Exploring the “Gap” Between Patient and Physician Perspectives in Inflammatory Bowel Disease

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SUMMARY

While physicians diagnose and manage “disease”, patients experience “illness”. It is intuitive that a “gap” exists between the patient and physician perspectives in relation to chronic diseases such as Inflammatory Bowel Disease (IBD). Indirect evidence for such a “gap” exists in the high frequency of health behaviours which deviate from physician recommendation, such as medication non-adherence and non-participation in colonoscopic cancer surveillance. This thesis reports on six studies published in the peer-reviewed literature investigating whether a “gap” exists between patient and physician knowledge and beliefs in areas of IBD that require patient health decisions.

The first two studies demonstrated a large and clinically significant gap, highlighting important misperceptions regarding the risk of infertility and the use of IBD medication during pregnancy. This novel work is likely to explain both the phenomenon of voluntary childlessness previously reported in IBD, as well as medication non-adherence during pregnancy. A further study demonstrated the dramatically positive effect of patient education on reproductive knowledge in IBD, suggesting that the gap can be modified with intervention.

This work has influenced international guidelines (European Crohn’s and Colitis Organisation and Toronto) regarding the management of IBD during pregnancy, particularly in relation to preconception counselling. In addition, it has prompted the development of both Australian national guidelines for physicians managing IBD in pregnancy and a patient information booklet regarding reproduction and IBD with state-wide endorsement across South Australia.

The fourth study investigated views regarding Colorectal Cancer in IBD, and also demonstrated a substantial “gap”. Individuals with IBD vastly overestimated both their cancer risk, and the ability of colonoscopic screening to mitigate this risk. This may have implications for participation in colonoscopic surveillance programs in individuals with IBD.

Studies 5 and 6 addressed attitudes towards conventional medication and Complementary and Alternative Medicine (CAM) in IBD. Two distinct types of medication non-adherence were identified; that of medication dose omission, which is well described, and "covert dose reduction", a lesser known phenomenon whereby patients deliberately dose reduce their IBD medication without their physician's knowledge. This distinction was important as contrasting patient beliefs were found to underlie the two types of non-adherence.

Study 6 provided further evidence for the "gap" in documenting high rates of Complementary and Alternative Medicine use (CAM) amongst individuals with IBD. This study provided an insight into the "hidden" influences on the "gap", such as the opinions of family and friends, as well as highlighting the importance of clear patient-physician communication.

Overall this body of work confirms the existence of a "gap" between patient and physician knowledge and beliefs across diverse areas in IBD. Patient misperceptions are frequent, although they vary in clinical significance. This thesis informs clinical practice in raising awareness of this "gap" and highlights the need for patient education as a highly effective strategy to empower patients and to optimise the patient-physician relationship.

DECLARATION

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Signed.....Rema Mountifield.....

Date.....7th July 2017.....

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CHAPTER 1: INTRODUCTION

In chronic disease, it is acknowledged that the patient perspective is different from that of the physician. Patients subjectively experience illness and its impact on their lives, work, family, and general wellbeing, whereas physicians provide more remote, objective, evidence-based advice and treatment. Patients are subject to multiple and often discordant information inputs, some evidence-based physician inputs, and other non-evidence based "lay" opinions. The weighting each input is given by an individual patient depends on a multitude of factors and will differ between individuals. Where greater emphasis is placed on non-physician inputs, a knowledge and beliefs "gap" is likely to exist between patient and physician. In this setting, knowledge is defined as the quantifiable understanding of medical evidence, and beliefs as firmly-held opinions about disease.

Identifying such a "gap" in the routine clinical encounter may be challenging. Patients may be uncomfortable expressing views that deviate from those of their physician, or feel reluctant to show their lack of disease knowledge by asking questions. In some care settings, patients may feel that their physician has insufficient time or inclination to address their concerns, their silence leading physicians to make an assumption of concordant disease beliefs which may not be justified. Suboptimal communication within the clinical encounter may not only promote malalignment of beliefs between patient and physician, but might also allow this "gap" to remain unrecognised and unacknowledged.

Evidence for a knowledge-beliefs "gap" is widespread across a broad range of chronic diseases. Patient understanding of the aetiology of diabetes and the need for treatment, the rationale for antibiotic prophylaxis in Congenital Heart Disease, the detrimental consequences of Atrial Fibrillation, the lack of serious consequences of Irritable Bowel

Syndrome, and the risks of medication used to treat Rheumatoid Arthritis (RA) have all been shown to be suboptimal[1-5].

A knowledge-beliefs "gap" between patient and physician can also exist in non-chronic disease settings. Pregnancy is an area in which misperceptions regarding health outcomes occur with high frequency. Studies of women during pregnancy have demonstrated suboptimal patient understanding of pregnancy complications[6], as well as poor understanding of the risk-benefit ratio concept governing medication use during pregnancy[7]. At the preconception stage, further evidence suggests that reproductive decisions are based on perceptions of disease that may or may not be accurate[8].

These knowledge-beliefs "gaps" have the potential to affect a multitude of patient health decisions, and thus health outcomes, particularly in those with a chronic disease. Decisions regarding medication-taking, cancer screening participation, medical appointment attendance, risk factor behaviour, and family planning are all likely to be influenced to varying extents by patient health beliefs and knowledge. One of the more thoroughly explored and deleterious consequences of malaligned beliefs between patient and physician is that of intentional medication non-adherence. The "Necessity Concerns" framework is a widely accepted psychological construct describing the balance of perceived necessity against medication concerns in an individual patient, and the strong relationship of this balance with medication adherence[9]. It has been shown to have broad applicability across a range of chronic diseases[10-13]. The use of Complementary and Alternative Medicines (CAM) is another potentially harmful behaviour associated with divergent patient beliefs, which is common in both healthy individuals and those with chronic disease[14-16].

Alignment of patient and physician views may be particularly important in the management of Inflammatory Bowel Diseases (IBD). These are long-term illnesses without a medical cure, with onset often taking place in adolescence or early adulthood. Affected individuals suffer significant interruptions to their work, study, and family life, and often have difficulty accepting the diagnosis and need for long-term treatment. Suboptimal patient-physician communication is known to be widespread in IBD[17]. In this context, a patient-physician "gap" may promote misinformed decision-making and lead to greater risks of adverse outcomes such as poorly controlled disease, bowel cancer, and surgery.

Potential behavioural consequences of a knowledge-beliefs "gap" are well documented in this population, with intentional medication non-adherence reported at similar rates to that seen in other chronic diseases (40-60%)[18], and CAM use with a similarly high frequency[16]. Other unexpected behaviours such as "voluntary childlessness"[19], and refusal to participate in cancer surveillance, have been noted amongst IBD patients, and while an association with disease beliefs may be intuitive, this has not been clearly established.

Statement of Problem – The Research "Gap"

Previous work has demonstrated both suboptimal disease-related knowledge and beliefs amongst IBD patients and the presence of deleterious health behaviours. However, the association between this patient-physician "gap" and health-related behaviours has been only minimally explored in relation to medication beliefs, and completely unexplored in specific areas likely to influence patient decisions such as pregnancy and cancer risk.

Although the diagnosis of IBD is usually made during the reproductive years, the relationship between patient fertility and pregnancy beliefs and reproductive decisions is

unknown. Similarly, colorectal cancer prevention and early diagnosis in IBD is encouraged by participation in colonoscopic surveillance, yet patient cancer perceptions which may affect participation are unexplored. While previous work has identified some risk factors for deleterious medication behaviours such as intentional non-adherence and CAM use, the focus has been on identifying socio-demographic and disease-related factors rather than attitudinal predictors.

Thesis Aims

This work aims to achieve a greater understanding of the knowledge-beliefs "gap" between patient and doctor in IBD; more specifically, whether a "gap" exists in areas of IBD such as fertility and pregnancy, colorectal cancer risk, and IBD medication and, in turn, whether such a "gap" influences patient health decisions and/or psychological wellbeing.

Description of Methodology

Six studies are presented exploring patients' knowledge and beliefs in important areas of IBD. Five studies are of observational design using cross-sectional questionnaires, and aim to define the "gap" by summarising the medical evidence based perspective, and comparing this with study findings of patients' views in each area. One further study is interventional in nature, assessing whether important knowledge gaps can be successfully addressed using targeted patient education.

Thesis organisation

Chapter 2 summarises previous work examining patient views regarding IBD and its treatment in the form of a systematic literature review. It demonstrates the existence of a "gap" between patient and doctor knowledge and beliefs, and supports the hypothesis that

the gap promotes detrimental patient health decision-making such as medication non-adherence and CAM use. The need for more specific studies to understand other areas of IBD in which a "gap" may be both present and deleterious is highlighted.

Chapter 3 reports a study of patients' views regarding fertility in IBD using a cross-sectional questionnaire. Common misperceptions held by male and female patients were described for the first time in the IBD literature and the clinical importance of these discussed. This study suggested an important role of misperceptions in influencing reproductive decisions and made an important contribution to informing why "voluntary childlessness"[19] might occur in IBD. The study described in Chapter 3 was peer-reviewed and published in 2009[20].

Chapter 4 reports on patients' beliefs regarding pregnancy and IBD with data coming from a separate section of the same cross-sectional questionnaire reported in Chapter 3. Again, patient misperceptions occurring at a high frequency were found, including important erroneous views regarding the risk-benefit ratio of medication use on pregnancy outcomes. The important clinical impact of active disease during pregnancy was confirmed, along with attitudinal drivers of non-adherence to IBD medication during pregnancy. This work, in common with the data in Chapter 3, was novel at the time of publication in 2010[21].

Chapter 5 examines the logical extension to the work described above, in assessing whether evidence-based patient education could improve IBD-specific reproductive knowledge and dispel misperceptions uncovered. This interventional study demonstrated that even a brief group education session which uses clear messages can have a dramatic effect upon patients' views. Importantly, this study, published in 2014[22], marked the first time that pregnancy education and its outcomes had been reported in IBD.

Chapter 6 presents a study which investigated patients' views regarding colorectal cancer risk in IBD. Patients meeting the criteria for colonoscopic screening were compared with IBD patients not yet considered to be at high risk, again using a cross-sectional questionnaire methodology. This work, published in 2014[23], described misperceptions regarding this important aspect of IBD, and demonstrated the complexity and individuality of the "gap" in its variable clinical impact on patient wellbeing and behaviour.

Chapter 7 reports on a cross-sectional questionnaire which examined patients' views in relation to medication in IBD. Two distinct types of medication non-adherence were described in this population, each associated with different patient attitudes. This further highlighted the complexity and individuality of the "gap" in its interaction with behaviour. Published in 2014[24], this paper described "Covert Dose Reduction" as a newly recognised behavioural consequence of the knowledge-beliefs "gap".

Chapter 8 examines the attitudinal associations of another potentially deleterious behaviour commonly reported in IBD, the phenomenon of Complementary and Alternative Medicine (CAM) use. This study, published in 2015[25], described doctor-patient communication quality as a specific aspect of the "gap" influencing CAM decisions, and explored the contributors to the "gap" external to the patient-physician relationship, such as input from social contacts.

Chapter 9 concludes the thesis by summarising the knowledge-beliefs "gap" between patient and physician that were identified in relation to IBD and reproduction, colorectal cancer risk, and medication beliefs. Findings across the six studies have been integrated to form a clearer picture of how the clinical impact of the "gap" varies across these areas, and potential ways to mitigate the "gap" are discussed. The limitations of the reported studies

are acknowledged, and directions for future research are proposed. Implications for clinical practice are discussed, detailing practical changes occurring as a result of this work, such as the development of a written patient information document based on international guidelines now in use across South Australia (Appendix A), and describing the real impact of this work on both international and Australian guidelines regarding preconception counselling. The conclusion highlights the complexity of the "gap" in its multitude of influencing factors and behavioural associations and offers an ethical viewpoint regarding its mitigation.

Conclusion

This chapter has described the rationale for study of the knowledge-beliefs "gap" between patient and physician in IBD. The studies presented in the following chapters explore patient perspectives on reproductive aspects of IBD, colorectal cancer risk perception, and medication views, and compare these with the evidence-based knowledge held by physicians. Clinically important behaviours resulting from these "gaps" will be described, along with the effect of specific education attempting to mitigate one of the important knowledge-beliefs "gaps" in IBD as an example of how intervention may address the issues described.

CHAPTER 2: LITERATURE REVIEW

Introduction

Disease-related knowledge and beliefs have been shown to diverge between patient and physician in many chronic diseases, and this "gap" appears to have an important impact upon patient behaviour. Individuals with Congenital Heart Disease have inadequate knowledge of their endocarditis risk and the need for prophylactic antibiotics before some medical procedures[2]. Only one-third of patients on long-term glucocorticoids are aware of the need for Osteoporosis prevention[26]. In Atrial Fibrillation (AF), only half of patients in one study were aware that AF predisposes to thromboembolism, and only a similar number (52%) knew that anti-coagulation prevents blood clots[3]. In Diabetes, many patients believe that they "only have Diabetes when the sugar is high"[1].Patient knowledge is suboptimal even in highly symptomatic conditions such as Chronic Obstructive Pulmonary Disease[27].

The consequences of divergent knowledge and beliefs are similarly wide-ranging and many are of high clinical importance. In Prostate Cancer screening, underlying patient beliefs exert greater influence upon screening participation decisions than the content of clinician counselling[28], while illness beliefs have been shown to strongly predict patient functioning in chronic pain[29].

Even in areas where overall knowledge is deemed to be satisfactory, clinically-relevant misperceptions may exist. For example, in a study of patient knowledge of anaesthesia and perioperative care, while subjects demonstrated good overall knowledge scores, 28% expressed their understanding of "fasting" as referring to the restriction of food but not fluid intake[30].

The clinical impact of patient knowledge deficits appears to be heterogeneous. While patients with Irritable Bowel Syndrome demonstrate a vast overestimation of the serious consequences of the disease, as well as a lack of awareness of a dietary role, the detrimental effect is likely to be that of unnecessarily increased healthcare utilisation and cost, rather than adverse health outcomes for the patient[4]. A smaller "gap" between patient and physician may improve other parameters such as patient satisfaction, as evidenced by studies examining the "shared decision-making" care model, whereby the consultation focus is on information sharing in which treatment decisions are made jointly[31].

Suboptimal medication knowledge and beliefs are a particularly frequent theme in the chronic disease literature. In Diabetes, the medication knowledge-beliefs "gap" is described as "psychological insulin resistance" whereby negative beliefs and inferior knowledge about the disease and treatment predict suboptimal adherence with insulin regimens, which has a detrimental impact upon disease control[32]. In a secondary prevention of Coronary Heart Disease study, general patient illness perceptions were only weak predictors of behaviours such as smoking, whereas the specific area of medication beliefs bore a stronger association with behaviour in the form of medication adherence[33].

In a study of Rheumatoid Arthritis subjects, 52% had "no idea" why they were having blood tests, and importantly, there was widespread confusion regarding the type and purpose of different medications for RA[5]. Similar misperceptions and divergent beliefs affect adherence to antidepressant medication[34]. In early stage Breast Cancer, negative patient beliefs predict cessation of therapy with tamoxifen[35], whereas medical evidence suggests that five years of therapy dramatically reduces the risk of recurrence and of mortality[36].

A knowledge-beliefs “gap” in Inflammatory Bowel Diseases (IBD) is suggested by similarly high rates of deleterious behaviours, such as deliberate medication non-adherence, to that of other chronic diseases. The predominant research focus, however, has been on socio-demographic rather than attitudinal predictors of such behaviour. Ulcerative Colitis (UC) and Crohn’s Disease (CD) are medically incurable diseases with onset usually in adolescence or early adulthood and, as a result, disease-related patient knowledge and beliefs influence health decisions over many years. Decisions based on misinformation may result in poorer disease control and lead to decreased Quality of Life (QoL), need for surgery, and the development of Colorectal Cancer, as well as potentially influencing other life decisions that remain, as yet, unexplored.

Purpose of the Review and Definition of Terms

The purpose of this review is to obtain a deeper understanding of the knowledge and beliefs held by patients about their IBD and its treatment that may differ from those held by their physicians – defined in this setting as the knowledge-beliefs “gap”.

Construction of this Review

A natural division exists between patient-knowledge studies, for which the methodology is predominantly quantitative, and the more subjective beliefs, fears, and concerns studies, which apply both qualitative and quantitative approaches. This review will thus present these two entities separately using a systematic approach presented in a thematic framework.

Aims

Primary aim: To investigate whether a "gap" exists between patient and physician knowledge and beliefs regarding Inflammatory Bowel Disease.

Secondary aim: If a "gap" exists, to determine whether it has a clinical impact upon patient health-related behaviours.

Search Strategy

To investigate patient knowledge and beliefs regarding IBD, a search was conducted in December 2008 using the SCOPUS, Ovid-Medline, Pubmed, and CINAHL databases. From the database search results, titles and abstracts were reviewed using the inclusion criteria outlined below, followed by a review of the full-text for articles deemed to be highly relevant. The reference lists for each paper reviewed were examined in full and further articles were sought based on those of potentially high relevance.

Inclusion Criteria

Key words used to find knowledge studies were Inflammatory Bowel Disease OR Crohn's OR Colitis OR Ulcerative Colitis, AND Patient Knowledge OR Understanding. Key words used in searching for patient belief studies were Inflammatory Bowel Disease OR Crohn's OR Colitis OR Ulcerative Colitis AND Patient Beliefs OR Concerns OR Fears OR Perspective.

The initial timeframe for article inclusion was from January 1998 to June 2008; however, upon reading the literature, it became evident that knowledge evaluation in numerous studies in this date range was based on a validated assessment tool developed prior to 1998. The search start date for knowledge studies was thus revised to include studies dating back to, and including, 1985. However, given the substantial progress in IBD treatment goals

over this 20 year period, articles published between 1985 and 1998 were considered as less relevant, and were only included if they were of high relevance and cited frequently by studies in the target date range.

Only articles with a primary focus on IBD patient knowledge or beliefs were considered for inclusion and only English language articles were included.

Exclusion Criteria

Articles published in a language other than English were excluded, as were those outside of the specified date range, unable to be obtained for review, involved only paediatric participants, included diseases other than IBD, or where the primary aim of the study was not patient knowledge or belief assessment.

Methodological quality appraisal

Quantitative studies

The methodological quality of the quantitative studies was assessed using a tool adapted from CASP, NICE, STROBE, and MOOSE guidelines for reviewing observational data[37, 38] [39] [40]. The following assessment criteria were decided upon: 1. Representativeness of studied population; 2. Power of study as indicated by power calculation, numbers studied, and questionnaire response rate; 3. Validity and reliability of the knowledge assessment tool used; and 4. Recognition of, and adjustment for, potential confounding variables.

Qualitative studies

Qualitative studies were assessed using a tool adapted from CASP and Cochrane[37, 41]. The criteria used were: 1. Clarity of study aims; 2. Methodological rigour (appropriateness of recruitment strategy and reliability of data collection method); 3. Systematic nature of data analysis; and 4. Clarity of presentation of findings.

Search Results

Studies of IBD patient knowledge

The initial search using the key words “IBD” and “Patient Knowledge/Understanding” yielded 326 studies, with 4 additional articles identified from the reference lists. After removing the duplicates, 205 articles were screened using the title and abstract, while 190 were excluded based on lack of relevance, leaving 15 articles to be included for the full text review. Of these, 6 met the criteria for inclusion in the review, all of which were quantitative in design (Figure 1).

Studies of IBD patient beliefs

The initial search using keywords “IBD” and “Patient Beliefs / Concerns / Fears / Perspectives” yielded 525 studies, with 6 additional articles identified from reference lists. After removing duplicates, 363 articles were screened using title and abstract and 345 excluded based on lack of relevance, leaving 18 articles for full text review. Of these, 12 met criteria for inclusion in the review, of which 9 were quantitative and 3 qualitative. (Figure 2)

Theme 1: Patient disease related knowledge in IBD

Types of studies included

Of the six quantitative studies meeting inclusion criteria, three involved cross-sectional questionnaires, one was a retrospective case control study, one a prospective comparative study, and one was an opinion piece in the form of a letter (Table 1). None of the knowledge studies were qualitative in design.

Results: Studies of patient disease related knowledge in IBD

Overall, patient disease-specific knowledge in IBD was suboptimal, although nearly all the studies assessing knowledge (4/6) used different non-standardised assessment tools, and

many did not use categories to rank knowledge. Some disease and patient-related factors associated with better knowledge were identified, as were sub-areas of particularly poor patient knowledge and misperception. Only three studies focused on the interaction between disease knowledge and health-related behaviours such as medication adherence and the use of Complementary and Alternative Medicines (CAM).

Disease-related knowledge amongst IBD patients

Five studies assessed knowledge using an assessment tool, two of which were validated. Of the three studies reporting scores divided into categories, two found that knowledge was poor, while one reported most patients as being "well informed" using an arbitrary cut-off value. Another two studies reported the knowledge score as a continuous variable and statistically compared scores across patient sub-groups, such as disease type or patient ethnicity. In these studies, numerical knowledge scores appeared to be low, although no categories were defined.

Overall knowledge scores were reported in all studies, with no consistent numerical sub-scoring for important areas such as medication knowledge or understanding of cancer risk.

Factors associated with patient knowledge level

Membership of a patient organisation, such as Crohn's Colitis Australia (CCA) or the National Association for Colitis and Crohn's Disease (NACC, UK), was examined as a variable likely to influence knowledge in four articles[42-45] and was found to be associated with better knowledge in each of these studies.

Regarding disease type, two studies found patients with CD to have higher knowledge levels compared with those with UC[42, 45]), while three found no association. Interestingly,

improved knowledge among CD patients was only observed among Caucasians in the Leong study[45].

Disease duration was positively correlated with knowledge in two studies, with no association found in a further two.

Leong et al demonstrated culturally-based differences, in that Chinese patients in Hong Kong had inferior disease-related knowledge to their Caucasian counterparts in Australia, although knowledge in both groups was suboptimal[45]. Patterns of knowledge deficit also differed between cultures, in that Chinese subjects were more likely to misidentify their disease type than Caucasians and also to misunderstand its aetiology ($p<0.001$). This is supported by the culturally divergent patterns of misperceptions evident in an Indian study by Sood et al[46]) compared with UK studies (Eaden et al[43]).

Quality of Life (QoL) was measured in two studies[42, 45], and was associated with knowledge level in neither.

Disease activity was only measured in a single study and did not correlate with knowledge[45].

Areas of poor knowledge and frequent misperceptions regarding disease

While not providing specific numerical sub-scores, all the studies reported sub-areas of knowledge that were most problematic for patients, in that the rates of misperceptions were especially high for that concept, or that misunderstanding was potentially of high clinical relevance.

Medication-related misperceptions were reported in all six studies and were emphasised as a clinically concerning knowledge gap. Eaden et al found that 76% of patients thought that

sulfasalazine and mesalazine were immunosuppressive drugs, while 56% felt that all steroid side-effects disappeared after the drug was ceased[43]. Only 5% of IBD patients with colorectal cancer studied by Eaden et al knew that azathioprine was immunosuppressive[44], while a lack of awareness of side effects was reported by a small but important proportion of azathioprine-taking patients in the Verma study[42].

The reproductive aspects of IBD, such as fertility and pregnancy, were also frequently misunderstood. Eaden et al found that only 26% of patients were aware that sulfasalazine causes reversible infertility in males[43], with this proportion being only 5% amongst the cohort of IBD patients with colorectal cancer reported in the later study by the same authors, while 79% had no understanding of the fertility implications of Crohn's disease[44].

Colorectal cancer risk was another source of confusion. Seventy eight per cent of patients in the Eaden study did not know which patients were at increased risk of cancer, and thus, who warranted surveillance[43]. In addition, only 7% believed that passing blood in their stools equated to a definite cancer diagnosis.

Smoking was another area of knowledge deficit. Verma et al reported that an alarmingly high proportion (92%) of Crohn's patients were unaware of the relationship between smoking and Crohn's disease[42]. This was supported by a similar rate (77%) of unawareness of this important risk in the Eaden study[43].

Sources of disease related information

Two studies[42, 45] specifically enquired into patients' sources of disease-related information. A cultural difference existed in that Caucasians were much more likely to derive knowledge from sources such as pamphlets, the Internet, and patient organisations

than Chinese patients (p<0.001)[45]. Verma's UK population was similar to Australian Caucasians in that patients reported that they had obtained most of their disease-related information from leaflets, videos, and their doctor[42].

Potential effect of poor knowledge upon health behaviours

The review article by Keohane[47] postulated that widespread confusion regarding medications amongst IBD patients contributed to non-adherence and the use of Complementary and Alternative Medical Therapy (CAM), although data to support this contention at the time of publication were scant.

One study addressed the relationship between knowledge and medication adherence, two examined CAM use, and one hypothesised the contribution of poor knowledge to the development of colorectal cancer.

Regarding adherence to conventional IBD medication, Sood et al found that increased disease awareness was associated with higher medication adherence (p<0.0001)[46]. Adherence was not assessed using a validated adherence measure, but rather as a dichotomous variable (yes/no) in response to the question "Do you stop or decrease the medicines on your own when symptom free?" A large proportion answered "yes" to this question (77.9%), but it is unclear what proportion decreased rather than ceased their medication, and whether "decreased" implied reduced frequency of full dose medication, or reduced dose taken regularly. The underlying beliefs driving these different patterns of medication non-adherence were not further addressed in this study.

Studies addressing CAM found rates of use to be high in IBD which was consistent with previous data[16, 48, 49], rendering this an important behaviour to investigate in relation to

patient disease understanding. While CAM use rates were similar between Chinese and Caucasian cohorts in the Leong study (approximately one-third of patients), use was associated with higher knowledge in Caucasian, but not Chinese patients[45]. The Indian population studied (Sood et al) contrasted in that their CAM use was very high overall (81.4%), and highest among those with lower disease awareness ($p<0.0001$)[46]. Leong's Chinese population showed no significant relationship between CAM use and disease knowledge, and this cohort was more likely to believe in the benefits of herbal medication in IBD treatment than Caucasians ($p=0.012$), perhaps reflecting a cultural bias[45]. This suggests that although CAM use is widespread in IBD, disease-based knowledge and beliefs underlying its uptake may differ by culture.

One cohort study (Eaden) explored the intuitive hypothesis that patients with poorer knowledge may be more likely to develop colorectal cancer as a result of poorly-controlled disease[44]. After investigating IBD patients with and without a history of colorectal cancer, no association was found between current IBD-related knowledge and cancer history. However, these patients were surveyed long after their cancer diagnosis and their knowledge may have improved as a result of the cancer treatment process. Medication adherence was not examined, nor was participation or lack thereof in surveillance programs or attitudes towards surveillance.

Quality appraisal of studies

Two studies met all four quality criteria, two met three of the four criteria, one met two criteria, and the letter met none (Table 2).

While most of the reviewed studies were likely to be adequately powered, and had attempted to measure patient knowledge objectively, the main limitation was the lack of

use of a validated instrument in four of the six studies. Results were expressed as a percentage of patients answering correctly for each question, or as a continuous summary variable compared across differing IBD populations to make relative conclusions about knowledge. Categorisation of satisfactory versus unsatisfactory knowledge was done using an arbitrary cut-off value, and sub-scores summarising important behaviour influencing areas such as medication knowledge were not compiled.

While development of the validated CCKnow addressed the need for standardised knowledge assessment, it was still not applicable or valid in all situations, particularly where translation would be required and cultural differences were reasonably expected to exist, such as in the Leong study. Additionally, in its reduction from 30 to 24 questions, factor analysis resulted in the exclusion of clinically important knowledge areas from the final CCKnow. While not statistically important in differentiating knowledge levels between patients, the six questions excluded due to low discriminating value included the effects of corticosteroids, smoking and cancer risk, and areas found to have high rates of misperceptions in other studies.

The observational studies reviewed are subject to bias, and even where evidence of a strong association was found (knowledge and patient organisation membership), causality was not established. It is likely that patients motivated to join a support organisation are information-seekers and may represent a group with higher baseline knowledge. The variability of results and clear differences between populations studied limited generalisability, and potential confounding factors were not measured and adjusted for in all studies.

Discussion

While acknowledging the methodological limitations of included studies, and the limitations of this review in terms of the small number of studies meeting inclusion criteria, a clearer picture of patient knowledge in IBD has emerged. It is noteworthy that only a relatively small number of studies aimed to investigate patient knowledge in IBD, whereas a large number in the same time period reported new and evolving medical and surgical treatments. Such progress in the development of new treatments is likely to be of lesser value in the context of suboptimal patient engagement, which is likely to result from the knowledge gap identified here.

Across all cultures and study settings reported, there exists varying degrees of knowledge deficit – which represents evidence of a "gap" between physician and patient. Perhaps more importantly, areas where widely held and clinically important misperceptions exist have been identified, although their impact upon health decisions remains unclear.

While there is consensus that patient organisation membership is associated with improved knowledge, causality is not implied. Other factors that are contentious but potentially associated with higher knowledge such as disease type and duration are not modifiable. Culturally-based differences in knowledge appear likely, and culture and language-specific assessment instruments to assess knowledge may be of value.

No other clear associations between disease knowledge and disease or patient factors have been identified by this review, with contradictory findings among the selected studies.

The relationship between the knowledge "gap" and relevant health behaviours has not yet been elucidated. It appears complex and partly culturally-based, although it is likely that

many other confounding variables complicate the association between knowledge and the two behaviours addressed in these studies, medication adherence and CAM use. Similarly, the study investigating the association between a cancer outcome and patient knowledge was negative, but the design is likely to have introduced bias, and other steps in the potential causality chain were not tested such as medication adherence, disease activity, and surveillance attitudes and participation. The development of cancer, medication non-adherence, and CAM use are deleterious outcomes, and their association with patient disease knowledge warrants further investigation.

While quantifying knowledge was seen as a strength of the reviewed studies, a qualitative approach may have yielded a deeper understanding of one area of frequent misperceptions, that of fertility and pregnancy in IBD. In studies addressing this issue, a maximum of one or two questions examined knowledge regarding the relationship between IBD and reproductive outcomes. The respondents were asked to provide a yes/no answer or to use a Likert scale to express relative agreement with a statement. The high reported rates of misperception in this area are worthy of more detailed study, as voluntary childlessness has been reported amongst IBD patients[19], yet the reasons for this have not been clearly established.

Improving general IBD knowledge through patient education was recommended by all investigators, but it is likely that only certain areas of misperception will have functional significance by influencing health decision-making, such as medication-taking behaviour or participation in cancer surveillance. In a letter commenting on the methodology of patient knowledge assessment, O'Sullivan argued that individual questions within knowledge

questionnaires should be weighted differently, as they are likely to have different levels of importance in influencing patient health behaviours[50].

This review has established the existence of a knowledge "gap" and identifies the need for deeper exploration of specific IBD patient knowledge deficits which may drive deleterious health behaviours. Understanding and addressing misperceptions has the potential to influence clinically-important health behaviours and result in improved outcomes in IBD.

Theme 2: Patient disease-related Beliefs, Fears, and Concerns

Types of studies included

Of the twelve studies meeting inclusion criteria, nine were quantitative (cross-sectional questionnaires) and three were qualitative studies, including one semi-structured interview study and two reviews (Table 3 and Table 4).

