited data	Limited data
Methotrexate	Teratogenic (do not use)	Unsafe (excreted in breast milk; accumulates in the neonate)

5-ASA = 5-aminosalicylic acid. TNF = tumour necrosis factor. ◆

pregnancy are very limited; no new concerns for pregnancy outcomes have been identified; however, the evidence is restricted by follow-up and sample size.[52] Current use of vedolizumab in pregnancy is limited to women with no other therapeutic options and is undertaken on a case by case basis.

Ustekinumab

Ustekinumab is a monoclonal antibody that is commonly used in psoriasis and has recently been approved for use in moderate to severely active Crohn's disease.[53] Data relating to ustekinumab in pregnancy for patients with IBD are extremely limited. The use of this agent in pregnancy is not currently recommended.

Mode of delivery

There are insufficient long term data regarding the impact of vaginal delivery compared with caesarean delivery on long term continence in women with IBD. The majority of women with IBD can have a vaginal delivery and the mode of delivery should be determined by obstetric need.[7,8] However, caesarean delivery is preferred for women with a history of ileal pouch anal anastomosis surgery or active perianal Crohn's disease in order to reduce the risk of anal sphincter and perianal injury, respectively.[7,8] A recent systematic review reported no significantly increased risk of developing perianal Crohn's disease with vaginal delivery compared with caesarean delivery in patients who did not have a history of perianal Crohn's disease.[54]

Breastfeeding

Breastfeeding should be encouraged in all patients, given the known beneficial effects for mother and child. It is considered safe with most IBD medications (Box), including prednisolone, 5-ASAs, thiopurines and anti-TNF-α medications. Low levels of these medications may be found in breast milk, but this is not thought to be clinically significant.[8]

Post partum management of inflammatory bowel disease

Patients should be closely monitored for a flare in the post partum period, especially in patients with ulcerative colitis when there is an increased risk of disease flare post partum.[26] In the prospective European cohort study that compared pregnant and non-pregnant women with IBD, only 60% of women with ulcerative colitis maintained remission during the 6 months after pregnancy compared with 81% of controls.[26]

Conclusion

The peak incidence of IBD overlaps with the prime childbearing years; thus, the issue of medication use and disease control in pregnancy is of particular relevance for both patient wellbeing and all treating physicians.

The most important factor in optimising pregnancy outcomes for women with IBD is to ensure their disease is in remission before and during pregnancy. Patients should be encouraged to continue their IBD medications in order to maintain disease remission. Patients with IBD require clinician-initiated preconception counselling and a consistent message regarding these factors. It is recommended that patients are reviewed regularly by their gastroenterologist during pregnancy and assessment of disease activity is performed in the form of objective, non-invasive markers, such as faecal calprotectin. In the event of a disease flare during pregnancy, the patient's gastroenterologist should be contacted promptly and appropriate escalation of therapy should be arranged.

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Appendix VI Gastroenterologist Fact Sheet: Pregnancy Fertility and Inflammatory Bowel Disease

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GASTROENTEROLOGIST FACT SHEET

Pregnancy, Fertility and Inflammatory Bowel Disease

- Inflammatory bowel disease (IBD) affects patients in their peak reproductive years
- Active IBD increases the risk of adverse pregnancy outcomes, including spontaneous abortion, intrauterine growth restriction and preterm birth
- Patients should be counselled about the importance of controlling disease with medication both before conception and during pregnancy
- Most IBD medications are safe during pregnancy and breastfeeding
- Early preconception counselling has been shown to improve pregnancy outcomes

Ideally, all women of childbearing age should discuss pregnancy plans with their general practitioner, gastroenterologist and any treating obstetrician and gynaecologist from the time of IBD diagnosis. In these discussions, practitioners should inform patients that pregnancy outcomes are very good when IBD is in remission and that active disease increases the risk to the baby. Establishing and documenting disease remission before conception and determining who is in the obstetric care team is important. Most IBD medications are low risk during pregnancy and breastfeeding, and their use should be continued.