Most articles investigated "concerns" rather than beliefs or fears, as a validated instrument to measure concerns has been developed and is widely used as part of QoL (Quality of Life) assessment in IBD (Drossman, 1991)[51]. The term "concerns" was used synonymously with fears in most articles, and reported "concerns" in included studies were thought to reflect health beliefs and, in some cases, a lack of understanding of the disease and its treatment.

Results: Beliefs, Concerns, and Fears of IBD patients regarding their disease and treatment

Drossman et al published a landmark study in 1991 reporting on the development and validation of a 25 item questionnaire known as the "Rating Form of IBD Patient Concerns" (RFIPC) which has been widely applied as part of QoL assessment. Including reviews, 9 of the 12 studies that met the inclusion criteria used this instrument, thus concerns and beliefs outside of the 25 items assessed were only addressed in the remaining three studies.

Overall concern levels regarding disease and treatment were high amongst IBD patients, and the ranking of concerns showed some degree of consistency across IBD populations in the included studies despite some demographic variations. The included studies focused on the identification of areas of greatest concern for patients, and the influence of various demographic and disease-related factors on these concerns. In terms of the behavioural impact of beliefs and concerns, two studies investigated medication-related health beliefs, and a further two sought beliefs and concerns associated with the use of CAM.

Major areas of concern for patients

Four main concern indices were identified by factor analysis in the original Drossman study of a community IBD population: impact of disease, sexual intimacy, complications of disease, and body stigma[51]. The factor analysis yielded different indices in the De Rooy study[52], whereby body image and interpersonal concerns were more important in this slightly younger population, which also differed by recruitment from a tertiary hospital outpatient sample.

Regarding individual items of the RFIPC, the areas of greatest concern across the studies were energy levels, effects of medications, and uncertainty of disease. While there is overlap on these major items, the two thematic review articles contrasted in their major findings. Irvine et al[53] reported that the most prevalent fears across the reviewed studies were life expectancy, ability to have a family and/or job, the need for surgery, IBD inheritance by children, cancer risk, uncertainty of next flare timing, adverse medication effects, and affordability of treatment. In contrast, Casati et al reported the greatest areas of concern to be loss of energy, loss of control, body image, fear and isolation, unreached potential, feeling dirty, and the lack of medical information received[54].

Effects of demographic, clinical, and psychological factors on patient concerns

Age and Gender

Drossman[51] and Mussell[55] found that being female was associated with greater overall concern levels, and De Rooy demonstrated an association between female gender, older age, and the specific concern of increased disease stigma[52]. In a post hoc analysis of three previous studies, Maunder[56] found women to have greater overall concern scores, as well as more specific gender-based differences. Women had greater concerns than men in relation to the ability to have children, body image, attractiveness, and feeling alone. The Casati review reported that women were more subject to fears regarding lack of attractiveness than were males with IBD[54]. However, the top three concerns in both genders in the Maunder study remained energy levels, medication effects, and the uncertain nature of disease.

Disease activity and severity

Two studies[51, 52] reported that the greatest impact on concern levels overall was from increased disease severity. Interestingly, a further study reported contradictory findings in that disease activity, severity, type, duration, and medication correlated poorly with concerns[57].

Disease Type

People with Crohn's disease in the Drossman study had higher levels of concern regarding energy levels, being a burden, achieving full potential, pain, financial impact, and passing on the disease[51]. However, after controlling for demographic factors and disease severity, the concern areas of body stigma and impact of disease were not statistically associated with disease type. In UC patients, greater concerns about developing cancer persisted after controlling for demographics and severity, and this was further supported by De Rooy's

findings[52]. A further study found no differences in overall concern score by disease type[55].

Disease Duration

Longer duration of disease was associated with greater disease stigma concerns (including concerns regarding cancer development) in older patients in De Rooy's study[52], although this was contradicted by Moser et al[57].

Educational levels

Lower educational status was associated with increased concerns in the Drossman study[51].

Disease-related knowledge levels

Disease-specific knowledge was alluded to without formal measurement by Moser et al[57], but was not assessed in any other beliefs/concerns studies reviewed. Using the subjective proxy of patient-perceived knowledge levels using a visual analogue scale, a strong correlation was seen between poorer perceived knowledge and greater concerns in this study. One review cited a lack of information from physicians as a source of fear and uncertainty for patients[54].

Sociocultural setting

The multinational European study (Levenstein et al) showed a large variation in concern levels, more than two-fold between countries[58]. This followed a geographic gradient between north and south, with greatest concerns in the southernmost countries. This could not be adequately explained by differences in education levels, but adjustment for disease and patient characteristics was not possible in this study. Patterns of concern also differed

by culture; concerns regarding cancer development was postulated by the authors to be lower in Mediterranean countries where cancer risk is typically downplayed.

Care setting

In the De Rooy study of a tertiary IBD centre sample[52], body image and interpersonal concerns were reported as explaining a much higher proportion of variance in RFIPC score than in the community sample reported by Drossman[51]. In a previous study, far higher concern levels were seen amongst hospital in-patients with IBD, and their concern profile differed from the community sample reported by the same authors[59].

Coping style and other psychological variables

Mussell et al demonstrated the importance of coping style, with a depressive style predicting a greater proportion of the variance in RFIPC score than demographic or clinical variables[55].

The impact of concern levels - associations with other health indices

Drossman et al found that of the four concern indices identified, greater impact of disease was associated with poorer perceived health and wellbeing, greater psychological distress, and poorer daily functioning using validated measures. Concerns over sexual intimacy were related to impaired psychological function, and complications of disease to poorer daily function[51].

Associations of beliefs and concerns with health behaviours

Two deleterious treatment-related behaviours were investigated for a relationship with health beliefs or concerns: deliberate medication non-adherence and CAM use.

Medication non-adherence

Goldring et al proposed a theoretical medication to IBD patients and manipulated the risks and benefits of this in a questionnaire to form a model predicting treatment intention[60]. The strongest predictor of medication adherence intention was health beliefs, with higher perceived threat levels from disease predicting medication-taking intention. An interaction with QoL was also noted in that less symptomatic patients with higher QoL emphasised risks related to medication in their decision-making. Physician recommendation strength was also predictive of medication-taking, accounting for 7% of the variance in the model, and this has been reported previously[61]. Strong physician recommendation was especially effective when there was a "shared decision-making" relationship, whereby patients received clear information, felt comfortable to voice concerns, and shared treatment decisions.

The study by Hall et al[62] contrasted in its design as a qualitative exploration of patient beliefs regarding medication. The interesting aspect of this work was the finding that attitudes were medication-specific (with higher concerns regarding corticosteroids), and that the balance of perceived necessity versus concerns changed over time in individual patients based on variation in their symptoms. Patients in this study reported a reluctance to discuss medication concerns with their physician, and reported that fear of the physician prescribing corticosteroids disinclined them from seeking healthcare. Additionally, in this study, many patients reported self-managing their medication to varying extents in ways that diverged from the recommendations of their physician.

CAM use

In the Rawsthorne study, attitudes found to be associated with CAM use were dissatisfaction with conventional therapy, viewing hospitals as dangerous, views that

alternative therapists should work in hospitals, and that their own medical situation was hopeless[63]. In Moser[64] and other studies[65], CAM use in IBD was used in addition to conventional therapy rather than as a substitute. Interestingly, patient perceptions of disease knowledge did not correlate with CAM use in this study, but this was limited by lack of objective knowledge assessment. Longer disease duration predicted CAM use in the 1996 study by Moser et al[64]. Both Moser and Rawsthorne et al emphasised the importance of attitude predictors, reporting no other clear socio-demographic or disease associations with use, although geographic variation was seen in the form of higher rates of CAM use in Los Angeles versus Cork in one study[63].

Critical Appraisal of Studies

Of the nine included quantitative studies, two met all four quality appraisal criteria, three met three of the four criteria, and four met two of the four criteria (Table 5).

Of the three qualitative studies, one met all four quality criteria, and the further two studies met two of the four criteria (Table 6).

Most of the studies that met the inclusion criteria used the RFIPC instrument to investigate IBD patients' concerns. The strength of this tool is that it has been validated, is positively associated with other measures of health status, and is easy to apply. However, the exploration of concerns was then limited to the 25 items comprising this instrument in most of the studies.

In a similar situation to the knowledge studies and CCKnow development, the factors not loading on the four main concern indices in the original validation study were de-emphasised, with limited further statistical analysis; however, these may be clinically

important. Examples of items not included in the concern indices developed are “ability to have children”, “passing the disease onto others”, and “being treated as different”. In the original Drossman article, the authors cited the case of a 27 year old female whose concerns regarding fertility precluded necessary surgery, and it was only after these concerns were recognised and allayed that she consented[51]. This suggests that reproductive and other decisions are made on the basis of such concerns and misperceptions, and therefore, are of clinical relevance. It is noteworthy that the mean age in this study was 42.8 years (similar across the other included studies), and it is likely that for a sub-group of younger patients, greater concern exists in relation to reproductive outcomes. Misperceptions among younger patients are likely to have an impact upon reproductive choices and are thus of greater relative importance.

Most of the included studies sampled a cross-section of IBD patients with varying demographics, with subsequent analysis by age, gender, and various disease characteristics. The most in-depth assessment of concerns by gender was in the post hoc analysis of three previous studies, in which the effect of gender had not been studied. It is intuitive that specific demographic and disease characteristic groups may have concerns which differ from that of other sub-groups and that the standardised, more generic RFIPC may be insensitive to detect.

The qualitative study reported that disease and treatment beliefs change over time and are situation-specific[62], and yet most studies included were cross-sectional rather than longitudinal in design and addressed general concerns in a validated instrument rather than specific ones that would be likely to influence treatment-related decisions.

Discussion

This review has added an important subjective perspective of the patient experience in IBD and provides further evidence of a "gap" between patient and physician. The included studies acknowledged that the major concerns held by patients were not likely to be the same primary concerns held by physicians managing IBD, and that disease beliefs held by patients frequently diverged from evidence-based realities. There was also agreement that failure to address patient concerns may have adverse consequences for psychological indices and for health behaviours such as medication adherence and CAM use.

The highest ranking individual concerns of energy levels, effects of medication, and uncertainty of disease were reasonably consistent across studies. There was considerable variation in the ranking of other concerns, with some demographic patterns of concern emerging, although these sub-groups were not explored in detail.

Women were more concerned than men about attractiveness and the ability to have children, while UC patients were more concerned about bowel cancer than those with Crohn's disease. Further to this, the effect of disease type and duration on concerns remains unclear. Disease-related knowledge level was not sufficiently robustly assessed to allow conclusions regarding an association with concerns, and while sociocultural differences in concerns were suggested, important variables that may confound this potential association were not examined.

It is noteworthy that at least 7 of the 25 individual RFIPC items could be explained by the physical effects of active disease. This instrument has been shown to correlate with disease activity[59] and in the De Rooy study, severity of symptoms had the greatest influence on concerns[52]. A minority of studies, however, objectively assessed and adjusted for disease

activity in their concerns analysis. Nevertheless, as IBD care has evolved to a more proactive model since 1991, with a higher proportion of patients in clinical remission, it is possible that the ranking of patient concerns has shifted to emphasise those less related to disease activity.

While low energy level was a highly ranked concern in most studies, and is a common feature of active disease, other treatable causes, such as iron deficiency and depression, were only considered in one study[55]. This study excluded patients meeting the diagnostic criteria for a depressive disorder, as many features of depression overlap with individual items within the RFIPC. Interestingly, 10% of potential subjects were excluded from the study by Mussell et al on the basis of likely depressive disorders[55], demonstrating the high frequency of undetected mood disorders in IBD.

Striving for improved disease control in all IBD patients, as well as seeking common co-morbid problems such as iron deficiency and depression, should be the first intervention in alleviating patient concern levels. Supporting this strategy was an early study of infliximab use in Crohn's disease which demonstrated reduced rates of worry with more effective disease control[66].

An association between beliefs/concerns and health behaviours, such as medication adherence and the use of CAM, is suggested by the included studies but the evidence is somewhat inconclusive. Health beliefs were the strongest determinant of treatment intention in the Goldring study[60], which is consistent with the previously reported Necessity Concerns framework relating to medication-taking behaviour[67]. Beliefs regarding the necessity of medication based on symptoms are weighed against concerns regarding medication risk in this model, which appears to apply equally in IBD. It was

interesting to note the dynamic nature of perceived necessity reported in Hall et al[62], as the balance between necessity and concern changed with time and was medication-specific. This implies that a much more complex relationship between beliefs and medication adherence exists which is subject to many inputs which are difficult to adjust for in study design.

The findings in relation to CAM use and its association with concerns was similar in that anti-conventional therapy attitudes were associated with alternative medicine use, but there was no attitudinal explanation as to why patients continued to take their conventional medication while using CAM as a supplementary treatment. The pattern of "co-therapy" that patients reported between the two types of medication was not defined, and beliefs underlying such practice not explored.

Like knowledge deficits, it is likely that not all patient concerns and divergent beliefs have a functional impact upon health behaviours, and that weighting of concerns based on their influence on decision-making may be appropriate. Of the concerns frequently reported by patients, the most likely to influence health behaviours were "effects of medications" (adherence), "developing cancer" (surveillance attitudes and participation), and "ability to have children" (reproductive decision-making).

These items are only minimally explored in the existing IBD literature and yet are likely to be very important in particular demographic groups, such as young patients planning families, and those with UC at particularly increased risk of colorectal cancer.

Despite cancer risk being ranked as an issue of great concern to UC patients across most of the studies, Hall et al reported an apparent lack of awareness amongst patients in their

study about the chemoprotective effect of 5ASA therapy[62]. It is not clear whether patients in this cohort were not aware of an increased cancer risk in UC, were not aware of chemopreventative strategies, or were reassured by participation in colonoscopic surveillance. Objective patient knowledge of cancer risk likelihood was not assessed in these studies, and their attitudes toward chemoprevention and surveillance colonoscopy were not explored. Supporting this heterogeneity in cancer risk perception was the European study[58] which introduced the possibility that concerns may differ by culture. While Italian patients, for example, may be less focused on cancer risk, in a country such as Australia where cancer risk is emphasised and patients are actively educated and enrolled in surveillance programs, it is possible that such emphasis has a negative psychological or QOL impact.

This review has highlighted not only a beliefs-concerns “gap” between patient and physician, but also gaps in the literature in relation to reproduction concerns, cancer views, and attitudes related to medication adherence and CAM use. Few studies published thus far have targeted specific concerns with education and counselling in an attempt to correct misperceptions and to narrow the “gap”, and this remains an important area for further study.

Conclusions

This review confirms and describes the existence of a knowledge-beliefs “gap” between patient and physician in their views regarding IBD. Areas of greatest patient concern and misinformation have been defined and patient groups most vulnerable to misperceptions identified.

The inclusion of both quantitative and qualitative studies is a strength of the review, as this informs a broader understanding of patients' views, which necessarily encompass both objective (knowledge) and subjective (beliefs and concerns) components.

While misperceptions may not negatively affect QOL directly, their effect on health behaviours is under-explored. Abnormal health behaviours resulting from impaired disease understanding may have a major influence on treatment success. Areas in which the "gap" is likely to influence important health behaviours are: knowledge and concerns regarding the reproductive aspects of IBD, cancer risk in IBD, and medication behaviours such as adherence to conventional therapy and the use of CAM.

At the time of initiating this review and planning the studies presented in this thesis (2008), no published studies examine patient knowledge and beliefs regarding IBD and fertility and pregnancy, or the potential impact of misperceptions in this area on reproductive decision-making, and medication taking behaviour during pregnancy. This research gap is highlighted in an expert editorial, in which it is suggested that patient fear of medication exposure during pregnancy may result in medication non-adherence during pregnancy[68], an action likely to be detrimental to pregnancy outcome. Similarly, studies of the effects of reproduction-specific education amongst IBD patients have not been performed.

Secondly, while concerns about the risk of colorectal cancer among UC patients are high, their perceived risk estimation and the effects of this perception on psychological wellbeing and attitudes toward surveillance are unexplored. This may have an important impact upon participation in cancer surveillance.

Thirdly, while health beliefs have been identified as an important factor influencing medication-taking behaviour, deliberate medication non-adherence has not been further stratified into sub-types in IBD. Such sub-types were suggested in the Indian study[69], but were not analysed separately nor explored further. It is intuitive that different types of non-adherence behaviours may be driven by different beliefs and attitudes, and this is worthy of further study.

Finally, CAM use is a potentially deleterious but highly prevalent behaviour amongst IBD patients, for which disease beliefs and concerns may be stronger predictors than demographic and clinical factors. A substantial role has been suggested for the suboptimal patient-physician relationship in increasing CAM susceptibility. This is indicative of the "gap" identified in this review, but it is currently unclear which specific aspects of the therapeutic relationship contribute to this disconnect. The Leong study demonstrated that attitudes towards CAM use are at least partly culturally-based, but appear to be complex and multifactorial. Factors that have not been extensively investigated in IBD are the role played by influences external to the patient-physician relationship, and the patterns of conventional medication use which accompany CAM uptake.

The chapters to follow report upon six studies which explore the knowledge-beliefs "gap" in specific areas of IBD which are likely to influence patient health decisions. Five cross-sectional studies seek to determine whether there is in fact a "gap" between patient and physician views in these specific IBD areas, and whether the gap is clinically relevant, by its impact upon psychological parameters and health behaviours. Specific IBD aspects investigated will be fertility and pregnancy, cancer risk, medication-taking, and the use of

CAM. In addition, one interventional study attempts to bridge the knowledge "gap" via IBD-specific reproductive patient education.

Implications for clinical practice

The physician should be aware that overall patient knowledge of IBD is suboptimal, and that a knowledge-beliefs "gap" exists between patient and physician. Misperceptions regarding the disease and, in particular, its medical treatment are prevalent. Such misperceptions influence health-related behaviours such as conventional medication adherence and the use of alternative medicines.

Objective instruments measuring knowledge in IBD patients are not designed to detect or explore subjective health beliefs and concerns that may predispose to dysfunctional health behaviours. There is thus no substitute for enquiring after health beliefs and knowledge in individual patients as part of the routine clinical encounter. Moreover, this discussion should be initiated regularly as concerns regarding medication in IBD change over time and vary between medications.

While the role of disease education and psychological support is vital in addressing patient knowledge deficits and concerns, the importance of controlling active disease and screening for depression and micronutrient deficiencies that may increase the risk of psychological and physical symptoms should not be underestimated.

Appendices

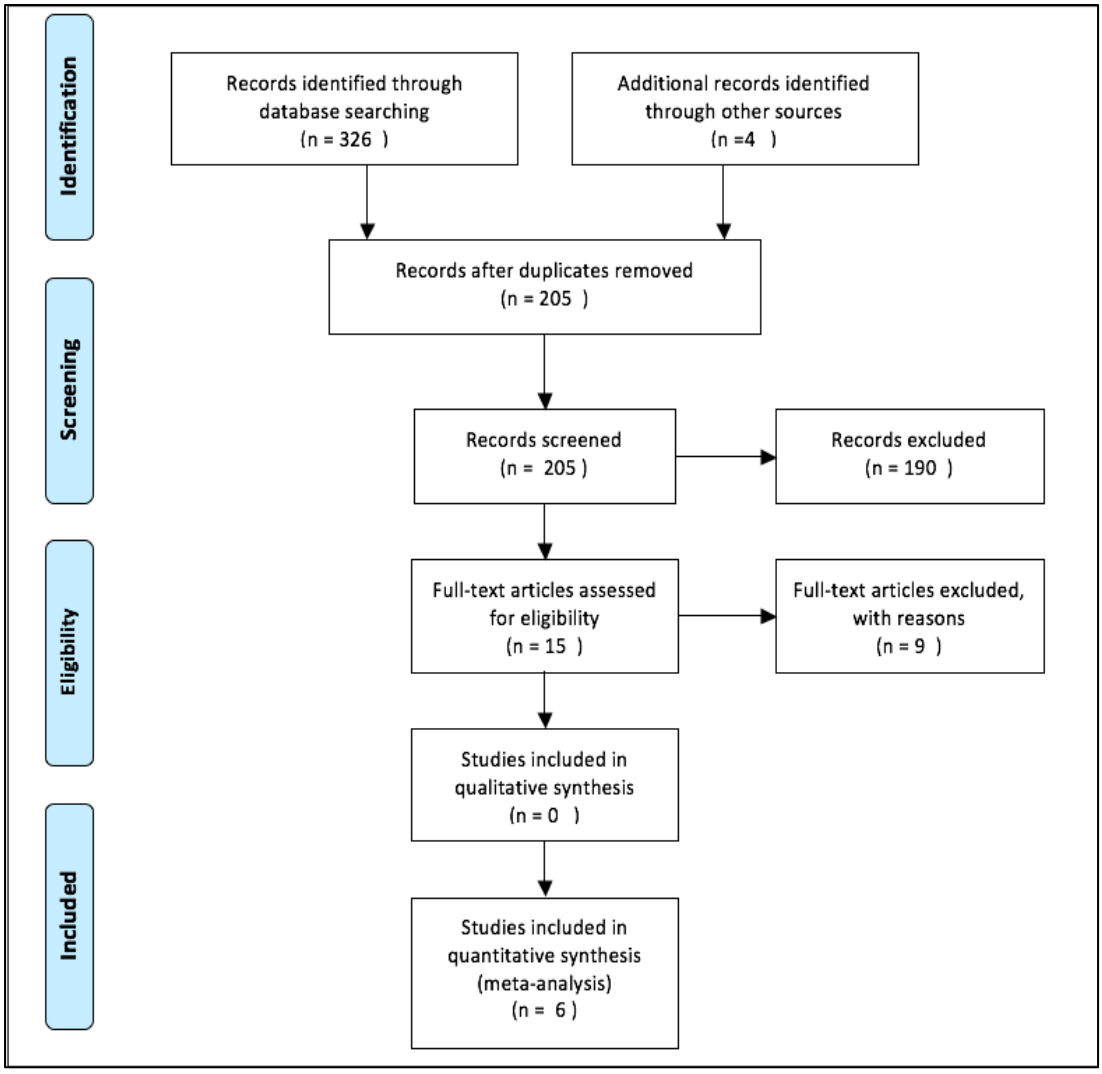

Figure 1: PRISMA Flow Chart Studies of Patient Knowledge in Inflammatory Bowel Disease

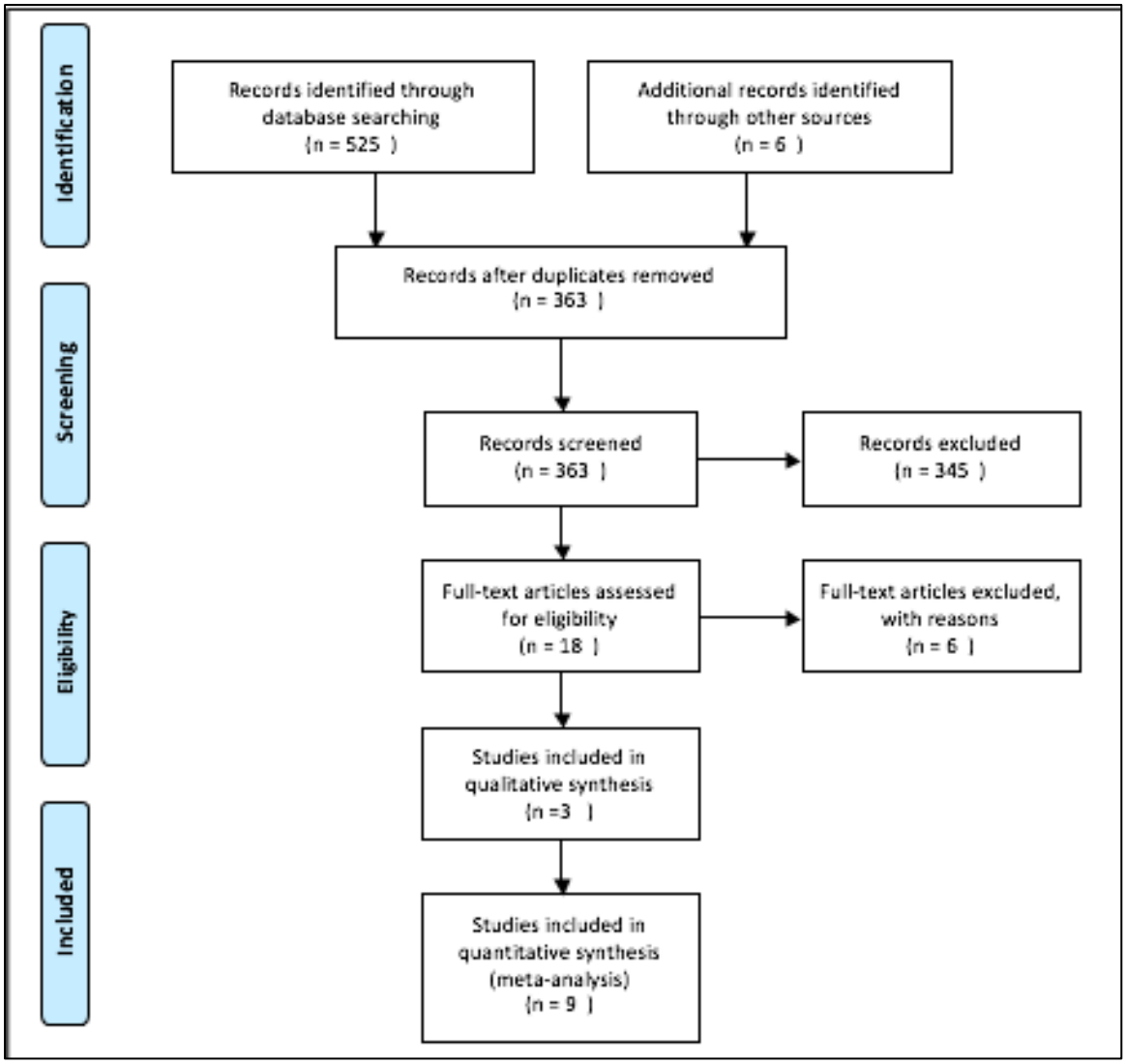

Figure 2: PRISMA Flow Chart Patients Beliefs, Concerns and Fears in Inflammatory Bowel Disease

Table 1: Characteristics of 6 studies investigating patient disease specific knowledge in IBD

Study Authors	**Study design**	**Sample characteristics**	**Knowledge Assessment tool used**	**Results**
Eaden et al (UK 1999)	Cross-sectional Validation of new knowledge questionnaire, subsequent testing	N=354, UC 200 CD 154 Mean age not reported	CCKnow (validation process reported)	Low knowledge scores for patients (comparable with lay persons) Patient misperceptions regarding smoking, medications, fertility, cancer NACC member scores higher ($p<0.0001$) No knowledge difference by disease type or duration
Eaden et al (UK 2002)	Retrospective case control study	N=86; 42 UC Cancer, 44 UC controls Mean age 59.8 years, 68% male	CCKnow (validated)	No association between patient knowledge and development of colorectal cancer in IBD Poor knowledge overall in both groups (only 12% and 18% with "good" score, p=NS) NACC members had higher knowledge scores Frequent misperceptions regarding cancer

Study Authors	Study design	Sample characteristics	Knowledge Assessment tool used	Results
				risk, medications, fertility
Keohane et al (Ireland 2008)	Letter	N/A	N/A	Acknowledgement that patient disease-related knowledge suboptimal in IBD Postulate that widespread confusion amongst IBD patients regarding medications contributes to non-adherence and the use of CAM
Leong et al (Australia and HK 2004)	Prospective comparative study Knowledge, QOL, and CAM use questionnaires administered to Caucasian and Chinese IBD patients in clinic	N= 162; 95 UC, 67 CD 81 Caucasian 81 Chinese Mean age 38 and 41 years 34% and 52% male	Knowledge (21 question) and CAMT questionnaire developed, English and Cantonese, non-validated QOL by IBDQ (validated) Disease activity by CDAI and CAI	Chinese IBD patients had poorer knowledge than Caucasians (p=0.001) Knowledge not associated with QOL CCA membership associated with higher knowledge CAM use and CD associated with higher knowledge among Caucasians More frequent misperceptions among Chinese:

Study Authors	Study design	Sample characteristics	Knowledge Assessment tool used	Results
				aetiology, smoking Longer disease duration associated with improved knowledge in Chinese patients Beliefs differed by culture: Chinese more likely to believe in benefit from herbal medicine in IBD treatment (p=0.012), and differed by source of IBD information
Sood et al (India 2001)	Cross-sectional Questionnaire assessing knowledge and seeking views regarding CAM use and medication adherence	N=145 (UC) 48% male Mean age at onset 31 years	Non-validated questionnaire in 2 parts in English, Hindi, or Punjabi	80% subjects had "low" or "very low" knowledge High rates of misperception regarding aetiology, cancer Poorer knowledge was associated with increasing CAM use (p<0.0001) Higher knowledge levels associated with higher medication adherence (p<0.0001) 78% of subjects decreased or

Study Authors	Study design	Sample characteristics	Knowledge Assessment tool used	Results
				stopped IBD medications when symptom-free Disease duration positively correlated with knowledge
Verma et al (UK 2001)	Cross-sectional, 2 questionnaires (QOL and Patients Information Score)	N=168 UC=91, CD=77 Mean age 45.5yrs	Knowledge questionnaire not validated, QOL questionnaire valid	75% CD vs 53% UC "well-informed" (p=0.006) NACC members higher knowledge scores (p=0.0006) No association between knowledge and QOL Many misperceptions regarding smoking, medications, immunisation

Table 2: Quality Appraisal of included knowledge studies of Quantitative Design

	Eaden et al 1999	**Eaden et al 2002**	**Keohane et al 2008**	**Leong et al 2004**	**Sood et al 1999**	**Verma et al 2001**
Representative sampling?	Random sampling from tertiary IBD database	Patients with UC and colon cancer, same database as 1999 study (different patients)	N/A	Chinese and Caucasian IBD patients in tertiary hospital outpatients in HK and Australia	Tertiary hospital inpatients or outpatient	Tertiary IBD outpatient clinic
Numbers studied?	N=354 RR=55%	N= 86 RR 60% (Ca), 44% (controls)	N/A	N=162 Power calculation reported 5 excluded of 167 approached	N=145 RR unknown	N= 168 RR= 66%
Validity of assessment tool?	Yes, validation reported	Yes	N/A	No (knowledge)Yes (disease activity and QOL)	No	No
Adjustment for confounders?	NACC membership disease type	NACC membership, cancer stage, gender, age, educational level	N/A	Disease activity, occupation, education, disease duration	Age, sex, education level, marital status, occupation data collected (without	Smoking, surgery, immunosuppressant therapy, NACC membership

	Eaden et al 1999	Eaden et al 2002	Keohane et al 2008	Leong et al 2004	Sood et al 1999	Verma et al 2001
					statistical adjustment)	
Limitations	After factor analysis, 6 questions of lower discriminating value excluded – topics cancer, steroids, smoking (likely to have clinical importance)	Bias related to timing of knowledge assessment (cross-sectional) – may have been poor at cancer diagnosis and improved during treatment	Letter only. Limited evidence linking poor knowledge with medication no adherence and CAMT use	Knowledge test not validated in both languages used	May have limited generalisability to Western IBD populations, knowledge assessment tool not validated	Knowledge assessment tool not validated, arbitrary cut-off for satisfactory knowledge Some clinically important areas of misperception reported with high frequency among patients, but as not measured using sub-scores, overall score could be satisfactory in the presence of management influencing misinformation