Preconception clinical and objective assessment

Ideally 3 to 6 months before conception, patients with IBD should attend for preconception counselling to confirm disease remission, receive pregnancy-related education and establish a pregnancy treatment plan that is also communicated to the patient's general practitioner and obstetrician.

Previous medical, surgical and obstetric history should be discussed, and clinical disease activity assessed. Objective assessment should be performed to confirm remission, including endoscopy and/or imaging, where relevant, and measurement of inflammatory markers, including C-reactive protein (CRP), nutritional markers (iron, vitamin B_{12}, red blood cell [RBC] folate, haemoglobin and albumin) and faecal calprotectin. Thiopurine metabolite concentrations should be measured, where available, and thiopurine dose optimised. It is strongly recommended that women achieve sustained remission, as confirmed by faecal calprotectin level or endoscopy, for at least 3 to 6 months before conception to maximise chances of a successful pregnancy.

The risk of adverse pregnancy outcomes associated with active disease should be discussed, and a recommendation to delay conception should be considered for patients with active disease, depending on the woman's age and situation.

General preconception health considerations should be addressed, including folate supplementation at least 1 month before conception, and ensuring patients have had their immunity to measles, mumps and rubella (MMR) checked.

Patients often worry about heritability of IBD and should be informed that the chance of a child developing IBD is about 5–8% when there is one affected parent and about 35% when there are two affected parents.

Table 1: Preconception checklist: 3–6 months before conception

Discontinue teratogenic medications (e.g. methotrexate)
Screen for substance use and advise cessation (e.g. smoking, alcohol)
Ensure folate supplementation (500 mcg daily or 2 mg daily if taking sulfasalazine; 5 mg folate daily if extensive small bowel Crohn's disease)
Update status of immunisation to MMR
Establish remission (endoscopy, faecal calprotectin level, imaging)
Blood tests, including full blood examination, vitamin B_{12}, RBC folate, iron studies and vitamin D
Cease allopurinol and optimise thiopurine metabolites
Record baseline weight
Plan pregnancy IBD medication(s)
Detailed letter to GP +/- obstetrician

Effect of IBD on fertility

Fear of infertility is common among patients with IBD. However, women with quiescent IBD generally have normal fertility, with the exception of women with very active Crohn's disease or past ileoanal pouch surgery. Ileoanal pouch surgery is associated with a 2–3 times increased risk of infertility, but this is lower with the newer laparoscopic-assisted approach. In vitro fertilisation results in women with IBD, including those who have had ileoanal pouch surgery, are similar to results seen in women without IBD. IBD does not affect fertility in men, but some medications, including sulfasalazine and methotrexate, may cause reduced sperm count. If women are unable to conceive after 6 months, assistance should be sought from a fertility specialist.

Effect of IBD on pregnancy

The chances of a successful pregnancy and a healthy baby are excellent if IBD is in remission at the time of conception and during pregnancy.

For women with active IBD, rates of adverse pregnancy outcomes, including spontaneous abortion, intrauterine growth retardation, preterm birth and low birth weight, are slightly higher than in the general population. Active disease at conception is strongly associated with disease relapse during pregnancy. Cessation of IBD treatment is associated with a high rate of disease relapse.

Monitoring during pregnancy

Patients should undergo regular clinical assessment of their IBD during pregnancy, with concurrent obstetric care. Patients should be reviewed at least once per trimester and more regularly if they have active disease. Clinical and laboratory markers are altered in pregnancy; albumin level is low and CRP level may be mildly elevated in normal pregnancy. Monitoring of faecal calprotectin level is helpful to detect relapse. Exposure to radiation should be avoided, and imaging, when required, should ideally be done using intestinal ultrasound or magnetic resonance enterography without gadolinium.

A small increased risk of preterm delivery after endoscopy has been shown in women with IBD, but this risk is not seen in women without IBD, suggesting that the risk is related to active disease rather than endoscopy (Ludvigsson et al, Gastroenterology 2017). Endoscopy can be performed if clinically necessary (e.g. flexible sigmoidoscopy in patients with severe acute ulcerative colitis) and with monitoring of the patient's blood pressure and oxygen saturation throughout the procedure, use of the minimum dose of sedating medication and left pelvic tilt position to avoid vena cava compression.

Management of a flare during pregnancy

In patients with a flare of IBD during pregnancy, appropriate treatment should be initiated without delay. Medication choices are similar to those for non-pregnant patients (see Table 2). A course of steroids may be prescribed when necessary to treat active disease, but steroids should not be used as maintenance therapy. Thiopurines and anti-tumour necrosis factor (TNF) therapy can be initiated or recommenced during pregnancy, including in the third trimester (Julsgaard et al, Gastroenterology 2016). Time to onset of action for thiopurines is 3–6 months, meaning a covering course of steroids is often required, whereas response to anti-TNF therapy is usually rapid. Patients who are naïve to thiopurines should be counselled about standard adverse events at initiation (10% discontinuation rate) and the need for blood monitoring. Thiopurine methyltransferase testing should be performed before commencing thiopurines.

Surgery is rarely performed during pregnancy due to the risk of precipitating spontaneous abortion or preterm labour. Non-IBD abdominal surgery (e.g. cholecystectomy, appendicectomy) carries a risk of preterm labour of about 1.8% for open surgery and 0.4% for laparoscopic surgery (Shigemi et al, J Minim Invasive Gynecol 2018). Evidence of outcomes of surgery for IBD complications is limited to case reports suggesting that laparoscopic ileal resection and right hemicolectomy are relatively safe, but that a need for colectomy is associated with preterm labour. Alternatives to surgery, such as ultrasound-guided abscess drainage, should be considered if clinically appropriate.

Standard venous thromboembolism prophylaxis with low molecular weight heparin should be administered to pregnant IBD patients requiring hospital admission. If the patient has evidence of active disease or a history of complex IBD, high-risk obstetric monitoring is recommended, including management in a high-risk antenatal clinic and additional ultrasounds in the third trimester to assess fetal growth.

Medication safety during pregnancy and lactation

Most IBD medications are considered low risk to the baby. Patients should be educated about the risk of birth defects in babies of healthy women (3–4%) and informed that current evidence does not suggest an increase in birth defects from use of IBD medications (with the exceptions of methotrexate, allopurinol and thalidomide). It is important to communicate with the patient's GP and obstetric team regarding the IBD treatment plan. Please refer to Table 2: IBD Medication Safety during Pregnancy and Lactation.

Mode of delivery

The mode of delivery is primarily guided by the obstetrician. Most women with IBD can have a vaginal delivery. The only IBD-specific indications for caesarean section are a history of active perianal disease, anal stenosis, significant prior sphincter damage or an ileoanal pouch.

Postpartum management

There is an increased risk of disease flare after childbirth in women with ulcerative colitis or colonic Crohn's disease. Patients should be closely monitored, including measurement of faecal calprotectin level at delivery and six weeks postpartum. If anti-TNF agents or other IBD medications have been stopped, they should be restarted as soon as possible after the birth.

Mothers should be told to seek medical advice if babies are unwell (particularly if exposed to combination immunosuppressive and anti-TNF therapy). All standard vaccinations should be given to the baby, except for babies exposed to anti-TNF therapy, in whom rotavirus and live travel vaccines should be avoided. Catch-up vaccination is not required, as the risk of significant consequences following rotavirus infection reduces with age.

Breastfeeding

Breastfeeding should be encouraged. IBD drugs, including 5-aminosalicylic acids, thiopurines and anti-TNF medications, are considered safe while breastfeeding. Low levels of IBD medications may be found in breast milk, but this is not thought to be clinically significant. Please refer to Table 2: IBD Medication Safety during Pregnancy and Lactation.