Table 3: Characteristics of 9 quantitative studies investigating patient beliefs, concerns and fears regarding IBD

Study Authors	**Study design**	**Sample characteristics**	**Beliefs / Concerns Assessment tool used**	**Results**
De Rooy et al (Canada 2001)	Cross-sectional questionnaire - demographics, disease data and concerns	N=241 Mean age 35.5 years 42.7% male	Rating Form of IBD Patient Concerns (RFIPC)	Most intense concerns physical (energy level, medication effects) and psychosocial (achieving potential, being a burden on others) Disease duration not associated with concern level Factor analysis revealed 3 main concern themes: body image and interpersonal concerns, physical impact, and disease stigma High concerns levels associated with impaired wellbeing Age and education affected some individual concerns but not overall scores
Drossman et al (USA 1991)	Cross-sectional questionnaire – standardisation of new concerns tool reported, and survey of psychological distress	N=991 UC = 320 CD = 671 Mean age 42.8 years	RFIPC (validation reported) Sickness Impact Profile (Validated)	Highest concern level in women, patients with increased disease severity, and lower educational status. Four concern indices developed after factor analysis Some concern indices positively associated

Study Authors	Study design	Sample characteristics	Beliefs / Concerns Assessment tool used	Results
				with perceived health and wellbeing, psychological distress, and Sickness Impact Profile
Goldring et al (US 2002)	Cross-sectional study testing a model of treatment decision-making in IBD	N=218 (57%CD)	No	Health beliefs strongest predictor of medication intentions Recommendation by the physician predicted intention mainly in the setting "Shared decision-making" relationship between patient and physician
Levenstein et al (Italy 2001)	International multicentre cross-sectional questionnaire	N=2002 (57%CD) Mean age (range 34.5 to 45.2 years across cohorts) 53% to 38.1% male)	RFIPC	Sociocultural differences in disease-related concern levels overall were noted in Europe Specific areas of higher concerns vary by country
Maunder et al (Canada 1999)	Post hoc analysis of 3 previous cross-sectional studies of IBD patient concerns	N= 343 (157 CD, 186 UC) Mean age 36.5 years 43% male	RFIPC	Women have higher RFIPC scores than men, indicating higher concern levels overall Specific concerns greater in women related to body image, attractiveness, feeling alone, and having children

Study Authors	Study design	Sample characteristics	Beliefs / Concerns Assessment tool used	Results
Moser et al (Austria 1995)	Cross-sectional questionnaire Patient concerns, perceived information level, demographic data, and disease activity	N=105 (72CD, 33UC)	RFIPC Disease activity by CDAI and CAI Perceived information score (proxy for disease knowledge)	Poor correlation between concern level and disease-related data (activity, severity, type, duration, location, and medication) Greater concerns associated with lower perceived information levels
Moser et al (Austria 1996)	Cross-sectional questionnaire Patient concerns, perceived information level, demographic data, and disease activity (same sample as 1995 study) Questions regarding type and use of CAMT	N=105 (CD 72 UC 33) Mean age 32 years 38% male	RFIPC Disease activity by CDAI and CAI Perceived information score	34% patients used CAM in addition to conventional therapy Concern type predictors of CAM use: feeling out of control, being treated as different, and having surgery No difference in overall concerns score between CAM users and non-users Longer disease duration associated with higher CAMT use No association between perceived patient information level and CAMT use
Mussell et al (Germany 2004)	Cross-sectional questionnaire Patient concerns, illness coping,	N=72 (47CD, 25 UC) Mean age 42 years	RFIPC (German translation)	Women greater concern levels than men

Study Authors	Study design	Sample characteristics	Beliefs / Concerns Assessment tool used	Results
	locus of control, disease variables, psychological symptoms		Disease activity by CDAI or CAI Freiberg questionnaire on coping with disease Illness and Health Locus of Control Scale Symptom Checklist (SCL-90) for psychological symptoms Freiberg complaint list (FCL) for somatic symptoms	No difference in concerns by disease type Coping style (depressive coping) had the greatest predictive value for higher concerns, more influential than demographic or disease-related variables
Rawsthorne et al (Canada 1999)	International multicentre cross-sectional questionnaire CAMT use patterns and attitudes	N=289 (51% CD) 53% male	Questionnaire seeking demographic information and CAMT use patterns and attitudes (non-validated)	51% of IBD patients reported using CAMT, with regional variation (more in North America than Europe) CAMT predictors were more likely to be single, have higher income, and be urban dwellers Age, gender, and disease type or duration were not associated with CAMT use Attitudes associated with CAMT use were:

Study Authors	Study design	Sample characteristics	Beliefs / Concerns Assessment tool used	Results
				dissatisfaction with conventional therapy, viewing hospitals as dangerous, view that alternative therapists should work in hospitals, and view that their medical situation was hopeless

Table 4: Characteristics of IBD patient beliefs, concerns and fears studies of qualitative design

Study Authors	Study design	Sample characteristics	Method of data collection	Results
Hall et al 2007 (UK)	Semi-structured interviews and focus groups to understand IBD patient medication beliefs	58 IBD patients scoring in lowest quartile for QOL by UK-IBDQ	Iterative approach – grounded theory principles	Main themes – medication necessity vs concerns, symptom impact, and self-management willingness Adverse effects of IBD medications a major concern affecting treatment decisions Attitudes to medications likely to be medication-specific, and fluctuate with time
Casati et al (Canada 2000)	Thematic review of qualitative literature – patient concerns in IBD (using case studies and	N/A	N/A – methodology of review not reported	Main concern areas identified in reviewed studies included loss of energy, loss of control, body image, fear and isolation, unreached potential, feeling dirty, and lack of medical information received

Study Authors	Study design	Sample characteristics	Method of data collection	Results
	literature review)			
EJ Irvine (Canada 2004)	Thematic review of quantitative and qualitative literature – patient fears in IBD	N/A	N/A – methodology of review not reported	Most prevalent fears across reviewed studies are life expectancy, ability to have a family and/or job, need for surgery, IBD inheritance by children, cancer risk, uncertainty of next flare timing, adverse medication effects, and affordability of treatment Summary of reviewed studies suggested that disease control paramount in reducing "worry" amongst IBD patients Similar concerns across both disease types

Table 5: Quality Appraisal of included Belief and concerns studies of Quantitative Design

	De Rooy et al (Canada 2001)	**Drossman et al (USA 1991)**	**Goldring et al (US 2002)**	**Levenstein et al (Italy 2001)**	**Maunder et al (Canada 1999)**	**Moser et al (Austria 1995)**	**Moser et al (Austria 1996)**	**Mussell et al (Germany 2004)**	**Rawsthorne et al (Canada 1999)**
Representative sampling?	Tertiary IBD outpatients	Community sample of Crohn's Colitis Foundation of America (CCFA) members	Tertiary hospital IBD database	Source of patients varied by local resources	Tertiary IBD outpatients	Tertiary IBD outpatients	Tertiary IBD outpatients	Tertiary IBD outpatients	Tertiary IBD outpatients
Numbers studied?	241 power calculation reported RR unknown	991 RR 83%	218 RR=42%	2002 RR and power calculation not reported	343	105 RR and power calculation not reported	105	72 No power calculation reported	289 No power calculation reported
Validity of assessment tool?	Yes (concerns)	Yes (RFIPC, SIP, and SCL-90)	Yes (IBDQ)	Yes (RFIPC)	Yes (RFIPC)	Yes (RFIPC) Yes (CDAI and CAI)	Yes (RFIPC) No (CAM usage	Yes (RFIPC, Locus of Control	No (Questionnaire assessed attitudes towards

	De Rooy et al (Canada 2001)	Drossman et al (USA 1991)	Goldring et al (US 2002)	Levenstein et al (Italy 2001)	Maunder et al (Canada 1999)	Moser et al (Austria 1995)	Moser et al (Austria 1996)	Mussell et al (Germany 2004)	Rawsthorne et al (Canada 1999)
	No (symptom severity)	No (disease severity)				No (perceived information level)	and perceived knowledge)	scale, SCL-90, FCL)	CAMT in IBD)
Adjustment for confounders?	Analysis controlling for age, gender, education, symptom severity	Regression analysis controlling for gender, age, education, disease type, disease severity	Hierarchical regression included previous treatment, threat, cost benefit, QOL, patient doctor relationship type, physician recommendation	No, not possible due to study design	Adjustment for disease severity	Age, gender, disease type and duration, disease severity	Age, gender, disease type and duration, disease severity	Regression analysis adjusting for age, sex, disease type, duration and activity, coping variables	Regression analysis adjusting for age, gender, and disease type and duration
Limitations	Divergent factor analysis results compared with Drossman et	Potential selection bias - community sample likely has milder	Hypothetical study in which medication described was oversimplified	Validity of RFIPC not established in all languages across countries	Post hoc assembly of sample limited data analysis	Disease knowledge assessed using a non-validated measure by	CAMT definition included special diets	Sample relatively small and no power calculation reported, although	CAMT definition broad (included exercise, prayer, counselling,

	De Rooy et al (Canada 2001)	Drossman et al (USA 1991)	Goldring et al (US 2002)	Levenstein et al (Italy 2001)	Maunder et al (Canada 1999)	Moser et al (Austria 1995)	Moser et al (Austria 1996)	Mussell et al (Germany 2004)	Rawsthorne et al (Canada 1999)
	al may suggest lower generalisability. Disease Severity Index not validated or objectively verified	disease and different concerns. No objective disease activity assessment		surveyed. Not possible to control for demographics or disease factors		subjective patient estimate on visual analogue scale rather than objective assessment, no patients reported to have "mild" disease (less generalisable)	Knowledge score subjective patient assessment only	rigorous design otherwise. Few patients with active disease (maximum "moderate" activity) – limited generalisation	massage) may limit generalisability Attitudes not statistically associated with CAM use not reported

Table 6: Quality Appraisal of belief studies of qualitative design

	Hall et al 2007 (UK)	**Casati et al**	**EJ Irvine (Canada 2004)**
Clear Aims?	Yes: explore subjective area of medication beliefs among IBD patients	Yes: to identify issues of concern to IBD patients	Yes: to identify issues of importance to IBD patients, and barriers to needs being met
Rigorous methodology? **Recruitment strategy** **Reliability of data collection method**	Yes IBD patients with low QOL Systematic, context outlined, triangulation used	Not systematic but thematic review using case study examples	Not systematic but thematic review
Data analysis systematic?	Yes, systematic based on grounded theory principles Analysis rich and reliable – context well described, authors carried out individual coding	No	No
Clearly presented findings?	Yes, perceived necessity weighed against concerns Findings integrated with current literature	Yes, 8 categories of concern identified from reviewed studies	Yes, 8 common concern themes identified

CHAPTER 3: FEAR AND FERTILITY IN INFLAMMATORY BOWEL DISEASE – A MISMATCH OF PERCEPTION AND REALITY AFFECTS FAMILY PLANNING DECISIONS

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R Mountifield was involved in study conception, design, seeking ethical approval, data acquisition, analysis and interpretation, drafting the manuscript and modifying and preparing the final paper. JM Andrews and P Bampton were involved in planning the study, seeking ethical approval and revising the draft manuscript. K Muller assisted with data interpretation and R Prosser with data entry.

Abstract

***Background*:** Smaller family size and voluntary childlessness has been reported in IBD, however the disease-related reasons for this from a patient viewpoint are not described.

***Aim*:** To 1) determine whether IBD patients' perceptions of the issues surrounding IBD, pregnancy and childbearing influence their reproductive behaviour, and 2) describe these specific perceptions and concerns related to fertility and pregnancy.

***Method*:** All contactable subjects between 18-50 years of age from a hospital based IBD database were surveyed by postal questionnaire. Data were obtained regarding age, gender, IBD diagnosis and treatment, body image and sexual relationships, as well as both objective and subjective data regarding fertility and pregnancy. Comparisons were made to community norms where data were available. Contingency tables with Fisher's exact test were used.

***Results*:** Of 365 subjects, 255 responded (70%). Mean age was 35.5 years overall, 34.7 years for women. 34% of participants were male, 127 had Crohn's Disease (CD), 85 Ulcerative Colitis (UC) and 5 Indeterminate Colitis (IC). The average fertility rate was no different between women with CD and UC (1.0 and 1.2 births/woman respectively; p=0.553), compared with 1.81 for all Australian women. Although 42.7% of IBD patients reported a fear of infertility, patients only sought medical fertility advice at the same rate as the general population. Fear of infertility was most evident in women, those with CD and those reporting previous surgery. Specific patient concerns, which appear to have decreased

patients' family size, included IBD heritability, the risk of congenital abnormalities, and medication teratogenicity.

***Conclusions*:** The unusually high response rate indicates the centrality of reproductive issues to IBD patients. "Voluntary" childlessness in this group appears to result from concerns about adverse reproductive outcomes that may not be justified. Patients require accurate counselling addressing fertility and pregnancy outcomes in IBD to assist in their decision making.

Introduction

Inflammatory Bowel Disease (IBD) commonly affects patients during their reproductive years, making the interaction between fertility, pregnancy and IBD an important issue for both genders. Despite the postulated interaction between a diagnosis of IBD and family planning decisions, there is a paucity of data in this area, particularly from the patients' perspective. The published literature predominantly addresses pregnancy outcomes or is limited to population based estimates of fertility and congenital abnormalities[70].

Studies in male and female IBD patients have not demonstrated great differences in fertility (the capacity to conceive or induce conception) when compared with the general population [71] [72] [73] [74], with the exception of notable subgroups. Active bowel inflammation appears to have a small detrimental effect on male[75] and female fertility[76], as do some surgical procedures such as rectal excision and pouch formation, although the literature is conflicting [77] [78]. Previous data suggest that high disease activity at conception increases infant risk of prematurity and low birth weight[73] [79], this may be minimized by planning conception during IBD remission.

IBD medications have not been shown to affect fertility in women[80], but reversible male infertility with sulfasalazine[76] [81-83] and methotrexate[84] is documented. These agents are easily avoided in modern IBD management, and should not necessarily influence reproductive opportunities.

To date, studies on reproductive decisions and family size have been observational[85] and thus do not inform us of patient perceptions or intentions with regard to the interaction between IBD and family planning.

"Voluntary childlessness" has been described in IBD[19]. However, whether this was due to IBD itself or to particular characteristics of the cohort (predominantly Caucasian, higher educational achievement) is uncertain. Despite this report, and Mayberry et al's observation about male IBD patients' family size, specific IBD-related reasons for having fewer children have not been specifically explored from a patient perspective. Given the fact that fertility appears to be reduced in only a small subset of IBD patients, it may be that "voluntary childlessness" is the main cause of the reduced fertility rate (number of live births per woman) reported in the IBD literature. We therefore sought to examine individual patient's perceptions of the interaction between their diagnosis of IBD and fertility and pregnancy issues, and how these perceptions affected their behaviour with regard to reproductive choices.

Aim

The specific aims of this study were to 1) understand whether, and to what extent IBD patients' perceptions of risk influence their reproductive behaviour, and 2) describe IBD patients' specific concerns related to fertility and pregnancy.

Methods

Subjects and Recruitment

All patients aged 18 to 50 years from a tertiary hospital based IBD database were surveyed by postal questionnaire (Appendix B). Each questionnaire was mailed with an invitation letter and "opt out" slip (Appendix C). After 4 weeks an IBD Project Officer not involved in direct patient care (RP) made 2 attempts to contact each non-responding patient by phone to establish receipt of the questionnaire, and encourage its completion or return of the opt out slip. The total data collection period was 13 months.

Survey content

The questionnaire sent to subjects was entitled “Quality of Life, Body Image, Sexual Function and Pregnancy in Inflammatory Bowel Disease: A survey of patients in their reproductive years” (Appendix B). It consisted of 94 questions divided into 4 sections; Parts A and B addressed body image and Sexual Function, Part C Fertility and Part D pregnancy outcomes. Data pertaining to patient age, gender, disease type and duration and previous surgery were also obtained. Many questions required free text qualification and subsection answers. As a result, a large amount of data was gathered and this paper reports only section C results. Data regarding Body Image and Sexual Function and also Pregnancy are presented elsewhere[21, 86].

The Fertility section of the questionnaire comprised both objective and subjective components, with multiple choice “check-box” and free text response fields. As this is a relatively unexplored area within IBD, there are no validated assessment tools available to apply, and as such no formal pilot validity testing was performed. Questions arose from concerns and ideas expressed by IBD patients and physicians over many years of collective clinical experience. Male and female subjects were asked to report how many children they had (live births), how many they wished to have, whether conception had been difficult, whether they feared infertility and the reasons for this, and whether they had received medical consultation about fertility and IBD. Patients were asked about previous IBD surgery, termination of pregnancy and the reasons for termination. Where available, population data were obtained from the Australian Bureau of Statistics[87] for comparison. Data obtained in Part A such as gender, age, disease type, and relationship status were recorded. Subjects were given an opportunity to offer free text responses describing their thoughts about the interaction between IBD and fertility and pregnancy.

Descriptive data are presented, and comparisons made using contingency tables with Fisher's exact test, except for mean fertility rate data, which were compared using a 2 tailed t-test. In all analyses a p value < 0.05 was considered significant.

Ethics approval for the questionnaire was obtained via the Flinders Medical Centre Ethics Committee (Appendix C and D), with receipt of a completed questionnaire taken as signifying individual patient consent. Each patient had given prior consent to be enrolled on the clinical/research IBD database.

Results

Demographic and Disease Data

365 subjects (146 male [M]; 219 female [F]) fell within the pre-specified age range (18-50 years) and had a current mailing address. Of these, 217 participated and 38 returned the "opt out" slip. 110 did not return the questionnaire despite 3 contact attempts (one postal and two phone attempts). Our final response rate was therefore 70% (255 /365) with a questionnaire completion rate of 59% 217/365. There were 127 respondents with Crohn's Disease (CD), 85 with Ulcerative Colitis (UC) and 5 with Indeterminate Colitis (IC). Overall 34% were male, with a mean age of 35.5 years. The mean age of female respondents was 34.7 years. As expected, a significantly higher proportion of those with CD as compared to UC reported previous IBD surgery (56.7% vs 15.3%, p=0.0001) (Table 7). Respondents were no different to non respondents with regard to disease type, gender and age.

71% of participants returned their questionnaire without need for telephone follow up. The average time taken for questionnaires to be completed and returned was 6 weeks.

Relationship status

Seventy seven percent of all IBD subjects reported being in a current relationship, with 5.5% having never been partnered. This is similar to rates observed in the Australian population. Additionally, rates of sexual intercourse reported by our study population in Section B appeared adequate to allow conception at normal rates, although no local population data are available for comparison addressing intercourse frequency.

Fertility Data

The average fertility rate amongst female IBD patients did not differ amongst those with CD and UC (CD – 1.0 live births per woman vs UC – 1.2; p=0.553). In the same time period, however, the average Australian women's "Total Fertility Rate" (the number of babies a woman would bear during her life if she experienced current age-specific fertility rates at each age of her reproductive life) was 1.81[87] (Figure 3).

Fear of Infertility, Behaviour and Patient Concerns

Overall 42.7% of IBD respondents reported a fear of infertility, with this being greater in patients with CD compared to UC (CD 47.2% vs UC 25.8%) p=0.0032 (Figure 4). Fear of infertility was significantly higher amongst female patients compared to males (F 47/87 (54%) vs M 13/40 (32.5%); p=0.035) (Figure 4). Interestingly, this gender based difference was not seen in UC patients, (F15/52 (28.8%) vs M 7/33 (21.2%) p=0.61). A history of prior surgery appeared to contribute to this fear, as 43/83 patients (52%) who reported a fear of infertility had a history of previous IBD surgery, compared to only 29/111 (26%) patients without a fear of infertility (p=0.0003) (Figure 5).

Despite the highly prevalent reported fear of infertility, only 19.4% of patients reported consulting a doctor for fertility problems, and this did not differ significantly between CD

and UC patients (21.3% vs 15.3%, p=0.27), despite the greater prevalence of this fear in those with CD (as reported above); nor did it differ from the currently estimated rates of fertility consultation for the non-IBD population[88] [89] (Table 8).

Childlessness, Choices, Intentions

Forty-two percent of IBD respondents reported being childless. 14% of childless IBD patients reported making this decision as a direct result of IBD. When considering only respondents with children, approximately one quarter reported having fewer children than desired or planned, with no difference between those with Crohn's disease and UC (CD 24.5% vs UC 23.5%; p=0.9) (Table 8). Directly comparable data are not available for the non-IBD Australian population, although in the developed world, there is an acknowledged gap between the number of children women plan to have and the number they eventually have.

Termination of pregnancy was reported in females with IBD or female partners of male IBD patients in 21 CD and 13 UC respondents (CD 16.5% vs UC 15.3%; p= 0.61), compared with 27% in Australian women without IBD[90] (Table 8). The decision to terminate a pregnancy was directly attributed to IBD in only 6 of the 34 respondents who reported a termination (17.7%). The IBD-related reasons for this decision fall into the areas listed in Table 9.

Forty eight subjects took the opportunity offered in the questionnaire to make subjective "free text" comments on their perceived interaction between fertility/pregnancy/family planning and their disease. IBD-related patient concerns that negatively influenced reproductive decisions could be divided into five themes. (Table 9) Of particular note, in these 48 patients, 17 (35%) reported their doctor advised against pregnancy "because of IBD or IBD surgery"; 14 (30%) described "concern about medication side effects"; 9 (19%) reported fear of congenital abnormalities; 7 (15%) were worried about "the genetic risk of

my child having IBD"; one male on sulfasalazine reported attempting conception for 15 years before being informed of the reversible infertility associated with this agent and one female reported severe IBD related fatigue which she felt would prohibit the care of a child. Other subjects gave adverse social circumstances or other medical problems as the reason for fewer children than desired.

Discussion

This is the first large study to examine this important issue from a patient-centred perspective. Moreover, the high response rate (70%) not only strengthens our data, but also indicates the centrality of these concerns to our patients.

Despite little evidence for decreased fertility (ability to conceive) in the IBD literature[74], our respondents have a lower observed or actual fertility rate (fewer children) than the non IBD population[87]. Our IBD patients demonstrated a much higher rate of concern regarding infertility than the Australian female population (>40% vs 9%[89]). Interestingly, despite lower observed rates of fertility, medical fertility advice was only sought with similar frequency between IBD and non IBD women.[88], suggesting this reduction in fertility may be at least in part "voluntary". This fear of infertility was most evident in those diagnosed with Crohn's Disease, females, and those reporting previous surgery. Of interest, whilst Mahadevan et al reported an increase in adverse conception outcomes in IBD patients with previous surgery compared with non IBD patients (OR 2.26 (1.12-4.55)[91], there was no difference in conception outcome between operated and non operated IBD subjects. Whilst there are other data supporting adverse effects of any IBD surgery on fertility, the rate of fear affecting decision making in our surgical patient population appeared disproportionately high.

These findings offer new and more generalizable insights into reproductive decision making in patients with IBD due to the very high response rate to our questionnaire (70% compared with approximately 20% in previous similar studies[19]. Additionally, our questionnaire's subjective, open ended nature, which allowed patients to report their own responses without categorical limitation, has added a greater depth of understanding in this area. Although "voluntary childlessness" in IBD patients has been previously reported[19] it was attributed to non-IBD (demographic) factors. Our data offer an open exploration of the IBD related concerns patients feel negatively influence or constrain their reproductive choices.

Interestingly, IBD-related reproductive risk appeared to be overestimated by our respondents, and this misperception seemingly altered their subsequent reproductive behaviour. To address respondents' specific concerns, the current literature suggests no overall fertility reduction and only slight increase in the risk of adverse pregnancy outcomes in most IBD subgroups[76]. As physicians, we need to more accurately communicate this message to our patients.

A recent population based meta-analysis suggests a 1.87 fold increase in prematurity in all IBD patients, a 2 fold increase in low birth weight (LBW), and a 1.5 fold increased risk of Caesarean section in Crohn's patients[70]. Importantly, however, population based, case control studies suggest no increase in more serious adverse outcomes including still birth, neonatal death and spontaneous abortion[92, 93] . Whilst most published data do not associate IBD with a risk of congenital abnormalities[94] [95], two studies suggested a slight increase in congenital abnormalities in patients with Ulcerative Colitis (UC) but not Crohn's Disease (CD)[96] [97], however, this risk, if present is very low, and certainly not of a magnitude to justify a medical recommendation to avoid reproducing.

Although long term safety data are not yet available for the biologic agents, accumulating evidence suggests a moderately favourable safety profile for most IBD medications[76]. Pooled analysis suggests no significant increase in the risk of still births, ectopic pregnancies, spontaneous abortions or Low Birth Weight (LBW) infants for 5-ASA agents, corticosteroids, azathioprine, anti-TNF agents, and cyclosporine[98]. A small increase in congenital abnormalities was noted for 5ASA, anti TNF agents and azathioprine[98], as well as a slightly increased risk of cleft palate with the use of systemic steroids in pregnancy. Most antibiotics are considered safe for brief periods in pregnancy, except for tetracycline, ciprofloxacin and sulphonamides. Breast feeding should be encouraged in most IBD patients, with exceptions for patients on thiopurines, methotrexate and cyclosporine[76] .

Regarding patients' fear of IBD inheritance, current data suggest that IBD does have a partial genetic component with disease concordance higher in monozygotic than dizygotic twins[100]. One parent with IBD confers a 2-13 fold higher risk of disease compared with the general population.[101] [102] . Looking at this from the converse, it should be emphasized that the risk of a child not having IBD is always far greater than the risk of a child developing IBD (>91% for one affected parent and >60% even if 2 parents are affected). It is important to emphasize to patients that a family history is neither necessary nor sufficient to predict IBD in their offspring, the absolute risk of UC and CD remaining low, at 1.6% and 5.2% respectively, being slightly higher in Jewish populations[19].

Somewhat disappointingly, several subjects attributed their negative reproductive decisions to medical advice. Unfortunately, one male patient reported unawareness of sulfasalazine induced infertility whilst trying to conceive for 15 years. A surprising number of other subjects reported receiving generic medical advice indicating that IBD or IBD surgery

rendered them infertile. The proportion of patients receiving such advice far exceeded the expected proportion of medically infertile patients in our sample. This tendency has been noted previously, in 1986, when more than 50% of IBD patients were counseled against having children by their physicians, and a similar proportion reported advice to terminate pregnancies for IBD related reasons[103]. More recent data published in 2007, suggest that 68% of IBD patients discuss reproductive issues with their IBD physician at some stage[19], providing an ideal opportunity for accurate education and correction of misperceptions.

Despite the fact that our study subjects were known to a tertiary hospital IBD Service, with access to specialist Gastroenterology care and a full time IBD Nurse, the level of misinformation was high. Patients whose IBD care is entirely community based may have even lower levels of IBD knowledge and thus an even higher rate of misperception regarding their reproductive risk. Physicians should instigate discussion about reproductive issues as part of routine IBD care in the under 50's, especially when treating women, those with Crohn's disease and those with previous IBD surgery.

The enthusiasm shown by IBD patients in returning the questionnaire highlights the importance of reproductive issues in this group, and the pressing need to incorporate realistic discussion and education into the IBD consultation. Patients should be encouraged to seek reproductive advice to address fears, and physicians should liaise with obstetric colleagues to provide individualized and specific counseling regarding fertility and pregnancy planning.