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Table 2: IBD Medication Safety during Pregnancy and Lactation

Medication	Use in pregnancy	Use in breastfeeding	Comments
Sulfasalazine (SSZ) and 5-ASA	Safe	Safe	2 mg/day folate required with SSZ.
Corticosteroids (prednisolone and budesonide)	Safe	Safe	Increased maternal risks of gestational diabetes, hypertension and pre-eclampsia.
Thiopurines (azathioprine and 6-mercaptopurine)	Safe	Safe	Potential concerns about neonatal anaemia not confirmed with recent studies.
Allopurinol	Safety uncertain	Safe	Consider original indication and current disease activity. Alternatives include split dosing to reduce shunting, or reduced-dose thiopurine monotherapy if on biologics.
Anti-TNF antibodies (infliximab [IFX], adalimumab [ADA] and golimumab)	Safe	Safe	No safety reason to cease early. Continued therapy recommended due to risk of relapse and small risk of failure to recapture response. Women in deep remission may elect to stop at 32 weeks (IFX) or 36 weeks (ADA). No live vaccinations for infant until 12 months of age.
Combination thiopurine–anti-TNF therapy	Safe	Safe	Increase in neonatal childhood infections (e.g. chickenpox).
Vedolizumab	Limited data but likely to be safe	Limited data but likely to be safe	Use only in patients with no alternatives.
Ustekinumab	Limited data but likely to be safe	Limited data but likely to be safe	Use only in patients with no alternatives.
Metronidazole	Safe in short course	Safe – may cause diarrhoea in infant	Safe in meta-analysis. Use in short course. Alternative: amoxycillin–clavulanic acid (Augmentin Duo Forte).
Ciprofloxacin	Safe in short course	Safe – may cause diarrhoea in infant	Safe in meta-analysis. Use in short course.
Ciprofloxacin	Safe in short course	Safe – may cause diarrhoea in infant	Safe in meta-analysis. Use in short course.
Tacrolimus	Limited data from transplant registries but appears safe	Avoid – baby may have therapeutic levels that may lower seizure threshold	Monitor carefully for hypertension.
Cyclosporine	Limited data from transplant registries but appears safe	Avoid – baby may have therapeutic levels that may lower seizure threshold	Monitor carefully for hypertension.
Methotrexate	Teratogen Do not use	Unsafe – excreted in breast milk and accumulates in neonate	Cease 6 months before pregnancy ideally, but minimum of one ovulatory cycle.

Appendix VII Letter: vedolizumab drug concentrations in neonates following intrauterine exposure

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Letter: vedolizumab drug concentrations in neonates following intrauterine exposure

Dear Editors,

We read with interest the study by Mahadevan et al regarding the initial experiences of vedolizumab in pregnancy and the subsequent letter by Julsgaard et al documenting vedolizumab levels in two mother-baby pairs at delivery.[1,2] There remains a paucity of data regarding infant vedolizumab levels and no data regarding time to clearance. We present a case series of five patients with IBD who were treated with vedolizumab during pregnancy and report the maternal vedolizumab levels at delivery, along with corresponding neonatal outcomes including vedolizumab levels. The current study is the first report of time to clearance in infants following intrauterine exposure.

Five women with IBD aged 24-40 years became intentionally pregnant on stable maintenance vedolizumab therapy 300 mg intravenously every 8 weeks following appropriate pre-conception counselling. Four women had failed and/or been intolerant to at least one anti-tumour necrosis factor (TNF) drug, while Patient 4 commenced vedolizumab after ceasing tofacitinib (clinical trial). Three patients remained in remission during pregnancy. Patient 1 elected to stop vedolizumab at 24 weeks as she had been in sustained remission, while Patients 2 and 3 received their last intrapartum doses at 32 weeks and 30 weeks respectively. Patient 4 had planned to cease at 26 weeks, but, due to a mild flare in the third trimester (Mayo 1 disease on flexible sigmoidoscopy) and history of intolerance to steroids, vedolizumab was given at 35 weeks. Patient 5 experienced active disease during pregnancy and had her last dose of vedolizumab at 30 weeks. All five patients delivered healthy babies at term (38-39 weeks) with normal birthweight and normal Apgar scores (Table 1). One infant had hip dysplasia, which resolved; all five infants were otherwise well up to 6 weeks of age.