Tables and Figures

Table 7: Respondent Characteristics

	Crohn's Disease N (%)	Ulcerative Colitis N (%)
Male	39 (31%)	33 (39%)
Mean Age (years)	35.1	35.9
Mean Duration of Disease (years)	12.9	11.2
Previous IBD Surgery	72 (56.7%) *	13 (15.3%)
Current Relationship	96/127 (76%)	67/85 (79%)

***p=0.0001**

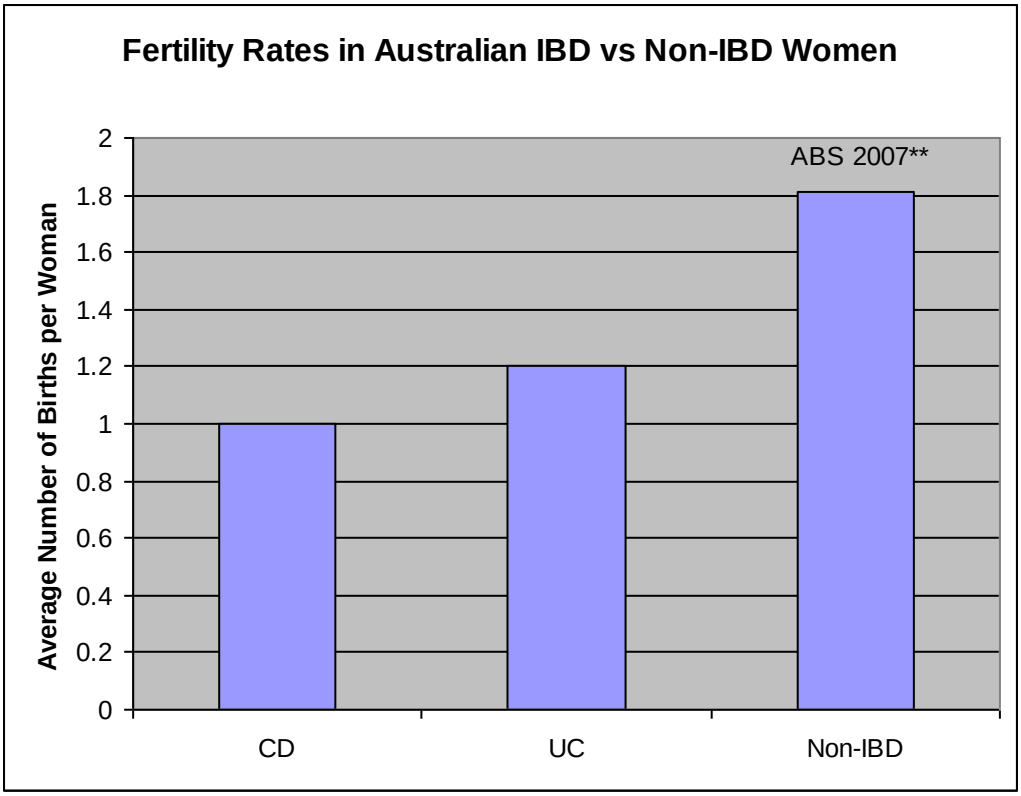

Figure 3: Fertility Rates in Australian Women with Inflammatory Bowel Disease versus Women without Inflammatory Bowel Disease

** Government of Australia. Australian Bureau of Statistics. Adelaide 2007

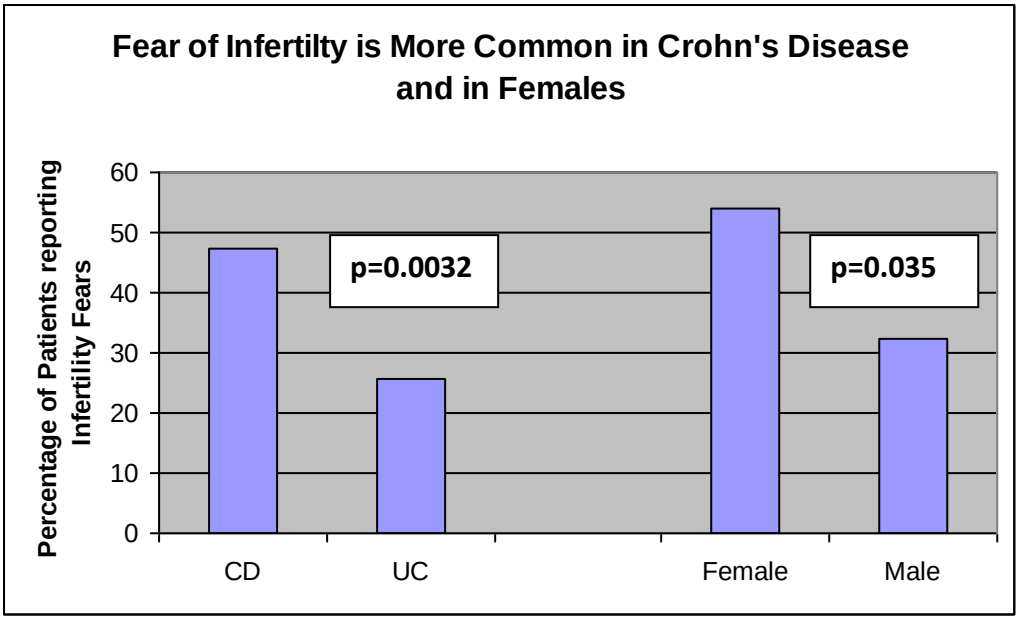

Figure 4: Fear of Infertility is more common in Crohn's disease and in females

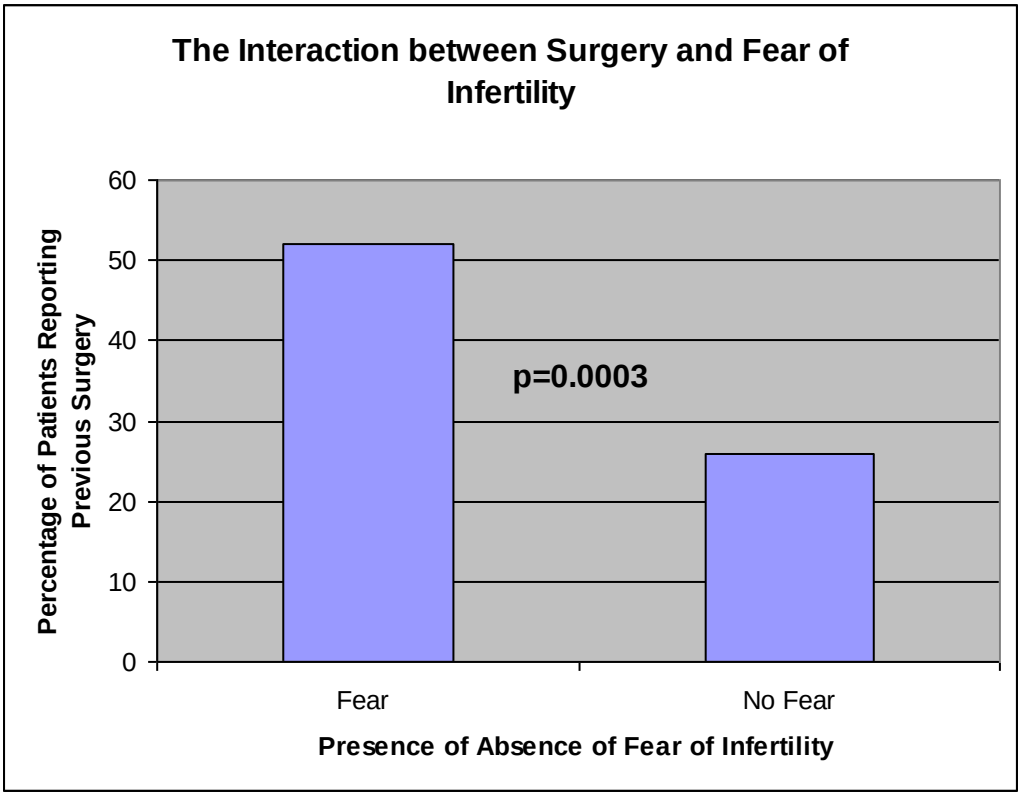

Figure 5 The Interaction between Surgery and Fear of Infertility

Table 8: Fertility Data

	Crohn's Disease	Ulcerative Colitis	Non IBD population
Never had children	62/127 (49%)	27/85 (32%)	24%[87]
Medical fertility opinion	27 (21.3%)	13 (15.3%)	20-26.4%[88, 89]
Difficulty conceiving	27 (21.6%)	18 (20.8%)	20-26.4%[88]
Fearing lack of fertility	60 (47.12%)	22 (25.8%)	*N/A
Fewer children than desired	31 (24.5%)	20 (23.5%)	#N/A
Termination of pregnancy (ToP)	21 (16.5%)	13 (15.3%)	27%[90]
ToP attributable to IBD	4 (3%)	2 (2.4%)	-

Population data not available

Table 9: Patient reported reasons for Voluntary Infertility in IBD

Area of Patient Concern	**N(%)**
Fear of IBD related congenital abnormalities	9(18%)
Concern about genetic risk of IBD in child	7(15%)
Concern about medication teratogenicity (Methotrexate and non-methotrexate)	14(30%)
Medical advice that conception not possible / inadvisable with IBD	17(35%)
IBD related fatigue prohibitive	1(2%)

CHAPTER 4: PREGNANCY AND IBD TREATMENT - THIS CHALLENGING INTERPLAY FROM A PATIENT PERSPECTIVE

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R Mountifield was involved in study conception, design, seeking ethical approval, data acquisition, analysis and interpretation, drafting the manuscript and modifying and preparing the final paper. JM Andrews and P Bampton were involved in planning the study, seeking ethical approval and revising the draft manuscript. K Muller assisted with data interpretation and R Prosser with data entry.

Abstract

***Introduction*:** Current data suggest exacerbations of Inflammatory Bowel Disease (IBD) during pregnancy worsen perinatal outcomes. However, patient perceptions regarding the interaction between pregnancy and IBD management are unexplored.

Aims: To (1) obtain pregnancy outcome data from local female IBD patients, and (2) to gain insight into patients' understanding of the interaction between IBD and pregnancy, and how this affects medication-taking behaviour.

Methods: Female IBD subjects aged 18-50 years were surveyed by questionnaire. This large retrospective study sought patient reported pregnancy outcomes and examined the relationship between major adverse outcomes, IBD activity and treatment. Subjective data regarding patient perceptions about IBD management and pregnancy were sought.

Results: 219 females were surveyed, 143 completing a questionnaire (68.1%). 342 pregnancies occurred, 298 for which outcome data were available. Overall IBD women reported adverse pregnancy outcome rates comparable to the local population. Major adverse outcomes were more frequent in the subgroup with severe disease during pregnancy (5/14 (35.7%) than those with inactive disease (14/284(4.9%), (OR 6.8 (95% CI 1.7-26.3), p= 0.006) Adjusting for disease severity, neither corticosteroid, azathioprine nor 5ASA affected pregnancy outcome.

Most female patients (84%) reported (unwarranted) concerns about the effect of IBD medications on pregnancy, free text responses indicating that this was of greater concern than any effect of IBD exacerbation.

Conclusions: Unwarranted fear of adverse medication effect on pregnancy is highly prevalent in women with IBD, yet awareness of the harmful effect of IBD exacerbation during pregnancy is poor. This information gap between patients and their gastroenterologists warrants attention.

Key Words*:* Inflammatory Bowel Disease, Pregnancy, Severity, Corticosteroids

Introduction

The interaction between Inflammatory Bowel Disease (IBD) and Pregnancy is of great importance, as disease onset often coincides with peak reproductive years, one quarter of patients conceiving after their IBD diagnosis[104, 105].

Whilst pregnancy is not thought to affect the activity of Inflammatory Bowel Disease (IBD)[79, 106-108], numerous studies suggest exacerbations during pregnancy worsen pregnancy outcomes, particularly increasing the incidence of Low Birth Weight (LBW)[103, 109-111]. Therefore, good disease control and compliance with medication documented to maintain remission is paramount.

Most IBD medications are regarded as less deleterious to pregnancy outcome than the risk of disease exacerbation during pregnancy[112-117], although a spectrum of potential teratogenicities is recognized. Sulfasalazine, corticosteroids[118] and probably 5ASA agents, for example, are not thought to confer an increased fetal morbidity or mortality amongst pregnant IBD patients, whilst Azathioprine and 6-Mercaptopurine (6MP) have produced a small increased risk in spontaneous abortion and fetal abnormalities in rats but in small studies have been found to be safe in humans[114]. Experience with the biologic agents is limited but preliminary data suggest the incidence of fetal abnormalities is not increased in patients taking Infliximab during pregnancy[98]. The main exception to the general safety of IBD medications in pregnancy is that of Methotrexate, which is widely known to be teratogenic.

Previous research addressing the interaction between pregnancy and IBD has primarily been population or hospital based and focused on birth outcomes from administrative databases of IBD patients. Few data address how women with IBD in the community view the

interaction between IBD, its treatment, and their own experience of pregnancy. Individual women are ultimately responsible for decision making regarding their IBD management during this time, and physician advice is more likely to be adhered to if women feel their concerns are understood by their doctor.

This observational study therefore sought to ascertain local pregnancy outcome data amongst women with IBD. Importantly, it also explored female patients' beliefs about the interaction between pregnancy and IBD management, and examined how these perceptions affected medication-taking behaviour.

Aims

To (1a) obtain pregnancy outcome data from local female IBD patients and (b) identify risk factors for adverse outcomes such as IBD activity or medication use during pregnancy, and (2a) to gain insight into patients' perceptions of the interaction between IBD and pregnancy, and (b) to assess how this affected women's medication-taking behaviour.

Methods

All contactable subjects 18-50 years of age from a hospital based IBD database were surveyed by postal questionnaire, with two telephone reminders one month after initial postage where no response was obtained. The questionnaire was entitled *"Quality of Life, Body Image, Sexual Function and Pregnancy in IBD: A survey of patients in their reproductive years."* (Appendix B). This large cross sectional study contained 4 parts, encompassing patient perceptions of body image, sexuality, fertility and pregnancy in both genders. Data concerning body image, sexuality and family planning are reported elsewhere[86, 119]). Here we report on pregnancy data from female subjects, covered in Part D of the survey.

This information was gathered by retrospective report by subjects and unless responses were unclear or appeared inconsistent, they were not independently verified or re-confirmed with subjects. The survey was initially tested on a small number of IBD patients to verify the clarity of instructions and ease of question understanding.

Subjects were asked 61 questions in Part D of the questionnaire, requesting a variety of categorical answers interspersed with the opportunity for free text responses. Demographic and disease data were taken from Part A of the questionnaire, with information regarding disease activity during pregnancy obtained by patient recall and classified as severe or non-severe.

Females were asked how many times they had been pregnant, the outcome of each pregnancy (ie termination of pregnancy, miscarriage, stillbirth, healthy baby) and asked to give details about any adverse pregnancy outcomes they reported. The number of pregnancies occurring after pouch formation was reported, as well as patient recall of IBD severity during each pregnancy, and whether surgery or admission was required. Subjects reported which medications they took for IBD during each pregnancy, whether they changed their medications, and estimated how often they missed medication doses during pregnancy. For any changes that were self-initiated rather than being physician-led, women were asked to state the reasons for these self-management decisions. A free text area was provided and subjects encouraged to expand upon their answers giving details about their pregnancy experiences and thoughts regarding the interaction with IBD.

After reviewing patient responses two investigators (RM and RP) divided reported adverse events into major and minor groups, whereby major included fetal malformations, low birth weight, pre-term labour or any permanent defect or problem requiring ongoing

management (See Table 1). Problems classified as “minor or unrelated” included brief neonatal jaundice, labour and breast feeding difficulties and successfully treated Rhesus incompatibility.

Descriptive data are presented, comparisons made using contingency tables with Fisher’s exact test. In all analyses a p value <0.05 was considered significant. Multiple logistic regression analyses were performed to test independence of disease severity and steroid use during pregnancy.

Ethics approval for the questionnaire was obtained via the Flinders Medical Centre Clinical Research Ethics Committee (Appendix C and D), with receipt of a completed questionnaire taken as signifying individual patient consent. Each patient had given prior consent to be enrolled on the clinical / research IBD database.

Results

Demographic and Disease Data

219 females were surveyed, 143 returning a completed questionnaire (68.1%). The mean age of female subjects was 35.5 years (range 20-50 years), 128 women having CD (59%), 86 UC (39%) and 5 Indeterminate Colitis (IC) (2%). 342 pregnancies occurred (183 in CD, 151 in UC and 8 in IC women,) 298 for which complete outcome data were reported (Figure 6). Of the remaining 44 pregnancies, 40 (27 CD and 13 UC) were deliberately terminated for non-medical reasons, and 4 pregnancies were ongoing at the time of survey.

Pregnancy Outcome Data

Of the 298 pregnancies not deliberately terminated, 154 were in CD women, 138 to women with UC and 6 with Indeterminate Colitis (IC). Two sets of twins were reported, one set born to a CD woman and the other to a woman with UC. The average fertility rate for

women reporting at least one previous pregnancy was 1.78 births overall (1.67 for CD and 1.94 for UC.) The average fertility rate for all females surveyed in this cohort has been reported elsewhere (Mountifield et al[119]) and was 1.18 births per woman. 4 patients reported surgery for pouch formation, (3UC, 1 CD), 2 of whom had completed pregnancy prior to surgery, and 2 of whom had never been pregnant.

Of the 298 pregnancies with known outcomes, 213 resulted in healthy neonates, and 85 "adverse outcomes" were reported by subjects. After review of each "adverse outcome" it was deemed that 20 events were "major" and 65 "minor". Minor adverse outcomes included neonatal problems including transient jaundice, sleeping or feeding difficulties, reflux, eczema, Rhesus incompatibility and lactose intolerance. Although reporting of minor problems was encouraged and a large proportion of women reported these, our results were calculated using the frequency of major adverse pregnancy outcomes, detailed in Table 10.

Risk Factors for Adverse Pregnancy Outcomes

Overall our IBD cohort reported a frequency of major adverse events similar to the local non IBD population. Subgroups of IBD women, however, appeared to have higher rates of major adverse outcomes compared with their IBD peers.

Disease Activity During Pregnancy

14 pregnancies were to women reporting severely active disease during pregnancy, 8 requiring hospital admission but none requiring surgery. In this severe group, 8 pregnancies were exposed to steroid. Of the 6 pregnancies not steroid exposed, ongoing active disease was treated using increased Azathioprine dosage in 2 patients, commencement of 6-Mercaptopurine in 1 patient, and a short Cyclosporine course in a further patient, whilst

non steroid management method was not volunteered by the remaining 2 patients. Major adverse outcomes were more frequent in those with severe disease during pregnancy (5/14 (35.7%) than those with mild or inactive disease (15/284(5.3%), (p=0.0009) (Figure 7). When adjusting for steroid use on logistic regression analysis, severe disease during pregnancy still had a significant negative effect on pregnancy outcomes, OR 6.8, (95% CI 1.7-26.3), p= 0.006

IBD Medication Exposure During Pregnancy

Of the 298 pregnancy outcomes reported, medication data were incomplete for 61, leaving 237 pregnancies available for analysis with regard to medication exposure.

161 pregnancies were not exposed to any IBD medication. Major adverse effects were reported in 9 (5.6%) of these 161 pregnancies, with similar rates amongst CD and UC women (5.9% vs. 5.3%, p=1.0). Severe disease activity during pregnancy was much less common in these patients on no medications (2/161) than those on any IBD medications (12/136) during pregnancy (1.2% vs. 8.8%, p=0.0041).

33 pregnancies were exposed to oral or IV corticosteroids. Major adverse pregnancy outcomes were increased in the group receiving steroids compared to those pregnancies not exposed to steroid (6/33 (18.2%) vs 14/253 (5.5%); p=0.02) (Figure 8). Steroid exposed patients were more likely to have had severe as compared to mild or inactive disease activity during pregnancy in both CD (29.4% vs. 2.3%, p=0.0006) and UC (18.8% vs. 3.1%, 0.038). Not surprisingly, rates of steroid use were higher in those with severe, active disease during pregnancy (57.1 vs. 9.4%, p=0.0001). Interestingly, patients with severe disease activity during pregnancy had the same rate of major adverse effects whether they did (3/8) or did not (2/6) receive steroid therapy (37.5% vs. 33.3%, p=1). Multiple logistic regression

analysis confirmed the confounding effect of disease severity on the relationship between steroid exposure during pregnancy and adverse outcomes. When adjusted for disease severity, there was no significant difference in major adverse outcomes in women receiving / not receiving steroids during pregnancy OR=2.2 (95% CI 0.7-7.5, p=.193)

Azathioprine was only taken during 5/237 (2.1%) pregnancies, partly because 95.3% of patients reported non-severe disease. Additionally, 7 women who reported taking Azathioprine prior to pregnancy ceased this at conception, several suggesting in free text responses that this decision was based on fear of adverse pregnancy outcomes. Forty-six pregnancies (19.4%) were exposed to 5ASA agents, in 18 CD and 28 UC women. No pregnancies were exposed to anti-TNF agents, likely due to lack of ready access to these agents in Australia at the time of the study (2005/06). Neither Azathioprine (40% vs. 13.3%, p= 0.14) nor 5ASA agents (39% vs. 30.5%, p=0.34) altered the risk of major adverse pregnancy outcomes compared with those not exposed. Adverse pregnancy outcomes amongst patients ceasing azathioprine at or around conception were not significantly different in frequency to those continuing azathioprine throughout gestation, (3/7, 42.8% vs 2/5. 40%, p=1.0). Similarly, no differences in adverse outcome frequency were seen amongst women ceasing 5ASA agents prior to conception (7/15, 47%) versus those continuing medication during pregnancy (18/46, 39%, p=0.76).

Patients' Beliefs about IBD and Pregnancy Outcomes, and Medication Compliance

In response to both direct questions and free text responses, a large proportion of subjects (84%) reported concerns that IBD medications would harm their pregnancy, whereas only 19% women reported concerns about the effect of active IBD on pregnancy. The overriding sentiment expressed by patients was that they would "rather put up with the disease

symptoms than harm my baby with medications", indicating a lack of awareness about the known adverse effect of active disease on pregnancy outcomes, and also the pregnancy related risks associated with fluid and electrolyte disturbances, anaemia and the need for surgery in the setting of poorly controlled IBD.

With regard to specific negative pregnancy outcomes, women reported being most concerned with the "deforming" effects of medication, and the risk of "congenital defects", whereas more common adverse outcomes in IBD pregnancies such as Low Birth Weight and Premature Delivery were not the focus of free text responses.

The effect of patient beliefs on medication taking behaviour

The strong patient perception that IBD medications contribute to adverse pregnancy outcomes appeared to affect medication-taking behaviour in our subjects. Amongst women changing IBD medication whilst pregnant 7/25 (28%) did so without their doctors' knowledge. In most cases changes involved reducing or ceasing medication. Corticosteroid and Azathioprine were the medications most frequently altered by women without medical supervision. Interestingly, free text responses indicated a tendency for patients to consider as required "rescue" steroid treatment for flares to be safer than ongoing prophylactic maintenance treatment during pregnancy, even amongst patients prescribed only 5ASA agents. Some patients reported the belief that "natural therapies" or "organic" products from a herbalist or other practitioner would be a "safer substitute" during pregnancy and thus ceased their conventional IBD medications in favour of this approach.

In many cases those women offering subjective responses reported their medication taking behaviour being more strongly influenced by family, friends and the internet than their doctors. Pharmaceutical company Product Information was also cited as a source of

compliance influencing information by several patients. Advice to "discuss this medication with your doctor in pregnancy" was reported by patients as ominous, and several did not follow this advice but subsequently decided upon medication cessation without supervision.

"Good" medication compliance "most of the time" was reported by 65.8% of subjects prior to pregnancy, and no overall improvement was reported during pregnancy.

Discussion

This study provides a unique insight into patients' understanding of the interaction between IBD, its treatment and pregnancy outcomes. The high response rate to our survey indicates the need amongst IBD women to address reproductive issues, and highlights the importance of physician led discussion to identify barriers to treatment uptake.

In accord with other studies, our IBD women did not report major adverse pregnancy outcomes to be more frequent than in the general population. However, patients with severe disease or taking corticosteroids during pregnancy did report a significantly higher rate of adverse outcomes than those with mild to moderate disease or taking no medication, respectively. After controlling for disease severity, steroid exposure conferred no additional risk to pregnancy outcome, which is consistent with outcomes from other reported IBD populations[112]. It is important to note, however, the wide confidence intervals of this regression analysis as a result of the relatively small number of patients taking corticosteroids during pregnancy in this study. Interestingly, we could not demonstrate the expected higher rate of adverse pregnancy outcome frequency amongst those women ceasing Azathioprine and 5ASA agents prior to conception compared with those continuing during pregnancy. This is likely due to the small numbers of patients

involved, and also the likelihood that patients advised to cease these agents had less severe disease than those advised to continue.

The novel revelation from our data, however, is that whilst an overwhelming (84%) proportion of women attributed adverse pregnancy outcomes to medications, particularly steroids, only a few (19%) recognised the known detrimental relationship between disease activity during pregnancy and adverse outcomes. Medication taking behaviour (reducing or ceasing therapy) during pregnancy reflected this attitude. And, of concern, this reduction in therapy was undertaken by patients without prior consultation with their physician in a substantial proportion of cases (28%). A frequently expressed erroneous belief was the concept that a brief course of flare-prompted medical treatment (often steroid) was better than more lengthy ongoing prophylactic treatment. This reflected the assumption by many patients that duration of medication exposure during pregnancy was more important than medication type and the presence or absence of active inflammation.

Interestingly, this potentially overzealous concern about medication use in pregnancy is not confined to IBD medication and IBD patients. A large survey addressing attitudes toward medication use to treat infectious disease in pregnancy showed that pregnant women had a very high level of concern about medication use, which was not influenced by reassuring advice from their own parents[120]. In IBD patients, fear-based medication noncompliance may precipitate flares, which in turn increase adverse pregnancy outcomes and reinforce this vicious cycle.

Inactive IBD during pregnancy confers a small increased risk of some adverse pregnancy outcomes, although numerous studies report similar risks to the general population[94, 121-124].

In CD a small increase in the risk of LBW and preterm delivery has been reported[70, 97, 125-127], especially in patients with ileal disease or previous surgery[128]. In UC women the rate of healthy delivery and healthy neonates is similar to the general population in some studies[79, 110, 129], whilst others report a small increase in preterm delivery and low birth weight infants[73, 92, 130]. An increased rate of spontaneous abortion has also been noted[131].

The increased rate of adverse outcomes amongst our subjects with severely active disease during pregnancy was not surprising. Accumulating evidence suggests that IBD activity during conception and pregnancy is the most influential determinant of pregnancy outcome, although this is controversial. Whilst a large study of pregnant women with predominantly mild IBD found no association between disease activity and pregnancy outcome[91], other data suggest exacerbations during pregnancy are detrimental[103, 110, 111] Numerous case control and cohort studies have reported an association between flares during pregnancy and pre-term delivery, low birth weight, and other adverse outcomes in both CD and UC[122] [109] [71, 103, 110, 111, 127, 132-134]. Khosla et al[111] demonstrated a miscarriage rate of 35% amongst IBD women with active disease at conception. A large nationwide Danish cohort study[135] found an increased risk of preterm birth only in CD women with moderate to high disease activity during pregnancy, Baiocco et al supporting the contention that the detrimental effect of disease activity is more pronounced in CD than UC[110].

Our finding of increased adverse outcomes amongst women taking corticosteroid during pregnancy was likely confounded by the high proportion of women with severe disease in this group (24%). Many other studies report the same methodologic limitation in elucidating

the relationship between IBD medication and pregnancy outcome. Corticosteroid therapy has been used extensively in pregnancy and has not been shown to cause fetal harm in IBD patients[71]. In a study of 531 women, 168 received extended duration steroid in pregnancy with no increase in prematurity, abortion, stillbirth or developmental defects[112]. As prednisolone is extensively metabolized by the placenta it is considered safer than uncontrolled IBD during pregnancy[136]. 5ASA agents may very slightly increase adverse outcomes[137], and azathioprine data are conflicting, some studies suggesting a small increased risk of fetal abnormalities[138] and others refuting this[114]. Although no long-term data are available for the biologic agents, most reports thus far suggest they are relatively safe in pregnancy[80, 98, 117, 139].

The generalisability of our findings is encumbered by several limitations. Whilst we endeavoured to clarify the nature of reported adverse outcomes and distinguish between major and minor problems, data were based entirely upon self report without external verification. It is thus difficult to make comparisons with normal population data arising from administrative databases. The retrospective nature may have introduced recall bias in subject responses, and this may explain why numerous respondents selectively answered some questions but not others. Data regarding smoking rates in our population would also be advantageous as this has a considerable impact on perinatal outcomes[140]

The importance of this study, however, is its identification of patients' attitudes and insights which create a barrier to treatment uptake in IBD. We have demonstrated no overall difference in risk of adverse pregnancy outcomes compared with the general population. Women with severe, active disease during pregnancy and those taking corticosteroids had increased adverse outcomes compared with other IBD women, although causality cannot be

established in the case of steroid as this relationship is confounded by the effect of increased disease activity. Fear of medication teratogenicity is highly prevalent, whereas awareness of the deleterious effect of IBD exacerbation during pregnancy appears limited. These negative attitudes toward IBD medication promote patient initiated cessation during pregnancy, which may prove detrimental.

The gastroenterologist plays a pivotal role in providing early, evidence-based counselling to facilitate informed management decisions, and to emphasise the importance of disease control during conception and pregnancy. The views of individual women need to be acknowledged and the opportunity to ask questions incorporated into the routine consultation, in order to optimise pregnancy outcomes in IBD patients.

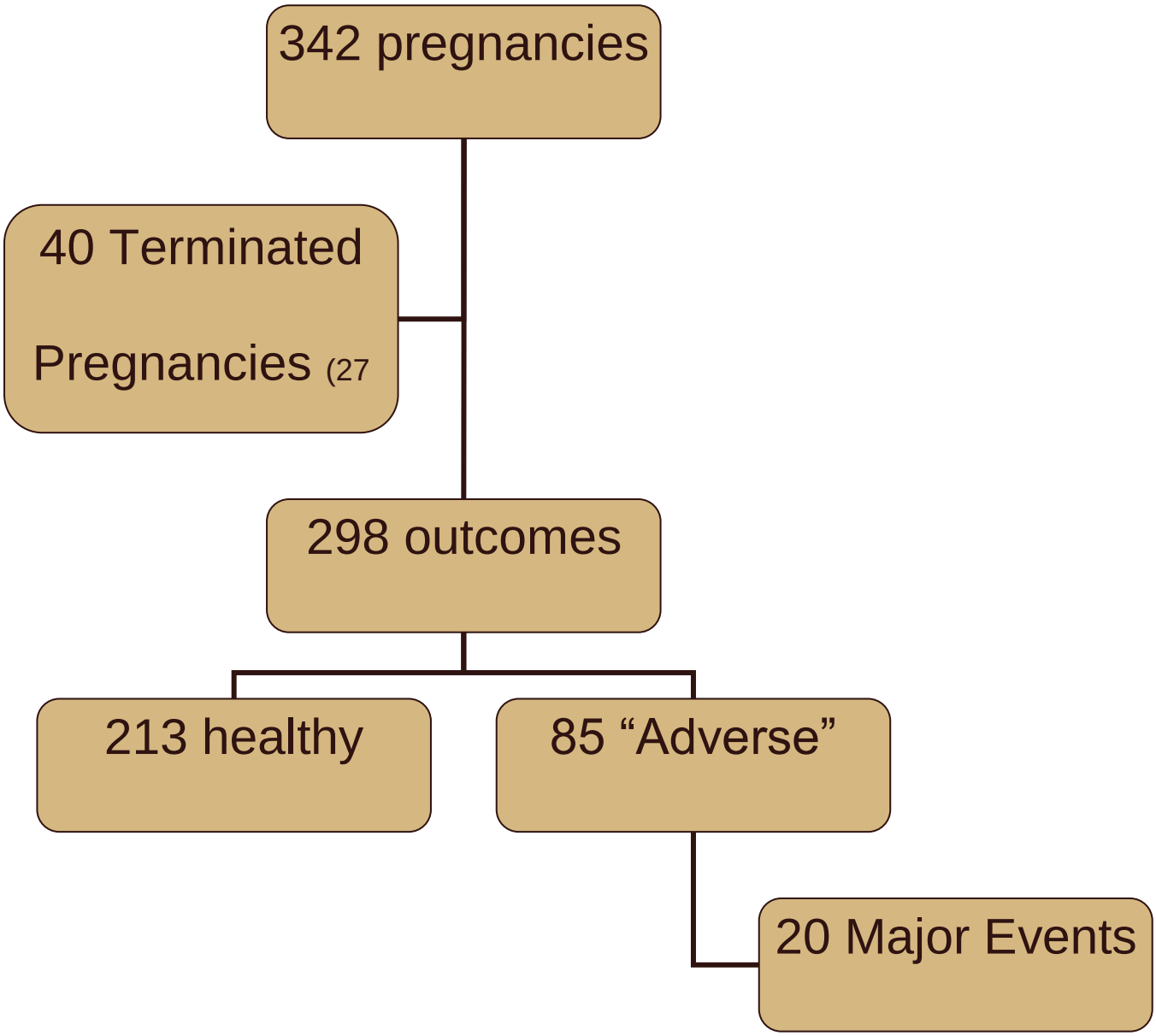

Figure 6:Reported pregnancy outcomes of female IBD respondents

Table 10: Self reported adverse pregnancy outcomes in IBD women overall, and subgroups taking no medication, those taking corticosteroids during pregnancy and those with severely active disease during pregnancy, compared with non IBD Australian population rates

Adverse Outcome Type	**All IBD women**	**No medication**	**Steroid Exposure**	**Severe Disease**	**Non-IBD population**
N (% Reported Pregnancy Outcomes)					
Stillbirth	2 (0.7%)	1 (0.62%)	0 (0%)	1 (7.1%)	0.7% #
Preterm delivery	7 (2.3%)	3 (1.9%)	2 (6.1%)	2 (14.3%)	10.2% #
Developmental Delay	1 (0.3%)	0 (0%)	1 (3%)	0 (0%)	1% #
Congenital Abnormality	1 (0.3%)	1 (0.62%)	0 (0%)	0 (0%)	2.3% #
Miscarriage	7 (2.3%)	4 (2.5%)	2 (6.1%)	1 (7.1%)	15-20% #
Low Birth Weight/Small for Gestational Age	2 (0.7%)	0 (0%)	1 (3%)	1 (7.1%)	7% #
Healthy Baby or Minor problems	278 (93.3%)	152 (94.4%)	27 (81.8%)	9 (64.3%)	-
Total	298	161	33	14	-

Chan A, Scott J, Nguyen A-M, Sage L. Pregnancy Outcome in South Australia 2006.

Adelaide: Pregnancy Outcome Unit, South Australian Department of Health, 2007.

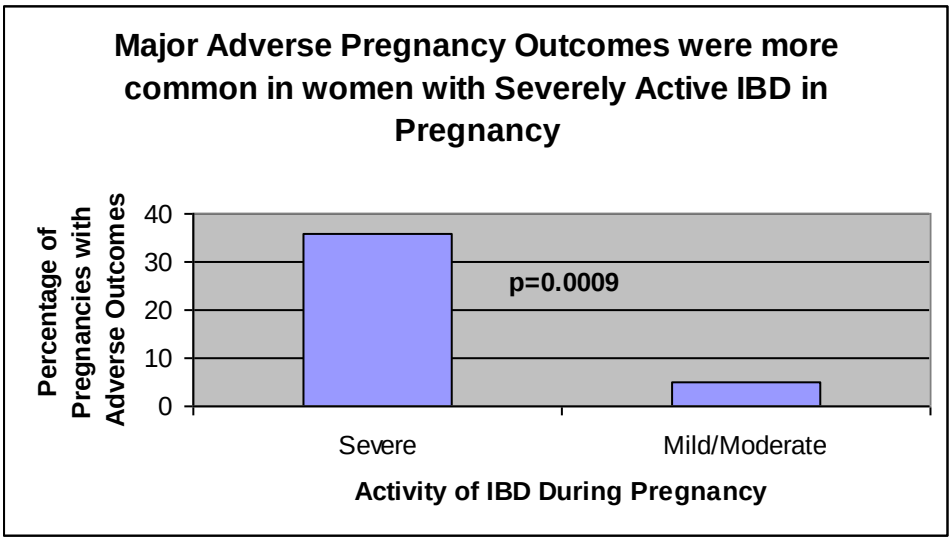

Figure 7: The relationship between severely active IBD during pregnancy and major adverse pregnancy outcomes

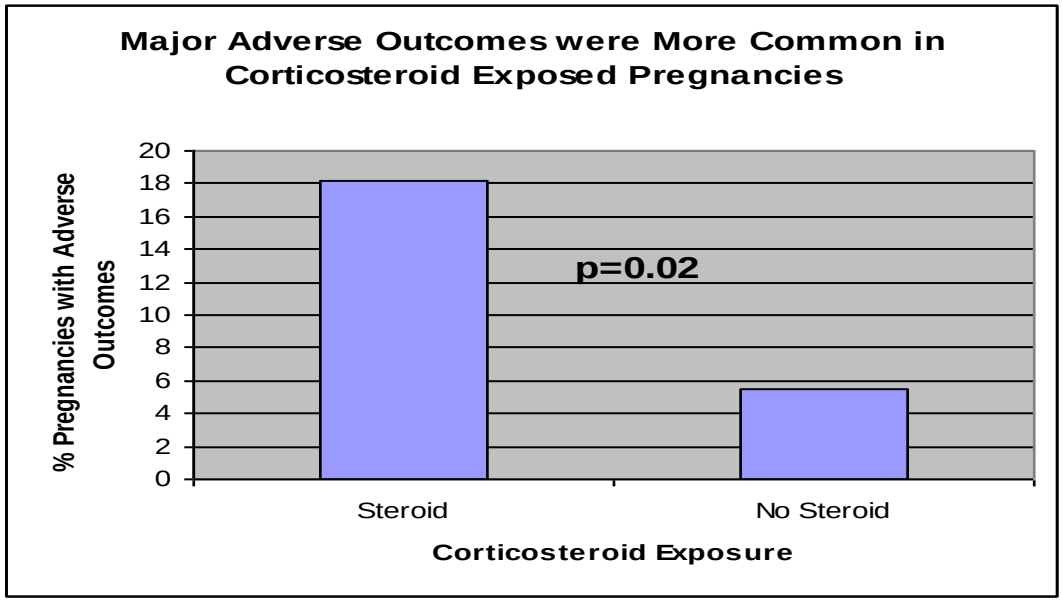

Figure 8: The relationship between corticosteroid exposed pregnancies and major adverse pregnancy outcomes

CHAPTER 5: IT IS WORTH THE EFFORT – PATIENT KNOWLEDGE OF REPRODUCTIVE ASPECTS OF INFLAMMATORY BOWEL DISEASE IMPROVES DRAMATICALLY AFTER A SINGLE GROUP EDUCATION SESSION

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AUTHOR ROLES

R Mountifield was involved in study conception, design, seeking ethical approval, administration of questionnaires, preparing and giving the educational lecture, data acquisition, entry, analysis and interpretation, drafting the manuscript and modifying and preparing the final paper. JM Andrews and P Bampton were involved in planning the study, seeking ethical approval and revising the draft manuscript.

Abstract

Background: Individuals with Inflammatory Bowel Disease (IBD) have poor knowledge regarding the implications of disease for fertility and pregnancy. Previous studies suggest this poor knowledge adversely influences reproductive decision making.

Aim: To examine the effect of a single group education session on IBD-specific reproductive knowledge in subjects with IBD.

Method: People with IBD attending an educational event were invited to complete the CCPKnow questionnaire, testing reproductive knowledge in IBD, before and after an evidenced based presentation on this topic delivered by a gastroenterologist.

Results: Of 248 attendees, 155 participated; 69% female, mean age 40.3 years. CCPKnow scores (maximum 17) were low at baseline and increased significantly post education (mean 5.4 pre versus 14.5 post education; $p<0.0001$). A large majority (65.1%) of subjects had "poor" (score <8) knowledge at baseline, compared with only 1.9% after education ($p<0.0001$). Whilst all subareas of knowledge improved after education, the most important improvement was in attitudes toward medication use in pregnancy: 33.5% of subjects indicated at baseline that women should avoid all drugs in pregnancy compared with only 1.2% post education ($p< 0.0001$).

Conclusion: A single group-delivered education event focussed on reproductive issues in IBD can dramatically improve patient knowledge. This has the potential to change reproductive behaviour and may reduce voluntary childlessness resulting from misperceptions amongst individuals with IBD.

Key Words: Inflammatory Bowel Disease, Pregnancy, Fertility, Patient Knowledge, Patient Education

Introduction

As survival is generally normal in Inflammatory Bowel Disease (IBD), quality of life and the opportunity to have a normal work, social and family life is a key aim of management. IBD usually has its onset during the reproductive years, but fortunately both male and female fertility outcomes as well as pregnancy outcomes overall are good amongst individuals with IBD[141] [91] [70], especially if good disease control is maintained[142] [143] [144]. Most IBD medications are considered safe to continue throughout pregnancy[145] [146] [147] [148], with the exception of teratogens methotrexate and thalidomide[145], whilst sulfasalazine causes reversible infertility in men[82].

Data, however, suggest that many IBD subjects have poor knowledge regarding IBD-specific issues relevant to fertility and pregnancy[149]. Moreover, it appears that this knowledge gap contributes to increased rates of voluntary childlessness as a result of misinformation[19] [20] [150].

Formal education of patients has been shown to be beneficial in improving general IBD knowledge and satisfaction in a Canadian study[151], but other studies have not demonstrated such a benefit[152] [153], and it is not known whether such a programme would be effective in improving reproductive knowledge in IBD.

The effect of group education of patients with IBD to address the interaction between disease, medications, fertility and pregnancy has not been previously addressed using a validated knowledge test.

Aim

To determine whether IBD-specific reproductive knowledge improves in patients with IBD after a single targeted group education session.

Methods and Materials

Crohn's and Colitis Australia (CCA) is a patient-run support group, holding regular information evenings in each state in Australia. One such evening was held at Flinders Medical Centre (FMC), a tertiary referral hospital with an active IBD Service, in South Australia in 2013. The evening consisted of a variety of presentations on different topics of interest which had been identified as being important by the members of CCA. The meeting was widely advertised, and was open to all patients and their families, irrespective of CCA membership. One of these presentations focused on the relationship between IBD and reproductive issues such as IBD inheritance, fertility, pregnancy, drug safety and breast feeding.

Upon arrival each attendee was handed a questionnaire which consisted of 2 copies of the "CCPKnow" test[149] (Appendix E), a validated tool assessing knowledge regarding IBD-specific aspects of reproduction. This test consists of 17 multiple choice questions with 5 option answers of which 1 is considered correct, covering subareas of IBD inheritance, fertility, the effects of IBD activity and medications on pregnancy, mode of delivery, perianal disease, pregnancy outcomes and breast feeding. The minimum score is zero and maximum 17, with scores of 0-7 indicating poor knowledge, 8-10 adequate, 11-13 good and 14-17 very good knowledge[149].

Subjects were also invited to state, using free text, their main sources of information regarding IBD and fertility and pregnancy.

Each attendee was seated by IBD nursing staff on arrival and invited to complete the first CCP Know test before the presentations commenced. Time and materials were supplied to enable this. It was stressed that participation was entirely voluntary and anonymous. If participants felt comfortable doing so they were asked to state their gender and age on the front of the questionnaire. The reproductive presentation was then delivered, consisting of 24 slides covering current evidence-based practice regarding the effect of IBD and medications on fertility for men and women, pregnancy, breastfeeding and inheritance, in simple language with visual aids and using repetition for major messages. All information presented was consistent with ECCO guidelines on the management of special situations such as reproduction and IBD[154] [155].

Directly after the reproductive IBD presentation audience members were invited to complete the second copy of the CCP Know in their questionnaire booklet without altering responses from their initial questionnaire. Ten to fifteen minutes was allocated for this. The other presentations then proceeded. At the conclusion of the evening all questionnaire booklets were collected and CCP Know scores calculated for each participant before and after the presentation, with the intention of determining whether improvement in reproductive IBD knowledge had occurred as a result of attendance.

Ethical Considerations

This study was approved by the Flinders Clinical Research Ethics Committee (Appendix F), with informed consent taken to be signified by the return of a completed questionnaire. Attendees wishing not to participate simply handed back their blank booklets.

Statistics

CCPKnow scores before and after the presentation were compared using a paired t-test, with Mann Witney U or unpaired t-tests for other comparisons as appropriate, using the SPSS program. A p value of <0.05 was taken as statistically significant. Contingency tables with Fisher's exact test were used to compare responders and non-responders and also to compare correct and incorrect responses for individual domains pre and post education and to perform comparisons by gender.

Results

There were 248 attendees, (170 female, 78 male), of whom 155 participated (69% female,) yielding an overall response rate of 62.5%. Mean age of respondents was 40.3 years, similar for females and males (39.0 years versus 41.6 years, p=0.55).

Of a maximum overall CCP Know score of 17, mean pre education score was 5.4 versus 14.5 after education (p<0.0001) (Table 11, Figure 9). Males and females both had low baseline scores, although male scores were significantly worse (Figure 10). Both groups improved significantly after education, and there was no gender difference seen in mean knowledge scores after education (Figure 10).

When assessing results by CCPKnow score category – poor, adequate, good or very good (as above), a high proportion of subjects overall demonstrated "poor" knowledge at baseline (65.1%), this proportion being higher amongst males (85.4%) than females (56.1%) (p=0.0004) (Table 12). Post education this gender difference was not evident, with only 2.1% males versus 1.9% of females demonstrating poor knowledge by CCP Know score (p=1.0) (Table 13). Overall in gender groups combined the proportion with poor knowledge was dramatically reduced post education (65.1% vs 1.9%, p<0.0001).

With regard to separate domains of the questionnaire, whilst overall improvement in knowledge was demonstrated in all areas after education, some improved more dramatically than others (Table 14). The question regarding the effect of disease activity on fertility and pregnancy was answered correctly in 76/155 (49.0%) at baseline, and 136/155 (87.7%) post education ($p<0.0001$). Of the 79 subjects answering incorrectly at baseline, 41% felt that active disease during pregnancy "does not affect the chance of having a healthy baby", and 59% felt that active disease "should be put up with to protect the unborn from drug effects". Of those with misconceptions regarding the impact of active IBD, 59 (74.7%) responded correctly after education. Of concern, with regard to medical literacy, 10 subjects wrote next to the term "active disease", "is this the same as a flare?" or similar.

Most interest amongst subjects appeared to be generated by the 5 questions addressing the effect of IBD medications in pregnancy, with at 24% of subjects free texting spontaneous comments around these questions. Whilst knowledge in this domain improved dramatically after education (Figure 11: Mean Subscore for Knowledge of IBD Medications in Pregnancy (Maximum 5) Pre and Post Education), misperceptions likely to influence medication taking behaviour were common pre education. Fifty-two of 155 (33.5%) subjects initially indicated that women should avoid all drugs in pregnancy compared with 2/155 (1.2%) post education ($p< 0.0001$). For questions regarding mesalazine, azathioprine, infliximab or adalimumab and methotrexate, a mean of 11.5% correct answers were seen pre education versus 89.3% after education ($p<0.0001$).

Pregnancy outcomes knowledge was assessed over 2 questions where the maximum achievable score was 2. The mean pre education was 0.2 and after education was 1.8 ($p<0.0001$) (Figure 12). The proportion of subjects who felt the chances of a woman with

IBD having a healthy baby were very good increased dramatically post education (35.9% versus 96.2%, $p<0.0001$).

Regarding patient sources of information regarding fertility and pregnancy in IBD, 42% cited their gastroenterologist as their primary source of advice, 29% their General Practitioner or Primary Care Physician, and 27% the internet, with 2% citing alternative care practitioners such as naturopaths or chiropractors. Many subjects stated that the discussion regarding fertility and pregnancy and its interaction with IBD had "never come up in consultation." Twelve percent of subjects indicated that they had initiated such a discussion with their IBD practitioner as they had significant concerns which had not been addressed.

Discussion

This is the first study assessing the effect on people with IBD of a targeted group education session on IBD-specific reproductive knowledge using a validated instrument, the CCPKnow[149]. Of concern, a very high proportion (65%) of the respondents had poor knowledge at baseline, yet after a simple intervention, this proportion dramatically reduced. The responses highlighted the fact that less than half of those with IBD received information regarding IBD and reproductive issues from their specialist, with many citing their family practitioner or the internet as their primary information source.

In the initial CCPKnow validation study by Selinger et al[149] of 145 IBD patients, 44.8% demonstrated "poor" knowledge, the remaining patients scored as "adequate" or better. Overall our cohort had a higher rate of "poor" reproductive IBD knowledge, with 65.1% subjects scoring in this range. Notably, the proportion of males with a poor score was greater than that seen in women, which has not been previously reported. This gender difference is not surprising, however, as it is reasonable to assume that females are more

focussed on reproductive issues than males, however it is reassuring that both genders responded equally well to education.

In two previous studies[149] [156], better knowledge was associated with Crohn's and Colitis Association membership, indicating that our CCA-recruited study population may exhibit selection bias, and in fact reproductive knowledge may be worse in the IBD community overall. It is also possible that the responsiveness to the intervention reflects a cohort more willing to learn and find out about IBD as they had attended the meeting.

Although all domains investigated by the survey demonstrated poor knowledge that improved after education, the most frequent and concerning misconception seen in subjects at baseline was the belief that IBD medications are more detrimental to pregnancy outcome than the effect of disease activity. Interestingly, many subjects who correctly answered that active IBD in pregnancy was detrimental also responded in favour of avoiding all medications throughout pregnancy due to greater concerns over teratogenicity. It is now recognised in the form of multiple large studies and international guidelines that active disease poses a greater threat to pregnancy than most IBD medications, with the exception of methotrexate[155].

Similar medication concerns have also been reported in other IBD populations, with 36% in one study stating the belief that all IBD medication is harmful to unborn children[157]. General attitudes in this group that "medication should be stopped prior to conception" and that "pregnant women should avoid IBD drugs" were associated with lower CCPKnow scores[157]. In a Danish cohort, fear of a negative effect on the fetus resulted in non-adherence with IBD medications during pregnancy in 45.5% of patients[158]

As drug knowledge score increased acutely more than threefold after education in our study, it was clear that subjects were able to distinguish methotrexate as the only teratogenic medication and understand the rationale for the use of other medications to avoid active disease and optimise outcomes in pregnancy.

Other studies addressing the effect of education on general IBD knowledge have not demonstrated the same findings. In one study evaluating an IBD education programme involving four sessions, no benefit was seen at one year in knowledge or psychological parameters[152] and in a similar study, again no improvement in IBD knowledge was demonstrated, but patients enjoyed the education and requested its continuance[153]

Our study also highlights the need to clarify patient understanding of IBD related medical language. More than 50% of subjects chose answer options suggesting that perianal disease was “common in Ulcerative Colitis” or “responds well to creams”. Additionally, the difference in terminology used by practitioners versus patients was emphasised as many subjects sought clarification of the meaning of “active” disease, and appeared more familiar with the term “flare” to indicate disease activity.

Less than half of our study subjects felt that their gastroenterologist was their primary source of information regarding reproduction and IBD, and similar results have been seen in other IBD populations[19]. Much emphasis was placed on the role of the General Practitioner by subjects and on the internet as an information source. Five subjects volunteered that they had “Googled” the topics to be presented in preparation to attend the education event. This implies that part of good patient care for this relatively young and Information Technology focussed group may be the provision of website addresses with accurate, referenced information that may assist the practitioner as a co-educator rather

than perpetuate misinformation. This approach has been effective in a previous study in IBD general knowledge[159]

An Irish study amongst General Practitioners found that 68% of GPs have regular contact with IBD patients, and that 41% of those GPs have not discussed family planning with these patients[160]. Sixty seven percent would refer to a specialist for advice about reproduction and 33% would not, indicating that many patients are managed in this setting alone. Education of General Practitioners may not be effective, however, as local Australian data indicate that GP knowledge and confidence in IBD management correlate poorly, and that each individual GP sees only a small number of IBD patients[161]. A more productive approach may be for IBD practitioners to initiate discussion regarding reproductive implications of IBD before family planning decisions are made.

This study may be limited by the lack of information regarding disease type, severity and duration, subjects' reproductive history, ethnicity, employment, educational achievement, relationship status and other factors seen in previous studies to influence disease knowledge[149]. It was beyond the scope of this study but would be important to evaluate whether the knowledge improvement demonstrated persisted in the longer term, as greater recall of IBD information has been associated with increased medication adherence[162] . The mean age of subjects in this study may also be older than the ideal target range for IBD reproductive education.

In summary, this is the first study demonstrating a dramatically positive effect on IBD related reproductive knowledge amongst IBD subjects after a single group education session. Most important to address was the widespread misperception that IBD medication is more detrimental to pregnancy outcomes than disease activity, a belief known to

negatively influence reproductive decision making. Clinicians and IBD Nurses should be encouraged to channel resources into IBD reproductive education before it is sought as many patients will base decision making on erroneous assumptions. The short term yield from this effort is high and may have widespread effects on long term reproductive decision making in the IBD population. The longer term benefit of this approach should be evaluated.

Tables and Figures

Table 11: CCP Know Score of Maximum 17 Pre and Post Education for All Participants

	Pre education	**Post Education**
Mean (95% CI)	5.4* (4.8-6.0)	14.5*(14.1-14.9)
Standard Deviation	3.58	2.22
Sample Size (n)	155	155
Standard Error of Mean	0.31	0.19
Minimum	0.00	6.00
Median	5.00	15.00
Maximum	17.00	17.00

*p<0.0001

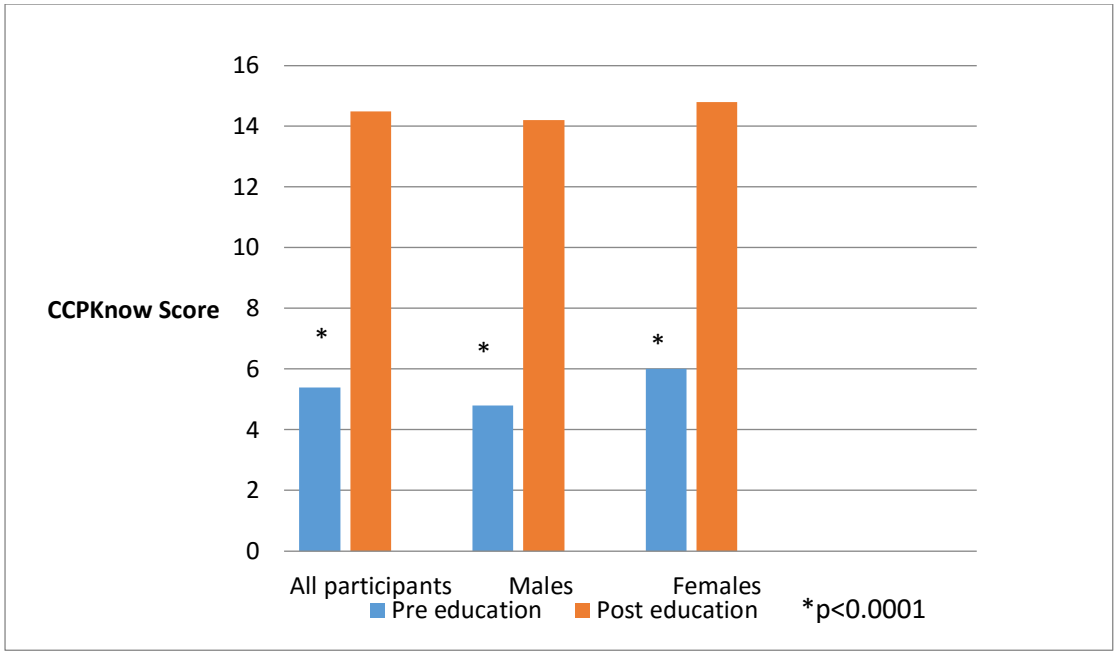

Figure 9: Mean Overall CCPKnow Score (Maximum 17) Pre And Post Education in all Participants and by Gender

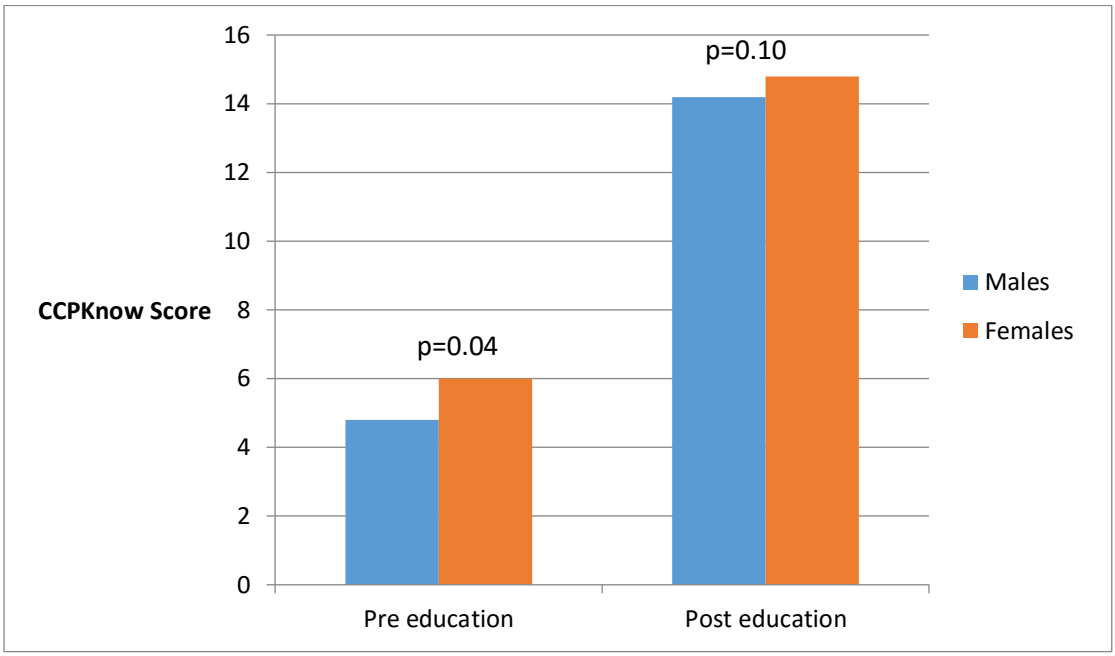

Figure 10: CCPKnow Score Comparing Males and Females Pre and Post Education

Table 12: CCPKnow Score (Poor to Very Good) at Baseline Overall and by Gender

	Poor (0-7) **N (%)**	**Adequate (8-10)** **N (%)**	**Good (11-13)** **N (%)**	**Very Good (14-17)** **N (%)**	**Total**
Overall	101 (65.1%)	41 (26.5%)	10 (6.5%)	3 (1.9%)	155 (100%)
Males	41* (85.4%)	6 (12.5%)	1 (2.1%)	0 (0%)	48 (31.0%)
Females	60* (56.1%)	35 (32.7%)	9 (8.4%)	3 (2.8%)	107 (69.0%)

* p=0.0004

Table 13: CCPKnow Score (Poor to Very Good) After Education Overall and by Gender

	Poor (0-7) **N (%)**	**Adequate (8-10)** **N (%)**	**Good (11-13)** **N (%)**	**Very Good (14-17)** **N (%)**	**Total**
Overall	3 (1.9%)	5 (3.2%)	24 (15.5%)	123 (79.4%)	155 (100%)
Males	1***** (2.1%)	0 (0%)	13 (27.1%)	34 (70.8%)	48 (31.0%)
Females	2***** (1.9%)	5 (4.7%)	11 (10.3%)	89 (83.2%)	107 (69.0%)

*p=1.0

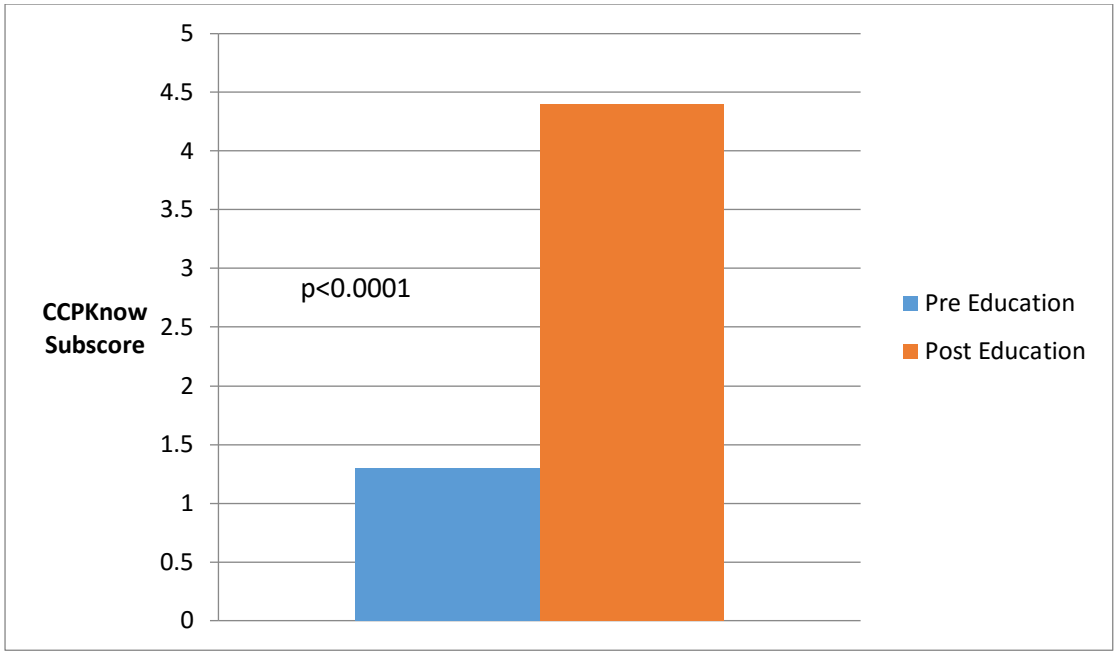

Figure 11: Mean Subscore for Knowledge of IBD Medications in Pregnancy (Maximum 5) Pre and Post Education

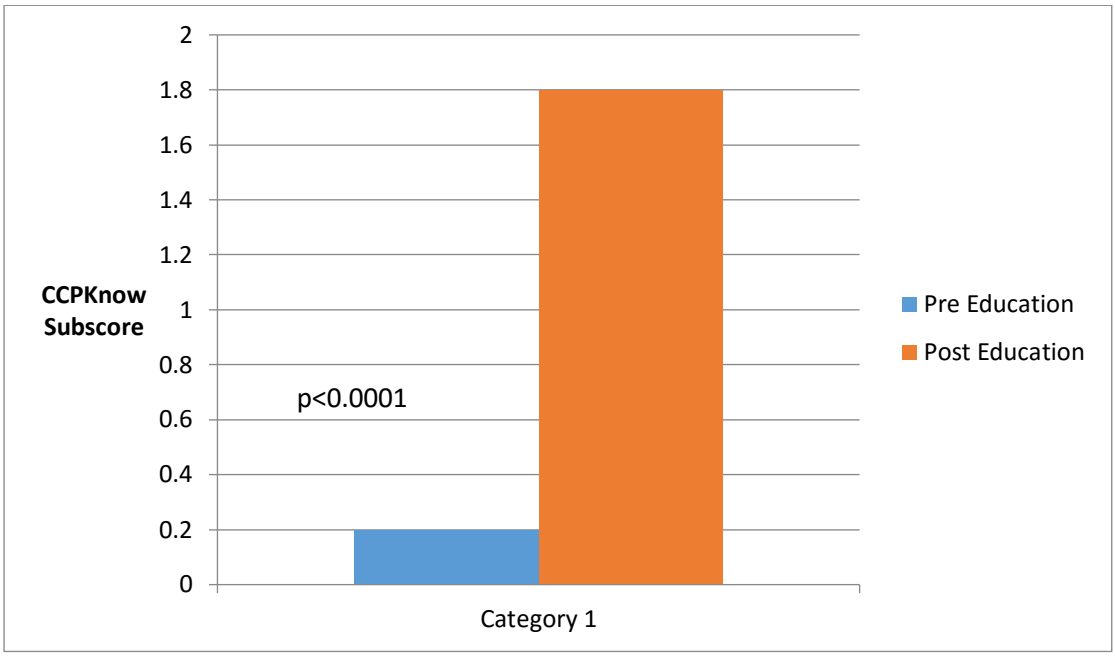

Figure 12: Mean Subscore for Knowledge of IBD Pregnancy Outcomes (Maximum 2) Pre and Post Education

Table 14: Proportion of 155 Subjects Answering Correctly Within Various Survey Domains Pre and Post Education

Domain of Survey	**Number of subjects answering correctly at baseline (%)**	**Number of subjects answering correctly after education (%)**	**p value**
IBD inheritance	67 (42.8%)	138 (88.9%)	<0.0001
Fertility	58 (37.4%)	142 (91.6%)	<0.0001
Effect of disease activity on fertility and pregnancy	76 (49%)	136 (87.7%)	<0.0001
Mode of delivery (vaginal or surgical)	47 (30.5%)	146 (93.9%)	<0.0001
Breastfeeding	44 (28.2%)	147 (94.7%)	<0.0001
Perianal disease	24 (15.3%)	60 (38.9%)	<0.0001

CHAPTER 6: COLON CANCER SURVEILLANCE IN INFLAMMATORY BOWEL DISEASE – UNCLEAR GAIN BUT NO PSYCHOLOGICAL PAIN?

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AUTHOR ROLES

R Mountifield was involved in study conception, design, seeking ethical approval, data acquisition, analysis and interpretation, drafting the manuscript and modifying and preparing the final paper. JM Andrews and P Bampton were involved in planning the study, seeking ethical approval and revising the draft manuscript. A Mikocka-Walus assisted with data interpretation and R Prosser with data entry

Abstract

Background: Surveillance for colorectal neoplasia in Inflammatory Bowel Disease (IBD) is widely practised despite a lack of convincing mortality reduction. The psychological impact of this approach is largely unexplored.

Aim: To examine psychological wellbeing amongst IBD subjects undergoing colonoscopic surveillance for colorectal cancer (CRC).