At the time of delivery, blood samples were taken from the mother and from the umbilical cord to measure vedolizumab concentrations by ELISA (Theradiag LISA TRACKER Duo Vedolizumab, LTV005, Marne La Vallee, France) according to manufacturer's instructions. Infant vedolizumab levels were repeated between 6 and 8 weeks, and at approximately 3 months.

Given that vedolizumab is an IgG1 therapeutic antibody, placental transfer is expected to begin in the second trimester and increase throughout pregnancy.[3] Our data show that neonatal levels of vedolizumab are lower than maternal levels at delivery unlike anti-TNF (Table 1). Similar results have been reported in the recent case series by Julsgaard et al and in seven mother-baby pairs from the PIANO registry data.[2,4] There was a negative correlation between days since last intrapartum dose and infant level at delivery (R^2=0.62). The vedolizumab levels were undetectable by 6-8 weeks in two infants, and by 15 weeks in one baby (Table 1). In the remaining two babies, further testing was declined.

These results indicate that both placental transfer of vedolizumab and infant time to clearance, respectively, may potentially be less than those documented with anti-TNF monoclonal antibodies. Vedolizumab levels in a larger number of exposed infants are required to more accurately predict clearance. Ongoing case study and registry data remain important to inform appropriate utilisation of vedolizumab in pregnancy.

STATEMENT OF ETHICS

All participants gave written informed consent prior to their inclusion in the study and each participant consented on behalf of their child. Ethics approval was granted through the St Vincent's Hospital Melbourne Ethics Committee (reference number 094/17).

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TABLE 1 Mother-baby characteristics and vedolizumab drug levels

	Patient and infant 1	Patient and infant 2	Patient and infant 3	Patient and infant 4	Patient and infant 5
Maternal characteristics					
Age at start of pregnancy (y)	32	33	24	40	33
Disease type	UC	UC	CD	UC	CD
Montreal classification	Left sided, E2	Left sided, E2	Stricturing ileal, perianal A2, L1, B2, p	Pan-colitis, E3	Colonic, perianal A2, L2, B1, p
Previous intra-abdominal surgery	None	None	Ileocolic resection	None	None
Disease duration (y)	15	10	3	20	14
Medications prior to vedolizumab	Infliximab	Infliximab	Infliximab Adalimumab	Azathioprine Methotrexate Golimumab Tofacitinib	Azathioprine Infliximab
Concomitant medications	MP 5-ASA	MP	Nil	5-ASA	5-ASA
Duration of vedolizumab therapy (at delivery, y)	2.2	1.4	1.7	1.3	2.3
Pregnancy and neonatal outcomes					
IBD state in pregnancy	Remission	Remission	Remission	Activity	Activity
Pregnancy complications	None	None	None	None	None
Gestational age at delivery (weeks)	38	38	38	39	38
Delivery mode	Normal	Elective CS	Elective CS	Emergency CS	Elective CS
Infant sex	M	F	F	M	M
Neonatal birth weight (g)	2900	3750	3547	3450	3350
Neonatal Apgar scores at 1 and 5 min	9,9	9,9	9,9	9,9	9,9
Breastfeeding	Y	Y	Y	Y	Y
Neonatal complications	None	Hip dysplasia	None	None	None
Days since last intra-partum dose	98	47	55	25	62
Maternal and neonatal vedolizumab levels (μg/mL)					
Maternal at delivery	2.50	11.40	9.90	14.40	1.10
Infant at delivery	2.10	4.90	5.90	8.70	1.00
Infant:maternal ratio	0.84	0.43	0.60	0.60	0.91
Infant at 6-8 weeks	0.20	0.70	0.86	0.00	0.00
Infant at 15 weeks	0.00	NA	NA	—	—

CD, Crohn's disease; UC, ulcerative colitis; MP, mercaptopurine; 5-ASA, 5-aminosalicyclic acid; CS, caesarean section; NA, not available, further testing declined.