Methods: A cross sectional study was performed by interrogating an IBD database for subjects currently enrolled in colonoscopic surveillance programs. Identified surveillance subjects were age and gender matched with IBD control subjects not meeting surveillance criteria. Subjects were mailed a questionnaire including demographic details, the SF 36 survey to assess Quality of Life (QoL), the Spielberger State-Trait Personality Inventory (STPI), the Multidimensional Health Locus of Control and a Risk Perception Questionnaire.

Results: 139/286 (49%) subjects responded, 53% male, 46% Crohn's Disease. 56% respondents were in the surveillance group. Surveillance subjects were older (55.4 vs 51.1 years; p=.048) with longer disease duration but otherwise had comparable demographics to controls. Overall QoL was not significantly different between cohorts (mean SF 36 63.82 vs.65.48; p=0.70). Groups did not differ on any locus of control classification (p=0.52), nor was there any difference between mean scores on "state"

subscales of the STPI: anxiety (p=0.91), curiosity (p=0.12), anger (p=0.81) or depression (p=0.70). Both groups grossly overestimated their perceived lifetime risk of CRC at 50%, with no difference between surveillance and control subjects (p=1.0).

Conclusions: Enrolment in colonoscopic colon cancer surveillance does not appear to impair psychological wellbeing in individuals with IBD despite longer disease duration. IBD patients overestimate their risk of CRC.

Key Words**:** Inflammatory Bowel Disease, Cancer Surveillance, Anxiety, Risk Perception, CRC

Introduction

Colonoscopic surveillance for Dysplasia and Colorectal Carcinoma (CRC) in Inflammatory Bowel Disease (IBD) is widely practised. Whilst Cochrane review data suggest such surveillance promotes the earlier detection of colorectal cancer, no clear mortality reduction has yet been demonstrated[163]. Moreover, several population-based IBD cohort studies have suggested no excess in CRC risk compared to the population within which they reside[164] [165] [166] This questionable long term benefit renders the psychological impact of screening an important consideration in justifying ongoing surveillance in the future, and at present this risk benefit ratio remains largely unexplored in IBD.

In screening for other cancers such as breast cancer by mammography, patients with increased perceived susceptibility to breast cancer experience significantly increased psychological distress which is not alleviated by screening. One study demonstrated the greatest level of post screening cancer specific concerns in women having false positive screening tests, suggesting the potential for deleterious psychological outcomes of screening[167]. A contrasting investigation of the psychological effect of breast cancer screening in patients post radiation for Hodgkin's lymphoma suggested a positive effect on psychological parameters, demonstrating that after screening, women had improved knowledge and a significant sense of reassurance[168].

Much research in CRC focuses on hard outcomes such as detection rate, mortality and cost effectiveness. Minimal published data address the potential psychological effects

of colonoscopic surveillance, important as such effects may impact upon patient adherence and ultimately the long term efficacy of this practice in reducing CRC. Existing data regarding “intangible” costs and benefits of CRC screening come from small studies.

The purpose of our study was to address this knowledge gap in the risk-benefit ratio of colonoscopic CRC surveillance in IBD, by assessing the psychological impact of this practice in a setting where evidence of overwhelming benefit from surveillance has not yet been shown.

Aim

To examine whether psychological wellbeing is impaired in individuals with IBD undergoing CRC surveillance using colonoscopy, compared with IBD subjects not yet enrolled in a surveillance program. Specifically we will examine Quality of Life, the Locus of Control to which IBD subjects attribute health outcomes, psychological state and trait including anxiety, depression, anger and curiosity, and perception of CRC risk.

Methods and Materials

A cross sectional study was performed by interrogation of a tertiary hospital IBD database including public and private patients currently enrolled in colonoscopic CRC surveillance programs based on Ulcerative Colitis (UC) or colonic Crohn’s disease (CD) duration greater than or equal to 8 years, with or without coexistent Primary Sclerosing Cholangitis[169] (PSC) of any duration. These individuals had received counselling by their treating specialist regarding the increased risk of CRC associated

with long standing colitis or coexisting PSC and had consented to colonoscopic surveillance. Subjects in this cohort could be anywhere in the surveillance cycle, ranging from having recently had a colonoscopy to immediately awaiting one.

Identified surveillance subjects were gender matched and age matched as closely as possible with other IBD patients in the database not yet meeting surveillance criteria based on shorter disease duration or refusal of colonoscopic surveillance. All eligible subjects were simultaneously mailed a written questionnaire, comprising demographic questions along with psychological surveys to assess Quality of Life, Health Locus of Control, psychological State and Trait characteristics, and Risk Perception with regard to CRC (Appendix G).

Demographics

Details such as age, gender, country of origin, primary language spoken, occupational status, car and house ownership, highest educational qualification and marital status were sought. A limited amount of data was available on the hospital database regarding extent of disease and coexistence of PSC and these data were gathered where possible and contributory.

Bowel Symptoms

Current bowel symptoms were sought in questions regarding constipation, diarrhea, wind, abdominal pain, incontinence, rectal bleeding and haemorrhoids to indicate level of disease activity at the time of questionnaire completion.

Quality of Life – SF 36

The four week SF 36 questionnaire[170] was used to assess Quality of Life (QOL), divided into mental and physical components and aiming to assess the level of limitation of daily activities imposed by symptoms over the past 4 weeks. Subjects were asked to respond to 36 questions which yield scores in 8 domains comprising physical function, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. A score out of 100 is calculated for each subject in each domain, then in overall physical and mental domains, where 100 indicates a better state of health or wellbeing., and lower scores are associated with reduced QoL. Australian population SF 36 data were used to compare QOL in overall physical and mental domains with each IBD cohort[171].

Locus of Control

The Levenson Multidimensional Locus of Control Scale[172] was incorporated into the questionnaire to determine the tendency of individuals to attribute control of health events to their own actions, that of others or to chance alone, and to compare these attributes between surveillance and control cohorts. This test asks subjects to numerically rate attitudinal statements according to how much they agree (+1 to +3) or disagree (-1 to -3) with each statement. Different forms of this test are available based on characteristics of the groups to be compared, and Form C[172] was applied in this study as this is a condition-specific measure of locus of control and all subjects in our study had IBD. Of the 18 statements, 6 indicate an “Internal” locus of control, 6 a “Powerful Others” Locus in, the case of Form C the powerful others being health

professionals, and a further 6 items assess a “Chance” related locus of control. A score is calculated for each subject on each locus to determine to which of the 3 they are most likely to attribute health events.

Anxiety, Depression, Anger and Curiosity

The Spielberger State-Trait Personality Inventory[173] [174](STPI) was used to assess and compare depressive symptoms, anxiety, anger and curiosity between cohorts in both the immediate (state) and long term (trait or personality characteristic). Subjects were asked to respond to 80 questions in total using a scale of 1 to 4 in terms of how they feel at that moment in time and also in the longer term (ranging from almost never to almost always) in response to a series of attitudinal statements. The lowest score is 20 and the highest score 80, higher scores indicating a greater level of anxiety, depression, anger or curiosity.) This test has been shown to be reliable and valid[175].

Risk Perception

A Risk Perception questionnaire[176] included 9 questions assessing subject perception of risk likelihood, susceptibility and severity regarding colorectal cancer. Subjects’ perceptions of surveillance efficacy and ease were also sought, along with their stage of readiness for surveillance participation (Table 7). All answers took the form of categorical variables or percentage estimation.

Questionnaires returned within 3 months were analysed, with one reminder letter sent after one month if no response was received.

Ethical Considerations

This study was approved by the Flinders Clinical Research Ethics Committee (FCREC) of Flinders University, South Australia (Appendix H). Informed consent on behalf of participants was implied in the form of a completed and returned questionnaire (Appendices I and J).

Statistics

QQ-plots were used to check normality of distribution. Chi-square and Fisher's Exact Test were used to compare groups on categorical variables. Depending on normality of data distribution, Mann-Whitney or t-tests were used to compare groups on continuous variables. Significance was reported at the 0.05 level.

Results

Of 143 subjects in each group, surveillance subjects were more likely to complete the questionnaire (78/143 (56%) vs 61/143 (44%), p=0.058) with an overall response rate of 139/286 (49%). 53% of respondents were male, and 46% had Crohn's Disease. Males and females did not differ in the likelihood of completing the survey (p=0.19) and disease type also did not appear to influence study participation (p=0.11)

Demographics

In comparing Surveillance subjects with controls, surveillance subjects were significantly older (55.4 vs 51.1 years; p=.048) but had comparable IBD type, marital status, education, language spoken and employment status to the IBD control subjects

(Table 15). By definition the surveillance subjects had longer mean disease duration than IBD controls (21.4 (range 8-50) vs 5.2 (range 1-12) years, p<0.0001)

Two Subjects were known to have coexisting PSC, both in the surveillance group. Four subjects in the IBD control group were not undergoing surveillance despite disease duration greater than 8 years, 2 as they had proctitis only, and a further 2 who refused the offer of surveillance.

Bowel Symptoms

With regard to bowel symptoms, diarrhea was reported more commonly amongst IBD control subjects (p=0.043) Consistent with this, IBD controls also demonstrated a trend toward more abdominal pain (p=0.057). No other difference in bowel symptoms was observed (Table 16).

Quality of Life

Overall QOL was no different between surveillance subjects and IBD controls (SF 36 mean 63.82 vs.65.48 respectively; p=0.70); nor were there any differences within each QOL domain nor for physical or mental component summary scores (Table 17). When analysing males alone, overall QOL did not significantly differ between Surveillance subjects and IBD controls, nor in any individual domain of QOL, and a similar finding was noted when comparing female Surveillance subjects and IBD Controls with one another (Table 18). Physical and Mental Component Summary Scores (PCS and MCS) for the age and gender matched Australian population[171] are similar to these findings in IBD subjects and are summarised in Table 18.

Locus of Control

Groups did not differ in mean score on any locus of control classification (Internal, Powerful Others and Chance Locus of Control, all p=0.52) (Table 19), indicating a similar perspective for the attribution of health events by the cohorts.

Anxiety, Depression, Anger and Curiosity

There was no demonstrated difference between IBD cohorts in mean scores on "state" subscales of the STPI: anxiety (p=0.91), curiosity (p=0.12), anger (p=0.81) and depression (p=0.70). Mean Spielberger "trait" scores for these four parameters were within expected normative ranges in both surveillance and control IBD groups, with no significant difference between IBD groups (Table 20).

Risk Perception

Interestingly, despite the age difference between groups, CRC Risk Perception did not differ between surveillance and control subjects (p=1.0), with both IBD groups grossly overestimating their perceived lifetime risk of CRC at 50%. A high proportion of subjects in both groups, however, agreed that surveillance would reduce their CRC risk (93.4% SS vs 89.8% CS, p=0.53) (Table 21).

Discussion

This is the largest study to our knowledge examining psychological parameters in IBD subjects undergoing versus not undergoing colonoscopic surveillance for Colorectal Cancer. Given the data addressing surveillance utility in this population remains

debatable, it is crucial to exclude the possibility of psychological harm as a result of such surveillance.

We have demonstrated no evidence of psychological harm or benefit amongst IBD patients undergoing surveillance colonoscopy compared with those not yet enrolled in a surveillance program. A striking and novel finding was that subjects in both surveillance and control groups vastly overestimated their lifetime risk of CRC at 50%, whereas current data suggest the actual risk of CRC in colitis (UC or Crohn's) is 2% after 10 years, 8% after 20 years and 18% after 30 years of disease[177].

This phenomenon of exaggerated risk perception has been observed in other endoscopic surveillance programs. Shaheen et al[176] reported that 63% and 38% of patients undergoing surveillance for Barrett's esophagus overestimated their 1 year and lifetime risk of cancer, respectively. Such risk overestimation has been associated with increased anxiety in other surveillance settings [178], but interestingly in our study surveillance was not associated with increased short or long term anxiety when compared with non-surveillance IBD subjects and also compared with general population norms. This may reflect confidence in the surveillance program, as a high proportion of our subjects felt that participating in surveillance colonoscopy would reduce their risk of cancer. It is also possible that participation bias is relevant here such that the 49% of invitees who responded may have done so as they are more comfortable with surveillance practices and the risk confrontation this entails.

Other studies addressing the psychological effects of cancer surveillance have produced mixed results. A Swedish study assessing anxiety and coping ability before and after surveillance colonoscopy in 41 UC subjects found no difference in these parameters when compared with UC subjects not yet eligible for surveillance[179]. A population based US study, however, suggested that people given 'information overload" about their cancer risk as part of screening or surveillance were more likely to report higher anxiety levels[180], whereas another study demonstrated improvement in the mental health and vitality domains of QoL after colonoscopic screening for CRC[181] This balance of positive and negative influences upon anxiety levels may result in the seemingly neutral effect of surveillance seen in our cohort.

Quality of Life also appeared to be unaffected by surveillance in our study. Very few studies have investigated QoL specifically in IBD populations undergoing surveillance colonoscopy. One recent prospective study included a subset of IBD patients in a QoL analysis pre and post colonoscopy for a variety of indications using SF 36 and found no difference in overall QoL pre and post procedure[182]. Interestingly, the decrease in the QoL domain of physical functioning reported in non IBD subjects one month after the procedure was not observed in the IBD subset.

Subjects in both IBD cohorts in this study tended to vastly overestimate their lifetime CRC risk. This overestimation may prove advantageous, as this characteristic has been shown in several studies to improve adherence to cancer screening programs[183] [184] [185]. Whether increased participation results in better outcomes is debatable

however, as a 2010 Netherlands study demonstrated that many IBD patients had limited understanding regarding surveillance, and that 70% of those present at an information session would refuse colectomy if dysplasia were found at colonoscopy[186]. Interestingly, subjects in this study estimated their CRC risk at 25%, half of that estimated by our cohorts.

Cancer risk perception has been shown to be subject to various factors, of which genetic risk and personal history of cancer appear to be the most important[187]. Predictors of higher perceived risk of CRC in a large population based study included being female, younger, having a positive family history of CRC, more bowel symptoms, poorer perceived health and higher anxiety levels[188] A study specific to IBD subjects identified predictors of higher perceived risk to be more than 5 IBD flares per year, knowing someone with CRC and being female[186]. Interestingly disease duration and type were not influencing variables in this study, similar to our finding of comparable risk perception in cohorts with contrasting disease duration and subject age. Our cohorts may have differed from each other in disease activity with IBD control subjects reporting more bowel symptoms, but this again did not appear to affect risk perception.

Cognitive factors also influence risk perception. Those who believe CRC is not a preventable disease have higher levels of perceived risk[189], and it is interesting to note that neither of our IBD cohorts demonstrated low internal locus of control, a characteristic likely to increase perceived cancer risk. An inverse relationship between

spirituality and risk perception has been found in two studies[190] [191], such that spiritual coping may reduce cancer risk perception, although an assessment of this as an example of an external locus of control was not undertaken in our cohorts.

This study is limited by its cross sectional nature and thus data regarding timing within the surveillance cycle were not gathered and this may have influenced results. It was also beyond the scope of this survey to undertake rigorous assessment of disease activity, medication regimen and adherence, disease severity, as well as family history of CRC, all of which may influence the psychological parameters assessed.

In summary, colonoscopic colorectal cancer surveillance does not appear to impair or improve psychological wellbeing in patients with IBD. Our findings do not impose ethical barriers upon continued surveillance at present, whilst more convincing mortality reduction data attributable to this practice are awaited. Clinicians have an opportunity to reduce CRC rates by promoting optimal disease control, whilst addressing the tendency toward overestimation of cancer risk in IBD patients by provision of accurate, numerical risk estimates as part of the routine clinical encounter.

Tables and Figures

Table 15: Subject demographics by group

		IBD Surveillance n=78	IBD Controls n=61	p
Age, Mean (SD)		55.4 (11.7)	51.1 (13.4)	.048
		Frequency (%)		
IBD type	CD	27 (34.6)	29 (47.5)	.155
	UC	49 (62.8)	32 (52.5)	
Marital status	Married/de facto	55 (71.4)	39 (63.9)	.348
Language spoken at home	English	76 (97.4)	61 (100)	.504
Education	Nil	8 (12.7)	7 (12.1)	.358
	High School	34 (54)	23 (39.7)	
	Diploma	9 (14.3)	14 (24.1)	
	University degree	12 (19)	14 (24.1)	
Employment status	Full time	28 (36.4)	28 (45.9)	.630
	Part time	13 (16.9)	10 (16.4)	
	Not working	10 (13)	8 (13.1)	
	Retired	26 (33.8)	15 (24.6)	
House ownership	Owner	42 (55.3)	22 (36.7)	.089
	Pays mortgage	24 (31.6)	25 (41.7)	
	Renting	10 (13.2)	13 (21.7)	

Table 16: Bowel Symptoms

	IBD Surveillance n=78	**IBD Controls n=61**	**p**
	Frequency (%)		
Constipation	29 (43.9)	23 (43.4)	.953
Wind	66 (85.7)	50 (84.7)	.874
Incontinence	12 (16.2)	16 (27.1)	.125
Hemorrhoids	34 (44.7)	21 (35)	.251
Diarrhoea	52 (66.7)	50 (82)	.043
Abdominal pain	47 (61.8)	47 (77)	.057
Blood	30 (38.5)	25 (41.7)	.703

Table 17: Median Score on SF 36 Subscales by Cohort

	IBD Surveillance n=78	**IBD Controls n=61**	**z**	**p**
	Median (IQR)			
Physical functioning	90 (70-95)	85 (70-95)	-.520	.603
Role physical	75 (25-100)	75 (25-100)	-.338	.735
Pain	72 (41-84)	62 (41-84)	-.930	.352
General Health	52 (35-72)	53.5 (27.7-69.2)	-.632	.527
Vitality	50 (25-70)	50 (30-65)	-.466	.641
Social functioning	75 (62.5-100)	75 (62.5-100)	-.262	.793
Role emotional	100 (33.3-100)	100 (66.6-100)	.007	.994
Mental health	76 (60-84)	68 (60-80)	-1.251	.211
Physical Component Summary	46.9 (36.2-53.1)	44.2 (38.1-52.9)	-.529	.597
Mental Component Summary	49.1 (38.6-54.2)	48.6 (40.1-53.7)	-.317	.751

Table 18: Quality of Life by SF36 – Physical and Mental Components by Gender

Females	**Surveillance n=33**	**IBD Controls n=30**	**z**	**p**
	Median (IQR)			
Physical Component	46.1 (35.9-53.1)	43.9 (38.6-52.6)	.500	.945
Mental Component	49 (37.6-52.9)	48.7 (39.1-54.5)	.534	.591
Males	**Surveillance n=44**	**IBD Controls n=33**	**z**	**p**
	Median (IQR)			
Physical Component	48.8 (36.5-53.1)	44.7 (33.9-53.6)	.595	.474
Mental Component	51.8 (38.9-55.9)	48.6 (41.6-52.8)	.590	.441

Australian Population Age Matched Mean Values[171]

	Females	**Males**
Physical Component	46.6	49.7
Mental Component	50.6	50.3

Table 19: Multidimensional Locus of Control Mean Scores by Cohort

	IBD Surveillance	IBD Controls	t	df	p
	Mean (SD)				
Internal Locus of Control	5.84 (0.67)	6.07 (0.79)	-.441	132	.660
Powerful Others Locus of Control	4.91 (0.57)	4.35 (0.56)	.825	132	.411
Chance Locus of Control	5.30 (0.61)	4.99 (0.65)	1.051	131	.295

Table 20: Spielberger State-Trait Personality Inventory

	IBD Surveillance n=78	**IBD Controls n=61**	**t**	**df**	**p**
	Mean (SD)				
State Anxiety	18.8 (4.1)	18.9 (3.5)	-.116	136	.908
State Curiosity	26.2 (7.1)	24.6 (4.8)	1.55	131	.122
State Anger	12.1 (5.1)	11.9 (3.7)	.248	136	.805
State Depression	17.7 (5.9)	18.1 (5.4)	-.385	132	.701
Trait Anxiety	20.6 (6.3)	20.3 (5.1)	.260	135	.796
Trait Curiosity	27.6 (5.9)	27.6 (5.3)	-.067	134	.946
Trait Anger	15.8 (9.8)	15.2 (5.1)	.393	137	.695
Trait Depression	18.8 (5.3)	18.9 (4.3)	-.163	131	.868

Table 21: Risk Perception of Colorectal Cancer in IBD Surveillance vs Control Subjects

		IBD Surveillance n=78	IBD Controls n=61	p
		Frequency (%)		
Risk of colorectal cancer if not participate in surveillance	It is likely	54 (70.1)	38 (63.3)	.401
How much more likely are you to suffer from colorectal cancer than the average person of the same gender and age	More likely than others	64 (82.1)	46 (76.7)	.679
How serious would it be if you were to suffer from colorectal cancer	Serious	72 (93.5)	54 (90)	.534
I am confident I can participate in colorectal cancer surveillance	Agree	73 (94.8)	52 (88.1)	.208
I will find it difficult to participate	Disagree	62 (81.6)	44 (77.2)	.534
Surveillance recommendations will reduce my risk	Agree	71 (93.4)	53 (89.8)	.533
No matter what I do the risk remains the same	Disagree	62 (81.6)	49 (83.1)	.824

CHAPTER 7: COVERT DOSE REDUCTION IS A DISTINCT TYPE OF MEDICATION NON-ADHERENCE OBSERVED ACROSS ALL CARE SETTINGS IN INFLAMMATORY BOWEL DISEASE

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AUTHOR ROLES

R Mountifield was involved in study conception, design, seeking ethical approval, data acquisition, analysis and interpretation, drafting the manuscript and modifying and preparing the final paper. JM Andrews and P Bampton were involved in planning the study, seeking ethical approval and revising the draft manuscript. A Mikocka-Walus assisted with data interpretation.

Abstract

Background: Non-adherence by dose omission is common and deleterious to outcomes in Inflammatory Bowel Disease (IBD), but covert dose reduction (CDR) remains unexplored.

Aims: To determine frequency and attitudinal predictors of overall medication non-adherence and of covert dose reduction as separate entities.

Methods: A cross sectional questionnaire was undertaken involving IBD patients in three different geographical regions and care settings. Demographics, medication adherence by dose omission, and rate of patient initiated dose reduction of conventional meds without practitioner knowledge (CDR) were assessed, along with attitudes towards IBD medication and psychological parameters such as anxiety, depression, personality traits and quality of life (QoL).

Results: Of 473 respondents (mean age 50.3 years, 60.2% female) frequency of non-adherence was 21.9%, and CDR 26.9% ($p<0.001$). By logistic regression, significant independent predictors of non-adherence were dissatisfaction with the patient-doctor relationship ($p<0.001$), depression ($p=0.001$), anxiety ($p=0.047$), and negative views regarding medication efficacy ($p<0.001$) or safety ($p=0.017$). Independent predictors of covert dose reduction included regular complementary medicine (CAM) use ($p<0.001$), experiencing more informative ($p<0.001$) and comfortable ($p=0.006$) consultations with alternative practitioners, disbelieving doctor delivered information ($p=0.021$) and safety concerns regarding conventional medication ($p<0.001$). Free text responses supported this. Neither the frequency of non-adherence ($p=0.569$) nor CDR ($p=0.914$) differed between cohorts by different treatment setting.

Conclusions: Covert dose reduction of IBD medication is more common than omission of medication doses, predicted by different factors to usual non-adherence, and has not been previously reported in IBD. The strongest predictor of CDR is regular CAM use.

Key Words: Medication Adherence, Dose Modification, Inflammatory Bowel Disease, Complementary and Alternative Medicine, Medication Attitudes

Introduction

Consistent medication adherence yields better outcomes in Inflammatory Bowel Disease (IBD). Currently available therapies have not only an important role in maintaining remission[192], but also in the prevention of colorectal cancer via inflammation reduction and possibly direct antineoplastic pathways[193, 194].

Non-adherence to IBD medication is common, most studies suggesting a frequency of 30-45% of patients[195], but a wider range is reported. Thus many studies have investigated risk factors for non-adherence, and although results have been inconsistent[195], some common themes have emerged. Demographic and clinical factors such as younger age[196], employed status[196] , being unmarried[197] [198], disease duration[199] , pill count[198] and medication type[200] have been associated with non-adherence, and whilst this is useful to identify at-risk patients, these factors are not modifiable.

Studies seeking behavioural reasons for non-adherence divide causes into categories encompassing forgetfulness (nearly 50%) and deliberate medication avoidance[199]. The latter relates to patient belief of necessity and concerns regarding medication effects[201] [199] [200], dissatisfaction with or poor recall of information regarding medications[202], physician patient discordance[202, 203] [204] [162], psychological stress, depression, anxiety[205] [206] [207], and poorer QoL[207].

Most instruments used to measure medication non-adherence primarily assess dose omission rather than dose reduction. This phenomenon of patient-initiated covert dose reduction (CDR) has not been studied as a separate entity in IBD, although it has been reported amongst patients prescribed antihypertensive medications[208]. Consistent under-dosing of IBD medication by CDR is likely to have as deleterious an effect on disease control as dose omission[209]. Therefore CDR

is important to identify as distinct from traditionally defined non-adherence by dose omission, as it may reflect different medication attitudes and require a different intervention.

Additionally, existing data suggest there is considerable variation in non-adherence rates between centres[210], which may affect generalizability of results from single centre studies. It is unclear whether such variation arises from cultural, geographic or care structure differences. This study simultaneously assessed the frequency and attitudinal and psychological predictors of non-adherence (using existing instruments) and covert dose reduction of IBD medication, and compared frequencies across three contrasting IBD cohorts in Australia.

Methods

Subject selection and recruitment

IBD patients from three different care settings in two distinct geographical locations in Australia were invited to participate.

The first cohort came from a large metropolitan teaching hospital IBD Service at Flinders Medical Centre (FMC), which offers specialist IBD physician and IBD nurse care. The second cohort consisted of IBD patients in an overlapping area, receiving their care in a metropolitan Private Practice setting by general Gastroenterologists. The third cohort included IBD patients cared for via Royal Darwin Hospital (RDH), a public hospital in a very remote location in Northern Australia. When this study was conducted, IBD care in Darwin was undertaken predominantly by General Practitioners (GPs) and General Surgeons.

Potential subjects were identified from IBD databases/hospital records in each location and mailed a questionnaire. Reminder letters were sent to non-responders after one and three months.

Questionnaire content

The questionnaire sought demographic details, views regarding conventional IBD medications, Complementary and Alternative Medicine (CAM), Quality of Life (QOL), and Psychological and Personality traits (Appendix K). Where possible, validated instruments were used as described below, with permission where necessary.

Standard medication adherence was assessed using the Morisky 4 item Self Report *Measure of Medication Taking Behaviour* (MMAS-4)[211] [212], a 4 item "yes" or "no" survey that has been validated in a broad range of diseases[213]. Each of the 4 items is scored 0 or 1, the sum of the 4 responses yielding a total of 0 to 4, whereby high adherence is indicated by a score of 0, medium adherence by 1-2 and low adherence by 3-4.

Currently no validated tests exist to assess CDR. This was therefore assessed in two ways; firstly as a dichotomous variable (yes/no) based on answer to the question "I take less than prescribed of my IBD medication without telling my doctor". A continuous variable representing CDR tendency was also generated using factor analysis.

Other medication attitude statements were put to subjects, seeking the extent of agreement or disagreement using a Likert scale, and additional free text responses were encouraged.

Anxiety and Depression was measured using the Hospital Anxiety and Depression Scale[214], Quality of Life using the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) [215], and the Spielberger State-Trait Personality Inventory[173] [216] (STPI) was used to assess depressive symptoms, anxiety, anger and curiosity between cohorts [175].

Statistical Analysis

Comparisons between cohort means and medians were performed using the Kruskal Wallis test for non-normally distributed values, and two tailed t test or ANOVA for normally distributed

values. Pearson's Chi-square or Fisher's exact test were applied as appropriate for categorical data.

Significant or trend associations at univariate level ($p<0.10$) determined which variables were included in regression analyses. Binary logistic regression was used to assess predictors of non-adherence and CDR as dichotomous dependent variables. For the purposes of binary logistic regression the medium and high categories for MMAS-4 were combined to create high (score 0-2) and low adherence (score 3-4) dichotomous outcomes.

CDR was also expressed as a continuous variable generated by exploratory factor analysis for ordinal data using M Plus software (V5.2). Multiple linear regression was used to determine predictors of CDR as a continuous dependent variable.

A p value of <0.05 was considered statistically significant. Apart from factor analysis, statistical calculations were performed using IBM SPSS Statistics for Windows, version 22, 2013 (IBM Corp).

Ethical Considerations

The study was approved by Flinders Clinical Research Ethics Committee (FCREC) on behalf of SA subjects and Menzies School of Health Human Research Ethics Committee for subjects cared for in Darwin (Appendices L, M, N and O).

Results

Demographic Data

Response rates to the survey differed between cohorts, with 337 /612 (55.1%) of FMC and 91/180 (50.5%) of SA Private invitees participating, compared with 35/100 (35%) in Darwin ($p<0.0001$). Non respondents did not differ from respondents by gender ($p=0.2$), but were younger than respondents (Table 22). Darwin subjects were more likely be current or previous smokers, and to receive a disability support pension (Table 23).

Medication Adherence by MMAS-4

"Low adherence" criteria were met by 21.9% of subjects overall, with no statistical differences between cohorts (p=0.569) (Figure 13). "Medium" adherence was present in 34.8% and high adherence in 43.3% of subjects.

Of the 241 subjects reporting which medication they were most likely to omit or forget, 31.7% said oral 5ASA or Sulfasalazine, 13.7% azathioprine or 6MP, 10% corticosteroid, 7.1% enemas, 1% adalimumab and 36.5% reported nonadherence to other medications, including methotrexate, probiotics, loperamide, and antibiotics. These proportions correspond approximately with local prescribing rates of each medication, the use of biologicals being infrequent at this time due to prescribing restrictions in Australia.

Of the 133 subjects offering free text reasons for low adherence, approximately half (50.6%) cited forgetfulness and disorganisation as the main reason for missing medication doses. The remaining 49.4% were deliberately low adherent, citing adverse effects (18.4%), medication cost (13.5%), perceived lack of efficacy (7.7%), finding enema use disagreeable (7.7%), or lack of convincing benefit based on doctor's explanation (2%), with no difference between cohorts (p=0.10).

Associations of Low Adherence – Univariate Analysis

Demographic factors associated with low adherence included female gender (27.3% versus 13.6%, p=0.001), permanent employment (26.0% versus 15.9%, p=0.008), younger age (mean 44.0 versus 52.0 years, p<0.001), and high pill burden (p=0.024). Disease type (UC versus CD) did not affect adherence (0.388).

Attitudes significantly associated with low adherence on univariate analysis include perceived medication inefficacy (p<0.001), adverse effects (p=0.041), negative relationship with the doctor (p=0.008), missing IBD appointments (p<0.001), desiring more control over IBD management (p=0.036), diagnosis of depression (p=0.007), lack of social support (p<0.001) and personal

relationship dissatisfaction (p<0.001). Preference for an alternative practitioner consultation style was associated with low adherence (p=0.047), whilst regular CAM use was not (p=0.263). Subjects scoring higher for anxiety (p=0.001), depression (p=0.002) and anger (p=0.002) and lower for curiosity (p=0.043) were more likely to report low adherence, whilst QOL did not affect adherence (p=0.116)

Low Adherence predictors by Logistic Regression Analysis

After adjusting for known influences on adherence such as age, gender, disease type, employment, relationship status, pill burden, and quality of life, associations that remained statistically significant are shown in Table 24. This model explained a significant proportion of variance in low adherence rates (adjusted pseudo R squared 0.240, goodness of fit by Hosmer Lemeshow p=0.347). The strongest predictive factor was a patient perception of a negative relationship with the IBD doctor. Psychological variables as well as medication beliefs such as doubts about efficacy and adverse effects were also associated with low adherence. The strong association with missing IBD appointments likely reflects the same underlying attitudes contributing to low medication adherence.

Covert Dose Reduction

When asking specifically about deliberate dose reduction of IBD medications without knowledge of their physician, more than a quarter of the cohort reported this, making it more common than low adherence (26.9% vs. 21.9%; p<0.001), with no difference between cohorts (Figure 13). Medications were proportionally affected by this behaviour in the same way as reported above for low adherence. Interestingly, the vast majority (68.8%) of subjects reporting regular CDR, reported themselves as highly adherent by MMAS-4, on the basis that they rarely missed medication doses, despite consistently under-dosing, unmasking a clinically relevant gap in this instrument's ability to represent true adherence to therapy as prescribed.

Significant associations of CDR on univariate analysis included regular CAM use (37.1% vs 18.9%, p<0.001), dissatisfaction with doctor communication (p=0.037) and information provision (p=0.001), a negative relationship with the doctor (p=0.027), personal relationship dissatisfaction (p=0.035), and increased anxiety (p=0.037). In contrast with non-adherence findings, gender did not predict CDR (p=0.306), although younger age was associated with CDR (47.69 versus 51.36 years, p=0.016). Again disease type did not affect CDR (p=0.144).

Covert Dose Reduction Predictors by Logistic and Linear Regression Analyses

Regular Complementary or Alternative (CAM) use was the strongest predictor of CDR, the 20.7% of subjects consulting an alternative practitioner being no more or less likely to dose reduce than those who obtained CAM independently (p=0.854). Of all subjects in the study, 45.4% reported regular CAM use (often or very often).

Adjusting for the same variables as for low adherence, associations of CDR are presented in Table 25 (adjusted pseudo R squared 0.178, goodness of fit Homer Lemeshow p=0.256). These predictive factors were confirmed in a linear regression model using factor scores for CDR; the overall model fit was adjusted R squared 0.234

Table 26).

Types of CAM used are reported in

Table 27. A theme emerged from the free text responses of CAM users that “natural therapies” were efficacious enough to allow dose reduction of “stronger” conventional meds, which might make them “safer”.

Psychological Variables and QOL in Contrasting IBD cohorts

No differences between cohorts were seen for HADS anxiety or depression, Trait anxiety, depression, anger, or QoL. The overall frequency of at least mild depression and mild anxiety (HADS>7) was 33.7% and 27.7% respectively, consistent with other IBD populations*[217].* There was a trend toward less curiosity amongst Darwin compared with Private subjects (mean Spielberger score 24.0 versus 26.8, p=0.065).

It was not possible to compare predictors of non-adherence and CDR by cohort due to the smaller size of Private and Darwin cohorts. On individual questionnaire items, a trend toward more doctor shopping was observed amongst FMC versus private subjects (38.3% versus 25.6%, p=0.080), and increased self-reported depression in Darwin subjects (45.7% versus 25.8% private, p=0.087), although no differences were seen between cohorts by HADS.

Discussion

This is the first study in Inflammatory Bowel Disease to investigate the important issue of Covert Dose Reduction as a distinct type of medication non-adherence, and identify its frequency and attitudinal and psychological predictors across three patient cohorts.

Traditional non-adherence by MMAS-4 was reported by 21.9% of subjects, associated with anxiety and depression, lack of social supports, negative beliefs about efficacy and adverse effects, and negative patient-doctor relationships. Covert dose reduction was reported more frequently (26.9%), and was not detected by MMAS-4 as only 32.2% of dose reducing subjects in our population met criteria for low adherence. Whilst other adherence measuring instruments such

as MMAS-8 and the Medication Adherence Response Scale[218] do assess dose reduction, responses to this contribute to an overall adherence score, which does not distinguish between dose omission and reduction. We also found that CDR has different behavioural predictors, including regular CAM use, more positive consultation experiences with alternative practitioners, and scepticism of doctor provided information.

The frequency of non-adherence and of covert dose reduction was similar across the three cohorts from contrasting IBD treatment settings, which indicates some generalizability of these results. Supporting this is the similarity between predictors of traditional non-adherence between our populations and those reported internationally.

Non-adherence rates in this study are at the lower end of that reported previously[201] [195] [219, 220] [199], which may result from participation bias and the self-reporting methodology. Also, a large proportion of subjects scored as "medium" adherent (34.8%) by self-report, many of whom may be classified as low adherent using more quantifiable adherence assessment methods.

Regarding predictors of non-adherence, the presence of a negative doctor patient relationship was the strongest attitudinal risk factor for non-adherence in this study, and has been observed in other populations[202, 206, 221]. Our finding of an association between less satisfactory information provision by the doctor and non-adherence contrasts with another Australian study, however. [201]

The association between medication efficacy doubts and non-adherence is also consistent with previous studies[200, 201, 206] as is the association with experience or fear of adverse effects, [201, 222] [200]. In the broader context of other chronic diseases, a recent meta-analysis examining the "Necessity-Concerns Framework", confirmed that higher medication adherence is associated with stronger perceptions of treatment necessity and fewer concerns about

treatment[223]. As in our study, depression has been identified as a risk factor for non-adherence in other IBD populations[224] [225] [226] [227] [228], but not all[229].

Whilst covert dose reduction of IBD medications has been noted in 18% of patients in a previous non-adherence study[220], until now associations of this behaviour as a distinct entity have not been sought. Independent predictors of CDR in this study were notably different from those predicting overall non-adherence. CAM use did not affect overall adherence in our cohorts, and this lack of association is supported in the literature[230] [199, 231]. It was, however, the strongest attitudinal predictor of CDR in this study, along with a preference for the consultation style of alternative practitioners in terms of information provision, comfort level and believability. This association between CAM use and patient driven conventional medication under-dosage has been reported recently in hypertension[208], and may apply in other chronic illness settings also. Consistent with this theme of preferring a holistic approach, many subjects (28.1%) reported wanting more of a psychological focus during doctor consultations, and this was another predictor of CDR.

Limitations of this study include the self-reporting nature of the questionnaire, which restricted the amount of verifiable clinical information available, such as the type and dosage of medication prescribed. Participation bias is likely, in that a very high proportion (98.7%) of subjects reported a good relationship with their doctor. It is likely that invitees with a less sanguine view may have chosen not to participate. Non-adherence rates may have been even higher in non-participants, with only the most adherent in the smaller Darwin cohort, for example, taking part, thus potentially masking true differences in adherence between IBD populations. Whilst a validated test was used to assess overall adherence, the CDR testing method has not yet been validated.

Covert dose reduction of IBD medication may be a distinct subtype of non-adherence with different attitudinal predictors to dose omission, which is not assessed as a separate entity using

current adherence scales. Further work is warranted to develop validated scales to measure this phenomenon and to confirm predictors identified in this study. The negative impact of CDR on disease control may be considerable and further investigation is justified not only in IBD, but in the broader chronic disease population.

Tables and Figures

Table 22: Respondent versus non respondent characteristics

	Respondents	Non-respondents	P value
Mean age (years)	50.3	43.7	0.065
% female	60.2	55.7	0.2

Table 23: Demographic characteristics in contrasting IBD cohorts

	FMC (n=337)	**Private (n=91)**	**Darwin (n=35)**
% Female respondents	60.2	60.4	60
% Crohn's disease	55.2	57.1	48.6
% Indigenous subjects	0.9	1.1	2.9
% Current smokers	11.1	13.6	17.1
% Receiving Disability Support Pension	1.8	1.1	5.7
% Employed	58.7	56.7	52.9
% Currently partnered	92.2	95.3	93.3

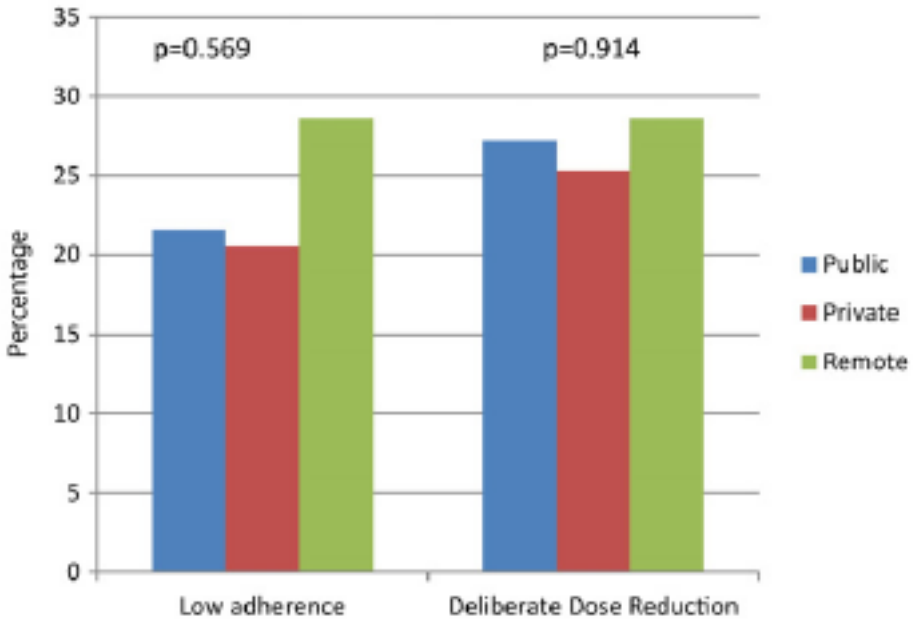

Figure 13: Rates of low adherence and covert dose reduction were similar across cohorts

Table 24: Independent predictors of low adherence amongst IBD subjects using logistic regression

Predictor	**Odds Ratio**	**95% Confidence Interval**	**p value**
Negative relationship with IBD doctor	5.425	2.437-12.075	<0.001
Missing IBD appointments	4.420	3.080-6.342	<0.001
Perceived medication efficacy	0.437	0.339-0.562	<0.001
Lack of social support	2.175	1.106-4.276	0.030
Satisfied with level of information re IBD from physician	0.500	0.331-0.754	<0.001
Antidepressant use	1.889	1.062-3.363	0.031
Satisfied with personal relationships	0.531	0.374-0.756	<0.001
Experienced adverse effects IBD medication	1.319	1.050-1.646	0.017

Depression- patient reported diagnosis	1.331	1.071-1.654	0.010
Anxiety (HADS)	1.110	1.001-1.230	0.047
Depression (HADS)	1.107	1.057-1.160	0.001

Table 25: Independent predictors of covert dose reduction using logistic regression

	Odds Ratio	**95% Confidence Interval**	**p value**
Regular CAM use	4.389	2.399-8.028	<0.001
Believes what doctor says about IBD	0.321	0.122-0.843	0.021
Feels alternative practitioner provides more information about IBD than doctor	3.104	1.650-5.839	<0.001
Feels more comfortable with alternative practitioner	2.193	1.254-3.836	0.006
Wants IBD doctor to focus more on psychological aspects	1.841	1.111-3.051	0.018
Experienced adverse effects conventional IBD medication	1.747	1.388-2.199	<0.001

HADS anxiety	1.119	1.071-1.170	<0.001

Table 26: Independent predictors of covert dose reduction by linear regression analysis

	Beta (correlation coefficient)	**p value**
Regular CAM use	0.228	<0.001
Adverse effects conventional medications	0.149	0.007
Believes what doctor says about IBD medications	-0.148	0.006
Wants doctor to focus more on psychological aspects	0.141	0.010
Feels more comfortable with alternative practitioner	0.145	0.091
HADS anxiety	0.100	0.094
Feels alternative practitioner provides more information about IBD than doctor	0.095	0.087

Table 27: Most commonly used CAM types reported by IBD subjects

Type of CAM	**Percentage of total CAM reported overall**
Herbal remedies (eg slippery elm, aloe vera juice, olive oil extract, green lipped mussel oil)	30.5%
Probiotics	22.6%
Fish oil	12.1%
Chinese medicine	10.5%
Acupuncture, massage, magnetism	10.5%
Other (prayer, meditation, exercise, dietary supplements, hypnotherapy)	13.7%

CHAPTER 8: DOCTOR COMMUNICATION QUALITY AND FRIENDS' ATTITUDES INFLUENCE COMPLEMENTARY MEDICINE USE IN INFLAMMATORY BOWEL DISEASE

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AUTHOR ROLES

R Mountifield was involved in study conception, design, seeking ethical approval, data acquisition, analysis and interpretation, drafting the manuscript and modifying and preparing the final paper. JM Andrews and P Bampton were involved in planning the study, seeking ethical approval and revising the draft manuscript. A Mikocka-Walus assisted with data interpretation.

Abstract

Background: Complementary and Alternative therapy (CAM) use is widespread in Inflammatory Bowel Disease (IBD), however the influence of health care delivery setting on its use is unclear. Predictors of CAM use in Australian IBD patients have not been previously examined.

Methods: A cross sectional questionnaire was administered to IBD patients in 3 separate cohorts which differed by geographical region and care setting. Demographics and frequency of regular CAM use were assessed, along with attitudes towards IBD medication and psychological parameters such as anxiety, depression, personality traits and quality of life (QoL), and compared across cohorts. Independent attitudinal and psychological predictors of CAM use were determined using binary logistic regression analysis.

Results: In 473 respondents (mean age 50.3 years, 60.2% female) regular CAM use was reported by 45.4%, and did not vary between cohorts. Only 54.1% of users disclosed CAM use to their doctor. Independent predictors of CAM use which confirm those reported previously were: covert conventional medication dose reduction ($p<0.001$), seeking psychological treatment ($p<0.001$), adverse effects of conventional medication ($p=0.043$), and higher QoL ($p<0.001$). Newly identified predictors were CAM use by family or friends ($p<0.001$), dissatisfaction with patient-doctor communication ($p<0.001$), and lower depression scores ($p<0.001$).

Conclusions: In addition to previously identified predictors of CAM use, these data show that physician attention to communication and the patient-doctor relationship is important as these factors influence CAM use. Patient reluctance to discuss CAM with physicians may promote greater reliance on social contacts to influence CAM decisions.

Key Words**:** Complementary Medicine / Therapy, Alternative Therapy, Inflammatory Bowel Disease, Patient-Doctor Communication, Medication Adherence

Introduction

The use of complementary and alternative medicine (CAM) is widespread in Inflammatory Bowel Disease (IBD), rates ranging from 31% to 74% in studies across Europe[48, 199, 232] Australasia[45, 233] and North America[234]. Studies examining the efficacy and safety of these treatments in IBD are heterogeneous and controlled data limited[235], thus it is difficult for physicians to advise patients regarding these potentially deleterious agents. However, the ongoing consumer demand for alternatives to conventional therapy means that IBD physicians need to be alert to CAM use, its associated behaviours and underlying health beliefs that may influence conventional IBD care.

Approximately three quarters of CAM taking IBD patients do not discuss its use with their IBD physician[48, 236], thus there is a need to identify surrogate markers or predictors of use that may prompt discussion about CAM during routine consultation.

Predictors previously established fall into demographic, clinical and attitudinal categories. Independent demographic predictors of CAM use include younger age[199, 233, 237], female gender[199, 233, 237], higher educational level[233, 237], income and employment[233, 236], and middle social class at birth[233]. Clinical predictors are more controversial[238, 239] but have included Crohn's disease[237], longer disease duration[240], medication type[199, 241], active disease[242], the experience of adverse effects of conventional medication[232, 242, 243], and a concurrent diagnosis of Irritable Bowel Syndrome (IBS)[244].

Some studies however, have suggested that health attitudes and behaviours are more important than demographics in influencing CAM use[245] [243], and there has been recent enthusiasm to identify attitudinal and behavioural predictors as these factors are potentially modifiable. Data

regarding such predictors are more limited and heterogeneous but suggest that a need for control over disease[245], desire for a holistic approach[245], lack of confidence in the IBD physician[245], poorer therapeutic relationships[246], and vegetarianism[233] are associated with CAM use. CAM use has also been suggested as a marker of psychological or social distress[244].

Disparity in findings between different studies may relate in part to cultural differences in IBD populations, as suggested by an Italian study which demonstrated regional variations in CAM type chosen, despite similar rates of use across the cohorts[242]. An Australian diabetes study suggested an effect of health care setting on CAM use frequency, reporting private health insurance as an independent predictor of CAM use[247]. In IBD patients in Australia, whilst overall frequency and potential ethnically based differences in CAM use have been previously examined[45], attitudinal and psychological predictors of its use are unexplored, as is the effect of the health care setting on CAM uptake.

Aims

To examine the frequency of regular CAM use in three Australian cohorts of contrasting care setting and geography, and identify independent attitudinal and psychological predictors of CAM use across all cohorts.

Methods and Materials

Subject selection and recruitment

IBD patients from three different care settings in two distinct geographical locations in Australia were invited to participate. This method has been reported previously[24].

The first cohort came from a metropolitan public teaching hospital based specialist IBD Service at Flinders Medical Centre (FMC). This is a large, government funded hospital, offering

secondary/tertiary care for a local regional population of 341 000 with a Gastroenterology inpatient and outpatient service, and IBD nurses available to patients within working hours.

The second cohort consisted of IBD patients in an overlapping area, receiving their care via a metropolitan Private Practice setting. These patients were under the care of one of four male general Gastroenterologists with extensive experience in managing IBD, without attachment to a specialist IBD unit, or access to IBD specialist nurse support.

The third cohort consisted of IBD patients cared for via Royal Darwin Hospital (RDH), a public hospital in a very remote location in Northern Australia. When this study was conducted, IBD care in Darwin was undertaken predominantly by General Practitioners (GPs) and General Surgeons, with no specialist Gastroenterologist residing in Darwin, and no IBD nurse. The nearest tertiary hospital is in Adelaide, SA, more than 3000 kilometres away.

Potential subjects were identified from IBD databases/hospital records in each location and mailed a questionnaire. Reminder letters were sent to non-responders after one and three months.

Questionnaire content

The opening section of the questionnaire sought demographic details including age, gender, disease type, indigenous, relationship and employment status as well as current or previous history of smoking (Appendix K).

In the following sections, A-D, participants answered questions assessing: A) Views regarding conventional IBD medications, B) Views regarding CAM C) Quality of Life and D) Psychological and Personality traits. Where possible, validated instruments were used as described below.

IBD-specific CAM use was assessed by asking subjects to rate the frequency with which they use complementary or alternative medicine to treat IBD on an ordinal Likert scale. A dichotomous

variable was then generated whereby “yes” responses encompassed those describing their use as “often” or “very often”, and “no” included responses “sometimes”, “rarely” and “never”.

Medication Adherence was assessed using the Morisky 4 item Self Report Measure of Medication Taking Behaviour. (MMAS-4)[211] [212], examining predominantly dose omission, and Covert Dose Reduction (CDR), the tendency to take less than prescribed of IBD medication without prescriber awareness was assessed as a dichotomous variable (yes/no) based on answer to the question “I take less than prescribed of my IBD medication without telling my doctor”. This has been previously reported[24].

Free text responses regarding attitudes towards IBD medication and dose modification were encouraged.

Other non-standardised attitudinal statements were put to subjects, seeking their views regarding IBD treatment beliefs and attitudes. Some Likert data were collapsed into categories “yes” and “no” for data presentation, but analysed as ordinal data or continuous data using factor scores for regression analysis.

Anxiety and Depression were measured using the Hospital Anxiety and Depression Scale[214], higher scores indicating higher levels of anxiety or depression. Quality of Life was measured using the reliable and valid Short Inflammatory Bowel Disease Questionnaire (SIBDQ) [215].

The Spielberger State-Trait Personality Inventory[173] [175, 216] (STPI) was used to assess and compare depressive symptoms, anxiety, anger and curiosity between cohorts in both the immediate (state) and long term (trait or personality characteristic).

Statistical analysis

Comparisons between cohort means and medians were performed using the Kruskal Wallis test for non-normally distributed values, and two tailed *t* test or ANOVA for normally distributed

values. Pearson's Chi-square or Fisher's exact test were applied as appropriate for categorical data.

Significant or trend associations at univariate level ($p<0.10$) determined which variables were included in regression analyses, along with demographic factors.

Additional continuous variables summarising themes across the questionnaire were generated using principal component analysis for ordinal data using M Plus software (V5.2), for the purpose of data reduction. An oblique (oblimin) rotation was used of 37 of the 55 Likert scale items assessing all aspects of IBD treatment. An examination of the Kaiser-Meyer Olkin measure of sampling adequacy suggested the sample was favourable (KMO = 0.618). When loadings less than 0.4 were excluded, the analysis yielded an 8-factor solution. Scores for each of these 8 factors were normally distributed.

Binary logistic regression was used to assess predictors of CAM use as a dichotomous dependent variable, adjusting for age, gender, employment and relationship status.

A p value of <0.05 was considered statistically significant. Apart from factor analysis, statistical calculations were performed using IBM SPSS Statistics for Windows, version 22, 2013 (IBM Corp).

Ethical Considerations

The study was approved by Flinders Clinical Research Ethics Committee (FCREC) on behalf of SA subjects and Menzies School of Health Human Research Ethics Committee for Darwin subjects (Appendices L, M, N and O).

Results

Demographic data

Response rates to the survey differed between cohorts, with 337/612 (55.1%) of FMC and 91/180 (50.5%) of SA private invitees participating, compared with 35/100 (35%) in Darwin ($p<0.0001$).

Non respondents did not differ from respondents by gender (p=0.2), but there was a trend toward non respondents being younger than respondents (mean age 43.7 versus 50.3 years, p=0.065). Darwin subjects were more likely to be current or previous smokers, and to receive a disability support pension. This population has been previously reported[24]. Demographic data are summarised in Table 28.

Frequency, Demographic and Clinical Associations of Regular CAM Use

Many subjects (45.4% overall) reported regular use of CAM, with no significant difference in usage frequency between cohorts (p=0.594) (Figure 14). Distribution of CAM type used is presented in Table 29, and was not significantly different between cohorts (p=0.626). The regular use of more than one CAM type (ie physical as well as homeopathic methods) was reported by 64.5% of subjects.

Rates of CAM use were higher amongst younger (46.69 versus 53.41 years, p<0.001), female (52.0% versus 35.5%, p<0.001), and permanently employed (51.1% versus 37.4%, p=0.004) subjects. However, CAM usage did not differ by disease type (p=0.394), conventional medication pill burden (p=0.784), smoking status (p=0.805), or vegetarianism (p=0.256) on univariate analysis.

Attitudes Towards CAM

Of the 206 subjects who reported regular CAM use, 52.5% felt that it was effective (worked “well” or “very well”), and 20.7% had obtained the therapy at consultation with an alternative practitioner rather than independently. The vast majority (83.3%) continued to use conventional IBD medications concurrently. Only half (54.1%) discussed their CAM treatment with their doctor, despite 87.6% of subjects reporting feeling comfortable doing so.

In contrast, of those reporting previous consultation with an alternative practitioner only 62.2% felt comfortable discussing conventional therapy with their alternative practitioner (p<0.001), and 16.6% reported the CAM practitioner discouraged their use of conventional IBD medication. With

regard to the consultation experience, 10.5% felt less intimidated by alternative practitioners than doctors, and 16.9% felt more informed about IBD by the alternative practitioner.

Reasons for CAM Use By Free Text Response

Of the 194/206 (94.2%) subjects who offered reasons for their CAM use, 33.0% reported safety concerns regarding conventional medications. Subjects who elaborated further expressed the belief that "natural" CAM would enable them to reduce reliance on "chemical" conventional therapy and dose reduce or cease these medications. Seeking a holistic approach to health in some way was cited by 32.0%, and 20.6% report advice from family, friends, colleagues, religious advisors, or the internet as their main reason for use. A smaller proportion (14.4%) cited lack of efficacy of conventional medications in treating IBD. No significant cohort based differences were observed.

CAM Use and Treatment Attitude Associations – Univariate Analysis

Attitudinal and behavioural associations of CAM use on univariate analysis are presented in Table 30.

Of all subjects including CAM users and non-users, 57.3% reported family or friends using CAM for any health purpose. Those with CAM-using contacts was more likely to use it themselves for IBD (59.9% versus 40.1%, $p=0.004$), free text responses suggesting that type of CAM chosen was influenced by social contacts.

The 54.9% of subjects reporting adverse effects of conventional medications were more likely to use CAM ($p=0.025$), as were the 26.9% reporting regular self-initiated dose reduction of medication ($p<0.001$). Lack of doctor communication satisfaction was reported by only a small proportion of patients (2.4%) but was associated with CAM use, as was seeking of psychological or psychiatric treatment ($p<0.001$) when analysed as individual items.

Analysis of HADS, QOL and Spielberger mean scores suggested that increased anxiety, higher quality of life and lower depression scores were associated with increased CAM use, whilst personality type did not influence rate of use (

Table 31).

Independent Predictors of Regular CAM Use

After adjustment for age, gender, disease type and employment level, attitudinal and psychological predictors of regular CAM use using binary logistic regression analysis are shown in

Table 32. This model explained a significant proportion of variance in low adherence rates (adjusted pseudo R squared 0.217, goodness of fit Hosmer Lemeshow p=0.161).

After adjustment for demographics a trend was observed toward higher CAM usage amongst non-smokers (OR 1.299, 95% CI 0.993-1.698, p=0.056).

Covert dose reduction, lower depression scores and subjects' propensity to seek psychological help predicted CAM use, the latter factor analysis generated variable encompassing use of antidepressants, and consultations with counsellors, psychologists or psychiatrists (

Table 32). Similarly, the factor analysis generated variable assessing dissatisfaction with doctor communication was an independent predictor of CAM use, and included satisfaction level with doctor relationship, doctor communication style, level of comfort in asking questions of doctor, and comprehension of information provided during consultation.

Discussion

This study demonstrates the high frequency of CAM use amongst IBD patients in Australia, and suggests that such use occurs independently of health care setting and geography. Newly identified attitudinal and psychological risk factors include dissatisfaction with patient-doctor communication, CAM use by social contacts and lower depression scores. We confirm both the known demographic risk factors for CAM use and known behavioural associations such as covert dose reduction, psychotherapeutic support seeking, and adverse effects of conventional medications.

The frequency of regular CAM use was slightly higher in our study population (45.4%) than reported previously in Australia[45], but within the range reported internationally[45, 199, 230]. Similarly to the Italian study assessing regional variation in CAM use[242], we found no difference in overall rates of CAM use between cohorts, but in contrast did not find regional variation in the type of CAM chosen either. Some variation in choice of CAM type is seen between populations globally, our predominantly Caucasian cohorts being comparable with New Zealand IBD subjects amongst whom herbs and vitamins were most commonly used[233]. Interestingly nearly two thirds of subjects used more than one type of CAM, however, overlapping physical and homeopathic methods and rendering further analysis by individual CAM type difficult.

Although the patient doctor relationship is known to affect CAM use[49], the more specific aspect of doctor communication quality as a predictor has not been previously reported. Subjects who were dissatisfied with the style of communication from their doctor, did not feel information was

presented in a comprehensible way, or felt that the consultation environment did not encourage patient questions, were significantly more likely to use CAM after adjustment for other factors. A Canadian study found that the wish for a more active role in treatment decisions was associated with CAM use[245], and the desire for more information from doctors was predictive of use in an Italian cohort[248].

The significant influence of CAM use behaviours amongst social contacts on CAM uptake decisions in IBD individuals has also not been previously reported. In our study this was adjusted for age, gender, and employment level but not for other demographics which may be common across family members and confound the association. Such influence would not be surprising, however, given the effect of marital status, for example, on other medication taking behaviours such as adherence to conventional therapy in IBD[198]. A study of healthy adolescents found that social contacts exert significant influence over the decision to use CAM[249], and further work to investigate this in IBD populations is warranted, especially given the escalating influence of social media on everyday decision making.

Previously reported predictors including covert dose reduction (CDR) of conventional medications, adverse effects of medications and increased QOL were confirmed in this study. Free text responses strongly suggested that IBD CAM users tend to reduce rather than omit doses of conventional medications on the assumption that CAM use will provide a "medication sparing" effect, the aim being to minimise adverse effects of conventional medications. This newly described phenomenon is the subject of a separate publication[24], which suggests that similar underlying health beliefs and desires drive both CAM uptake and CDR behaviour. Although abundant free text data from this study support this hypothesis, formal path analysis has yet to be undertaken to confirm the direction of causality in the association between CAM use and CDR.

Those subjects seeking psychological input such as counselling, psychologist or psychiatrist review, or antidepressant medication were significantly more likely to use CAM in this study, and this has been previously demonstrated in two European studies[199, 241]. Free text responses suggested that CAM was not being prescribed by the psychological care provider, but rather both behaviours were the result of a desire for a holistic health approach with active ways of coping, and this has been previously reported[241]. This may be supported by our new finding that lower depression scores were associated with CAM use, perhaps indicating the presence of successfully treated depression in this population who may be more receptive to psychology.

Gastroenterologist awareness of CAM use was similar in our study to the 46% seen in a French web based study of IBD patients[238] ,but greater than that found elsewhere[48, 236, 250]. This communication gap may be contributed to by both consultation participants, a study examining CAM use in IBD patients from the physician perspective finding that only 8% of IBD physicians had initiated CAM conversations themselves, and only around 50% were comfortable discussing CAM with their patients[250] .

The confirmation of previously reported demographic and attitudinal CAM predictors suggests that our study population is similar to others, and thus the results generalizable to some extent. The limitations of this study include the small amount of clinical information obtainable from subjects by self-report, including disease activity and response to conventional therapy. Additionally, comparisons between cohorts were hampered by the uneven group sizes and response rates across different treatment settings. Statistical analysis differentiating by CAM type is likely to be important but was not feasible in this study as most subjects (64.5%) reported using more than one therapy type. Also, the definition of CAM is not uniform across studies and in this case, was defined as what subjects felt was outside of “conventional” therapy.

CAM use is highly prevalent and appears independent of care setting and geography in IBD, and its importance to patients is often under-recognised by physicians. The quality of patient doctor communication is a key determinant, and failure to actively address CAM use in consultation may promote patient "default" to other advice sources such as family, friends and other social contacts, which ultimately undermines the patient doctor relationship.