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LINKED CONTENT

This article is linked to Mahadevan et al and Julsgaard et al papers. To view these articles visit https://doi.org/10.1111/apt.13960 and https://doi.org/10.1111/apt.14837.

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Letter: the effect of sirolimus on recurrence and survival in liver transplant recipients with hepatocellular carcinoma

EDITORS,

As hepatocellular carcinoma (HCC) increases as an indication for liver transplantation, and as some centres push to include patients with more advanced tumours, it is crucial that we have a good understanding of strategies used to mitigate the risk of recurrence.

We therefore read with interest the systematic review and meta-analysis by Menon et al,[1] which investigated the effect of sirolimus vs calcineurin inhibitor-based immunosuppression on tumour recurrence and survival in patients undergoing liver transplantation for HCC.

Although this was published in 2012, it continues to be influential and relevant, and has been cited 11 times since the beginning of 2017, including in the most recent International Liver Transplantation Society consensus statement.[2] Unfortunately, their review contains data extraction and methodological errors, which we believe compromise the reliability of the results. These are listed below:

Data extraction:

1. In their table, Menon et al correctly reported the total recurrence in Zimmerman et al[3] as 3/45 (6.7%) and 9/52 (17.3%) in the sirolimus and calcineurin inhibitor-based groups, respectively. However, in their pooled meta-analysis, these values inexplicably change to 7/45 (16%) and 15/52 (29%).
2. Recurrence-related mortality with sirolimus was recorded from Zimmerman et al[3] as 4/45, even though the number with tumour recurrence was extracted as 3/45. These figures were incongruent.
3. Overall mortality from Chinnakotla et al[4] was reported as 12% (15/121) and 32% (34/106) with sirolimus and calcineurin inhibitor immunosuppression. The correct values in the primary study were 16% (19/121) and 50% (53/106), respectively.
4. One-, 3- and 5-year recurrence-free survival from Chinnakotla et al[4] were extracted as 94%, 85% and 80%, respectively, which was identical to the figures they state for overall survival. This is illogical, and in fact, in the primary study and its appendix, there is no mention of recurrence-free survival data.

Methodological errors:

1. The authors inappropriately switched to the less conservative fixed effect model if I^2 was below 50%. This practice is strongly discouraged, as the decision about which model to use should be based on an understanding of the primary studies, and not the outcome of heterogeneity statistics.[5] As the maximum amount of pooled studies was three, this test will be notably under-powered. Since there were clear differences in tumour characteristics and immunosuppression protocols, the random-effects model would have been more suitable.
2. Regardless, there is an error in their heterogeneity statistics for the meta-analysis of recurrence-related mortality. Menon et al calculated I^2 = 0%. Visual inspection of the forest plot suggests that this was incorrect. Using the same data, we re-calculated I^2 as 67%, which under their methods, indicates that a random-effects model should have been used. It appears Menon et al inadvertently copied the same heterogeneity statistics from the overall mortality meta-analysis, which were identical. When we re-performed the recurrence-related mortality pooled analysis using a random-effects model, the summary effect no longer reached significance.

Peer review of meta-analyses poses some difficulties for journals because reviewers do not have the resources to check all the input data for themselves. In fact, a meta-analysis on the same topic published this year also contains extensive extraction mistakes that compromise the results.[6] However, it is encouraging that *AP&T* has led

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