Tables and Figures

Table 28: Demographics in Contrasting IBD Cohorts

	FMC (n=337)	**Private (n=91)**	**Darwin (n=35)**	**p value**
Mean Age Respondents (years)	50.3	52.2	48.4	0.35
Mean Age Non Respondents (years)	43.0	48.1	39.9	0.20
Female Respondents (%)	60.2	60.4	60	0.99
Female Non Respondents (%)	55.7	52.4	40.7	0.07
Crohn's Disease (%)	55.2	57.1	48.6	0.70
Indigenous Subjects (%)	0.9	1.1	2.9	0.37
Current Smokers (%)	11.1	13.6	17.1	0.09
Previous smokers (%)	25.8	25.0	42.9	0.09

	FMC (n=337)	Private (n=91)	Darwin (n=35)	p value
Receiving Disability Support Pension (%)	1.8	1.1	5.7	0.006
Employed (%)	58.7	56.7	62.9	0.19
Currently partnered (%)	92.2	95.3	93.3	0.61

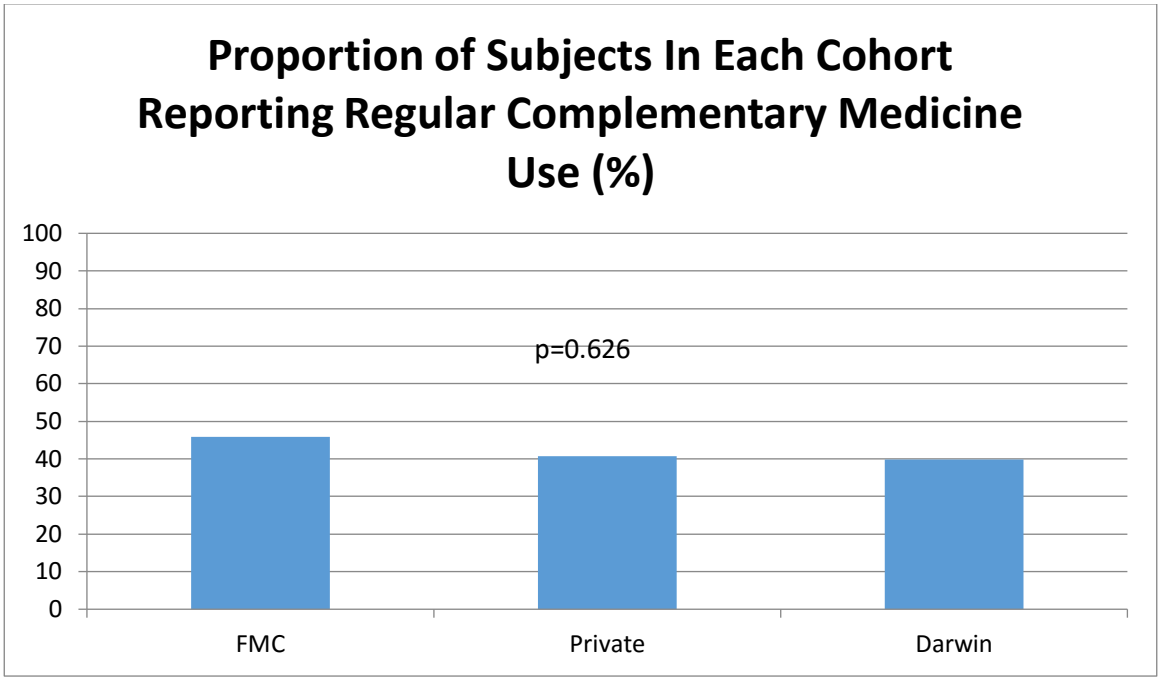


Figure 14: Proportion of Subjects in Each Cohort Reporting Regular Complementary Medicine Use (%)

Table 29: Distribution of CAM types Reported by IBD Subjects

Primary (first mentioned) CAM Type	**Percentage of total CAM reported overall**
Herbal products (eg slippery elm, aloe vera juice, olive oil extract, green lipped mussel oil, other herbs)	30.5%
Probiotics	22.6%
Fish oil	12.1%
Chinese medicine	10.5%
Acupuncture, massage, magnetism	10.5%
Other (prayer, meditation, exercise, dietary supplements, hypnotherapy)	13.7%

Table 30: Attitudinal and Behavioural Associations of Regular CAM Use – Univariate Analysis

		Regular CAM Use				p value
		No		**Yes**		
		n	%	n	%	
Deliberate Dose Reduction	No Yes	197 46	61.4 38.7	124 73	38.6 61.3	<0.001
Family or Friends use alternative teratments	No Yes	88 85	55 40.1	72 127	45 59.9	0.004
Experienced adverse effects IBD meds	No Yes	89 129	59.7 48.3	60 138	40.3 51.7	0.025
Satisfied with communication IBD doctor	No Yes	1 246	9.1 55.7	10 196	90.9 44.3	0.002
Previous psychological counselling	No Yes	197 49	61.6 38.0	123 80	38.4 62.0	<0.001

Table 31: Anxiety, Depression, Quality of Life and Personality Traits in Users versus Non-Users of CAM in Inflammatory Bowel Disease – Univariate Analysis

	Regular CAM Use	Mean	Std. Deviation	Std. Error Mean	2 tailed p value
Anxiety (HADS)	No	8.3312	3.50750	.09032	**0.017**
	Yes	8.6365	3.18002	.08969	
Depression (HADS)	No	6.8774	2.85105	.07354	**0.002**
	Yes	6.5556	2.67318	.07540	
SIBDQ	No	56.0152	9.71282	.25137	**<0.001**
	Yes	58.1210	9.57504	.27126	
Trait Anxiety	No	21.0042	2.53088	.06539	0.341
	Yes	21.0957	2.48538	.07019	
Trait Curiosity	No	25.8310	6.13307	.15836	0.916
	Yes	25.8549	5.71720	.16158	
Trait Anger	No	11.3837	3.93971	.10169	0.385
	Yes	11.5097	3.60996	.10202	
Trait Depression	No	18.9960	3.59568	.09293	0.744
	Yes	19.0385	3.12376	.08818	

Table 32: Independent Attitudinal Predictors of Regular CAM Use in IBD – Logistic Regression Analysis

	Odds Ratio	**95% Confidence Interval**	**p value**
Covert Dose Reduction	2.588	2.135-3.138	<0.001
Seeking psychological treatment	1.888	1.563-2.280	<0.001
Family and Friends are regular CAM users	1.710	1.434-2.044	<0.001
Dissatisfied with doctor communication	1.561	1.304-1.869	<0.001
Adverse Effects conventional medications	1.208	1.006-1.467	0.043
Depression (HADS)	0.910	0.878-0.943	<0.001
Quality of Life (SIBDQ)	1.022	1.011-1.032	<0.001

CHAPTER 9: CONCLUSION

Introduction

The focus of this work has been to seek evidence of, and to define, a knowledge-beliefs "gap" between IBD patients and their physicians, focusing on areas in which such a "gap" is likely to have clinically significant consequences, and to assess the clinical importance of this "gap". Behavioural evidence of this shortfall is suggested throughout the IBD literature in the form of medication non-adherence, CAM use, and voluntary childlessness. However, attitudes which underlie divergent patient decision-making have previously been underexplored, and in the case of reproductive decision-making, completely unexplored.

Understanding patient views which contribute to divergent health behaviours is critical to inform patient decision-making and to optimise clinical outcomes.

In this thesis, the selected studies have investigated this potential gap across four clinically important areas of IBD: reproductive aspects, colorectal cancer risk, medication adherence, and the use of CAM.

This chapter will summarise the data presented in this thesis, and will integrate this information so that it addresses three crucial questions:

- Is there a knowledge-beliefs gap in specific areas of IBD?
- Is the gap important clinically?
- Can the gap be addressed through education?

The contribution from each area of study will be discussed. Implications for clinical practice and recommendations for future research will then be presented, followed by the limitations of the thesis and a conclusion.

Is there a knowledge-beliefs "gap" in specific areas of IBD?

Across each of the four sub-areas examined, substantial gaps were observed between accepted evidence-based physician knowledge and that of IBD patients. The knowledge-beliefs "gap" varied in size, nature, and clinical importance across these sub-areas.

Fertility and Pregnancy in IBD

The most notable gap found here was between evidence-based medicine and patient understandings of the reproductive aspects of IBD. This was a novel finding not previously reported.

Physician perspective

Fertility is normal in patients with IBD with the exception of males on sulfasalazine, and females after pelvic surgery or with active disease[251].

Increased disease activity during pregnancy is deleterious to pregnancy outcomes and IBD medications, apart from methotrexate, are considered safe to use throughout pregnancy and lactation[251-253].

Patient perspective

Our study demonstrated surprisingly frequent fear of infertility in both genders, which was out of keeping with expected infertility rates in this population. Similarly, the pregnancy study uncovered important misperceptions whereby a large proportion of women did not understand the important role played by disease activity in pregnancy outcomes, and were unnecessarily fearful of the effects of IBD medication on the foetus.

Further observations

The publication of Chapters 3 and 4 in peer-reviewed journals in 2009 and 2010 marked the first time this important area of misperception had been described in the IBD literature. As a result of this work, in 2012, a new tool for measuring reproductive IBD knowledge was developed and

validated by Selinger et al, the "CCPKnow" (Crohn's Colitis Pregnancy Knowledge Scale)[149]. Subsequent testing of wide-ranging IBD populations confirmed the high frequency of suboptimal patient knowledge in this area, thus supporting the generalisability of our initial findings[149, 254-257]. This welcome development enabled valid testing of knowledge before and after reproductive education and was thus employed in the study reported in Chapter 5.

Studying the knowledge-beliefs gap as previously defined has highlighted an assumption that may be erroneous in some care settings. The physician's viewpoint is presumed to be well-informed, evidence-based, and current, with the patient being the only party considered to be vulnerable to misperception. In these studies however, the absence of a gap could be equally deleterious where both parties have been misinformed. Of the subjects offering free text comments, 35% reported their doctor advising against pregnancy because of IBD, well beyond the expected rates of adverse fertility and pregnancy outcomes for this group. Following up on this observation, other investigators subsequently demonstrated the poor knowledge held by General Practitioners and Obstetricians in this area[258], which is problematic as they are often consulted regarding IBD medications in pregnancy. This highlights the need for both gastroenterological input and patient education prior to conception.

Colorectal cancer risk

A knowledge-beliefs "gap" was also evident in relation to colorectal cancer risk perception and perceived surveillance benefit amongst IBD patients.

Physician perspective

At the time of study design, the risk of colorectal cancer amongst patients with colitis was thought to be 2% after 10 years of disease, 8% after 20 years, and 18% after 30 years[177]. No clear mortality benefit as a result of surveillance was demonstrated in a Cochrane review at this time[163], although subsequent studies have been more encouraging[259].

Patient perspective

Subjects in this study vastly overestimated their risk of developing colorectal cancer (50%), but similarly overestimated the benefit derived from surveillance colonoscopy, with approximately 90% of subjects feeling reassured that surveillance colonoscopy would reduce their cancer risk.

Further observations

Further work by other investigators has supported a knowledge-beliefs "gap" here. The study of a comparable population reported that while colon cancer is one of the most prominent patient fears, especially among UC patients, actual knowledge regarding risk and chemoprevention was suboptimal[260].

Medication beliefs

The "gap" between physician and patient in relation to medication beliefs is long recognised, complex, and specific to the individual. It has been reported across IBD and other chronic diseases, but the novel finding in our study is that of two different types of medication non-adherence associated with distinct medication attitudes. Covert dose reduction (CDR), while seen in hypertension, is a novel finding in IBD. This finding highlights the complexity and heterogeneity of the "gap" in producing different medication behaviours.

Physician perspective

Long-term maintenance medication in IBD controls disease, reduces rates of surgery and colorectal cancer, and improves QoL [261]. Consistent adherence to the prescribed dose of medication is important to prevent relapse[262]. Major adverse effects are uncommon, and the risk-to-benefit ratio favours the use of conventional therapy in IBD.

Patient perspective

Patients who regularly omitted medication doses were more likely to believe that their IBD medication was ineffective or causing adverse effects. These patients also reported higher levels of dissatisfaction with their physician.

In contrast, patients who chose to dose reduce their IBD medication had different beliefs; that CAM was effective, that they obtained more information and comfort from their alternative practitioner than the physician, and that information from their physician was not believable. Qualitative data suggested that this group of patients believed that conventional therapy at full dose was effective but was also associated with adverse effects, and by using CAM along with reduced dose conventional medication, efficacy could be maintained while minimising the adverse effects.

Further observations

This study highlighted an important limitation of current medication adherence measuring instruments. Most do not examine CDR as a separate entity; rather, they incorporate that behaviour into an overall score to summarise behaviours likely to deviate from physician recommendation without assessing the different paths of logic resulting in a decision to dose reduce as opposed to dose omit medication. Both behaviours are likely to be clinically detrimental.

CAM-related beliefs

Patient beliefs regarding CAM in IBD appeared more subject to psychosocial influence than to knowledge differences between physician and patient. This work highlighted the importance of external influences on the "gap" such as the social influence of family and friends' health beliefs, as well as the psychological influence of physician communication style.

Physician perspective

While the overall physician viewpoint regarding CAM in IBD is that it is non-evidence based, lacks efficacy, and may be harmful, the heterogeneity of CAM types makes this generalisation problematic. While some treatments classified as CAM have scientific plausibility in their potential benefit in IBD (curcumin, probiotics), others such as iridology are unlikely to confer real benefit.

The broad spectrum of CAM types makes it difficult for the physician to give clear advice in this area.

Patient perspective

Many patients in our study reported their belief that CAM was effective, safe, and "natural" in treating IBD. The qualitative data highlighted a theme that CAM may allow dose reduction of conventional medications and make them "safer".

Further observations

The "gap" between patient and physician is harder to define with regard to CAM beliefs, as the definition of CAM used in this and other studies is broad and thus the "gap" is variable. Further studies have examined the physician perspective regarding individual CAM types. One US study[263] found that the majority of IBD physicians had recommended probiotics, while half had suggested acupuncture; thus, the gap here is small, whereas views towards homeopathy are more divergent. It is likely that receptiveness to CAM also differs between physicians from different cultures, with Swedish IBD physicians and nurses acknowledging the importance of CAM to patients and wanting to learn more[264]. It is likely that some forms of "CAM" such as exercise have a therapeutic benefit in IBD.

Further complexity is suggested in a study reporting that the intended purpose of CAM use (whether for IBD or general health) may be associated with different beliefs and behaviours[265].

Is the gap important clinically?

The impact of a knowledge-beliefs "gap" varied across the four aspects of IBD examined, from being clinically detrimental and affecting important health decisions, to possibly being beneficial in improving motivation for colonoscopic surveillance. Interestingly, the absence of a "gap" proved to be detrimental where both physician and patient beliefs were aligned with one another but not

with the current evidence, exemplified by the surprisingly high proportion of patients reporting their doctor as the source of misinformation in Chapter 3.

Fertility and pregnancy

Reproductive decision-making was detrimentally affected by the knowledge-beliefs "gap" in both fertility and pregnancy studies.

Fear of infertility and adverse pregnancy outcomes provide a behavioural explanation for the voluntary childlessness previously reported[19], and this reasoning was confirmed by the qualitative data in these studies. The important relationship between poor reproductive IBD knowledge and family planning has now been acknowledged in other large, well-designed studies[254, 255].

An alarmingly high proportion (84%) of women reported concerns that IBD medications would harm their pregnancy, compared with only 19% who were aware of the deleterious effects of active disease on pregnancy outcomes. This was the rationale for medication non-adherence during pregnancy reported by many of our study subjects, and since replicated in other IBD populations[266]. This is clinically important as adverse pregnancy outcomes were associated with active disease during pregnancy in our study, and a wealth of data supports this finding[267].

The absence of a "gap" in which both parties were misinformed appeared to affect not only patient medication adherence but also physician behaviour in terms of prescribing during pregnancy. We reported in the pregnancy study that out-dated and unbalanced pharmaceutical product labelling contributed to fear of teratogenicity amongst doctors. This widespread problem has now been recognised at an international level and, in 2015, the FDA passed legislation abolishing pregnancy drug categories A, B, C, D, and X, in favour of a more balanced discussion of

the competing risks of poorly-controlled disease activity as opposed to the potential adverse effects of medication in pregnancy.

Colorectal cancer risk

In contrast to the detrimental effects of the reproductive knowledge gap, the cancer risk and surveillance benefit overestimation in our IBD population appeared to exert a neutralising effect, with no impact on QoL or psychological parameters.

It is interesting to note that a substantial knowledge gap still exists in a tertiary hospital setting in which specialised IBD nurses and physicians provide readily available care and education. It may be that the care setting of the "gap" can mitigate its impact; in this case, providing over-reassurance about surveillance benefits to ameliorate the increased anxiety which often accompanies elevated risk perception.

While it is ethical to educate all patients to the best of a practitioner's ability, there is a theoretical risk that providing accurate information may reduce the motivation to participate in surveillance by reducing cancer risk perception. An Asia-Pacific study suggested that those patients who felt the need was high had greater intent to participate in surveillance in most care settings[268], although more accurate knowledge was associated with intent to participate in surveillance in another study[269].

In a recent study summarising the findings of overall IBD patient knowledge studies to date, it was observed that while greater patient knowledge is empowering and can have a positive effect on coping, it does not improve anxiety or reduce the risk of bowel cancer[270]. In fact, other authors have also noted the dilemma in improving knowledge, in that greater knowledge may result in increased anxiety[271, 272] with no QoL benefit[273].

In relation to colorectal cancer, further evidence has now emerged supporting surveillance benefits, and the AGA position statement now suggests at least a moderate decrease in colorectal cancer risk as a result of surveillance[259]. This makes cancer surveillance participation particularly important; thus, a combination of accurate education along with a strong physician recommendation toward surveillance would appear to be the most ethical and effective direction for patient counselling.

Medication beliefs

The "gap" proved deleterious in relation to the effect on medication-taking behaviours. Two types of divergent medication-taking behaviours emerged from our study, deliberate non-adherence by dose omission and covert dose reduction. These appeared to be driven by different beliefs, and reinforce the impression that the "gap" is individualised and complex.

While extensive study has been undertaken across a variety of chronic diseases in relation to the impact of non-adherence by dose omission, few have specifically examined the clinical impact of CDR, and none yet in IBD. It is intuitive that regular dose reduction would have a similarly negative impact to frequent dose omission, but this would likely vary by medication type.

While there is substantial overlap between objective knowledge and more subjective beliefs, they may behave as distinct entities in their complex interaction with adherence[274]. The relationship between objective patient knowledge and medication adherence in IBD remains unclear, with some studies suggesting no association[201], some a positive association[262], and others a negative one[274]. Beliefs however, were strongly linked to behaviour in our study and this is consistent with the previously described "Necessity Concerns" framework.

Further complexity in understanding the gap is evident in that medication adherence and beliefs have been shown to differ by medication type[201], and are likely to change over time in

individual patients[62]. It is likely, for example, that CDR may increase for medications with more short-term adverse effects such as corticosteroids, but further study is required to examine this.

Research by Selinger et al has helped to clarify the relationship between knowledge, beliefs, and adherence by demonstrating that the specific way in which risk is expressed to patients affects their medication beliefs and adherence[275]. Importantly, this suggests an important role for carefully designed patient education in relation to IBD medication.

CAM-related beliefs

CAM use was common in our cohort as a result of divergent beliefs which differed from beliefs driving conventional medication non-adherence. While negative views regarding the efficacy and safety of conventional medications promoted both non-adherence and CAM use, a communication style gap between physician and patient was an important influence upon CAM decisions.

Patients who felt distanced from the practitioner by consultation style, duration, or insufficient information were likely to be more susceptible to other influences on CAM decisions such as advice from family, friends, and the Internet. In relation to causality, it is unclear whether pre-existing health beliefs that differ from those presented by the physician promote scepticism and a poor patient-physician relationship, or whether a poor relationship with ineffective communication reduces the believability of the information presented.

This and other studies suggest that the CAM-promoting “gap” is less influenced by disease factors than by psychological and self-perception factors[276], psychological mindedness, and communication needs. A New Zealand study reported that IBD patients use CAM at similar rates to the general population[233], and that this is associated with socio-demographic rather than disease-related factors.

The other important behavioural association with CAM use is that of missed physician appointments. Both detrimental behaviours are likely to result from the same underlying beliefs and reflect suboptimal patient-physician relationships and communication.

Can the gap be addressed with intervention?

One study in this thesis addressed the question of whether the gap can be minimised using an educational intervention.

This was the first study reported in the IBD literature exploring whether reproductive-specific education is effective in addressing the knowledge-beliefs "gap". This simple study demonstrated a dramatic improvement in knowledge after group education in a single session. The most clinically important areas of improvement were in relation to medication safety, and the critical concept of risk benefit with regard to disease activity versus medication effect on pregnancy outcomes.

Other studies

Subsequent studies have confirmed that physician-led individual education on the reproductive aspects of IBD can correct misperceptions[257] and that physician counselling can lower the odds of voluntary childlessness[255].

As IBD-specific reproductive education is likely to be effective, the question arises whether the target for education should be the patients themselves, or General Practitioners (GP) who perform much of the routine care of IBD patients in Australia and who, based on our findings, may be providing suboptimal advice to patients. Ideally, both groups would be educated, but given that each GP has only a small number of IBD patients, it may be more cost-effective to empower patient groups with knowledge. This may "immunise" against misinformation which we must acknowledge is sometimes perpetuated by doctors who lack IBD experience. In conjunction with Professor Jane Andrews (Royal Adelaide Hospital), I have recently developed, and had endorsed by

SA Health, an evidence-based patient information booklet on fertility and pregnancy in IBD, with a section entitled “Information for your GP”, with the intention of educating General Practitioners via their individual patients. This is being made available as a statewide resource for both patients and doctors across South Australia.

Implications for Clinical Practice

Many of the implications for clinical practice arising from this thesis have already been recognised and implemented given the timeframe over which the work has been undertaken. Specific practice modifications arising from this work can be divided into changes in the way IBD care is delivered at international, national, and local levels, as well as changes suggested within the individual patient encounter.

Influences of the work on IBD care internationally

The publication of Chapters 3 and 4 in international journals has raised awareness of misperceptions regarding fertility and pregnancy amongst IBD patients, prompting the development of a standardised test (CCPKnow, Appendix E) which subsequently showed the problem to be widespread across diverse IBD communities worldwide. This important observation is now specifically highlighted in both the European Crohn’s and Colitis Organisation (ECCO)[267], and Toronto guidelines for the management of reproductive issues in IBD[253]. The publication demonstrating the efficacy of group education (Chapter 5) is also cited in the updated ECCO guidelines, heralding international recognition that proactive care in the form of preconception counselling is preferable to reactive care in treating active disease during pregnancy. Such education of patients regarding the risk-benefit of IBD medications during pregnancy is likely to produce lower rates of complications such as prematurity, and thus reduce morbidity and long-term health-care costs.

Influences of the work on IBD care nationally

The need for national guidelines for the management of IBD before and during pregnancy has been recognised as a result of this work. In conjunction with other key clinicians across Australia with expertise in this area, I have been involved in writing a "clinical update" on this subject for the Gastroenterologic Society of Australia (GESA). I have written 2 of the 9 chapters of this document, one addressing the content of preconception counselling, and the other providing guidelines for the investigation of IBD in pregnant women (Appendices P and Q).

The importance of preconception counselling is further acknowledged by the development of specific IBD preconception counselling clinics in tertiary centres across Australia. The focus has shifted towards early counselling of young people with IBD, often now incorporated into transition stage care from paediatric to adult IBD services, as well as in patient group education.

Influences of the work on IBD care locally

On the basis of this work, I was awarded the Ferring IBD Clinician Establishment grant of $60,000 administered by GESA over the past 2 years. This funding has been used to establish a pregnancy IBD service within the Southern Adelaide Local Health Network. The service incorporates an IBD nurse-led preconception counselling service, a pregnancy IBD database to monitor pregnancy outcomes and the effectiveness of this approach, and the development of the patient information booklet described above (Appendix A), which now has statewide endorsement.

Additionally, I have conducted further consumer group education sessions focusing on the reproductive aspects of IBD on the basis of positive patient feedback as well as the evidence-based justification of this approach presented in Chapter 5.

Implications for the individual patient encounter

Misperceptions regarding fertility and pregnancy, cancer risk, and IBD medication should be actively sought and addressed. Individual education to correct specific misperceptions is vital, with

issues of concern followed up at subsequent encounters to ensure that the information is retained. Men and women should be provided with early preconception counselling at, or soon after, diagnosis as many pregnancies are unplanned.

"Invisible" inputs into patient health belief systems, such as family and friends' views, should be acknowledged and discussed in the IBD consultation, and specific questioning regarding adherence to the prescribed dose of medication should be routinely incorporated. Physicians should educate themselves about CAM sub-types which may be beneficial in IBD, and discuss these with patients routinely in an attempt to "bridge the gap" and communicate a sense of openness to discussions about CAM.

Recommendations for future research

The effects of reproductive education at the point of diagnosis should be followed prospectively to determine whether establishing high knowledge levels prior to reproductive decisions can be sustained, can improve adherence to IBD medication during pregnancy and thus improve pregnancy outcomes and reduce voluntary childlessness rates. The effects of providing written and/or online information on long-term knowledge is another area for further study, while a cost effectiveness study of group education would be worthwhile.

It would also be beneficial to study the relationship between patient cancer risk overestimation and surveillance participation by assessing risk perception in those suitable for surveillance but who declined to take part in surveillance and comparing this with our surveillance participating cohort. Further work investigating whether narrowing the cancer perception gap through accurate education affects cancer surveillance participation is also recommended.

The development and validation of an instrument to examine Covert Dose Reduction as a distinct variant of medication non-adherence in IBD would also be informative.

Limitations of the Research

The methodology involving cross-sectional questionnaires is subject to numerous types of bias. Participation bias is likely, and this suggests that an even larger knowledge-beliefs "gap" may exist in community IBD patients who declined to take part in these studies. Attitudes and behaviours are the result of complex inputs and thus many confounding variables are likely and difficult to control for. Additionally, these are studies of association, and thus, causality cannot be attributed.

This thesis has been conducted over a period of nine years. As a result, the literature review is now somewhat out-dated and some clinical recommendations, particularly in relation to pregnancy IBD management, have changed. However, importantly, the thesis has a chronological integrity from the literature review through the studies executed and published. The lengthy course of this thesis may be regarded as advantageous as the results of its earliest published studies on fertility and pregnancy have had an opportunity to circulate in the global IBD literature and to promote an accumulation of further studies. This has allowed the work to progress and has prompted the educational intervention study presented in Chapter 5, thus affording a more longitudinal view of the impact of this research.

Conclusion

The novel studies presented in this thesis have provided evidence for the existence of a knowledge-beliefs "gap" between patients and physicians in IBD in relation to reproductive aspects, views on cancer, and medication-related perspectives. Important health behaviours have been demonstrated to be affected such as reproductive decision-making, medication non-adherence, and CAM use, with one study suggesting that the "gap" may be reduced through education. Whether reducing the "gap" positively affects health behaviours and improves disease outcomes warrants further investigation.

These findings have put the management of IBD during pregnancy into the international spotlight, influencing ECCO guidelines which have prompted the development of Australian guidelines, a validated test to quantify patient knowledge, and a widely endorsed written patient information document.

On a more individual level, important recommendations have arisen from this work to guide the course of the IBD clinical encounter. It is important to assess patients' disease-specific knowledge, enquire about deleterious behaviours that may result, and to correct misperceptions. Men and women with IBD have the right to accurate disease information to enable informed health decisions. In the case of the pregnant IBD patient, the physician's responsibility extends to the foetus as well. The unborn have a right to receive the best care available to prevent mortality and long-term morbidity which results from prematurity and other adverse outcomes resulting from poorly controlled IBD during pregnancy.

Beyond the aspects of fertility, pregnancy, cancer, and medications examined here, it is likely that a "gap" exists between patient and physician views in other areas of IBD to varying extents and clinical significance.

Acknowledging the complexity of influences on health attitudes and associated behaviours, it is reasonable to assume that the "gap" will never be closed, but attempts should be made to understand the individual patient perspective and education should be offered where needed. The role of the physician should not be paternalistic, but instead, should be seen as a partner in disease management, empowering patients to co-manage disease in a shared decision-making model. It is our responsibility to provide the best evidence-based information and care; however, it is the patient's right to decide what emphasis to place on information received in the context of their own belief system.

Where the patient-physician “gap” is largest, the clinical consultation can be challenging and so patients risk becoming further disengaged with care unless differences are recognised and addressed in an open and non-confrontational manner. Physician communication should be informative and clear, with strong recommendations being made for important advice. On points of persistent disagreement, overall care engagement should be prioritised and the physician-patient relationship protected through a philosophy of understanding and respect.

The overall goal of care in IBD must be to optimise outcomes by empowering patients with knowledge and encouraging a care partnership with the physician.

APPENDICES

Appendix A – Statewide Fertility / Pregnancy Patient Information Sheet

**Based on numerous international guidelines and adapted for South Australian Health approval

FERTILITY, PREGNANCY AND INFLAMMATORY BOWEL DISEASE

- IBD pregnancies have the best outcome if planned for and if women conceive during remission
- Flares of IBD during pregnancy give a greater risk of harm to mother and baby than most IBD treatments
- Most IBD medications are safe to continue during pregnancy and breastfeeding, but it is important to discuss this with your doctor before pregnancy or as soon as you recognise you are pregnant
- Birth defects are NOT increased by IBD medications except for methotrexate
- Stopping your medication during pregnancy without specialist advice may harm your baby

Crohn's Disease (CD) and Ulcerative Colitis (UC) are the 2 most common forms of Inflammatory Bowel Disease (IBD), frequently affecting people who are contemplating having children. If you or your partner has IBD, you may be wondering about how this will affect your ability to have children, and how pregnancy will affect your IBD.

It is important to discuss these issues early, to help people consider all aspects, well before planning a pregnancy.

The good news is that the great majority of women and men with IBD have normal fertility, and women can expect a normal pregnancy and delivery, and development of a healthy baby.

Remember that a healthy mother is required for a healthy baby.

Pregnancy and Fertility in women WITHOUT IBD

Even in the general population, pregnancy does not progress normally in all cases. Problems or complications affecting the baby's health occur in about 15% of cases.

All pregnancies have a risk of 3 to 5% for birth defects, and at least 15% for miscarriages. Some medical conditions may increase these risks especially when they are not well controlled. Many pregnancies are unplanned, and this is why it is important to control your IBD well in the long term, and understand the implications of IBD on fertility and pregnancy before you are planning a family.

Pregnancy and Fertility in women WITH IBD

Part A: Fertility

Will I be able to conceive?

<u>For Women</u>

Ulcerative Colitis (UC)

If you have UC, your chances of conceiving are unaffected by the disease.

Even if you need to have a colectomy, fertility only appears to be reduced if you have undergone pouch surgery.

Reduced fertility appears to be much less of a problem when colectomy with an ileostomy / stoma – is done. This is an alternative to pouch surgery. Women who may need colectomy should discuss these issues early with their IBD Specialist and surgeon, as with planning good fertility and obstetric results can be achieved.

Crohn's Disease (CD)

If you have well controlled CD, your chances of conceiving are the same as the general population.

When you are having a flare of CD, your chances of conceiving are reduced. This is thought to be due to a number of possible mechanisms:

Severe inflammation in the small intestine can sometimes affect the normal functioning of the ovaries and the fallopian tubes.

Previous abdominal operations, especially if adhesions are present.

Reduced levels of general health, including nutritional status.

Reduced libido. Complications such as abscesses and fistulae in the pelvic and anal area, and general difficulties associated with living with IBD, such as fatigue, abdominal pain, diarrhoea, and a poor body image, can all contribute.

Special attention should be given to your general nutritional status. It is important to have adequate levels of folic acid, vitamin B12 and iron before pregnancy, since the need for these vitamins and micronutrients increases in early pregnancy. Folic acid is also required to reduce the risk of birth defects.

The good news is that if these issues are addressed and your CD is brought into a remission, your fertility and chance of a healthy baby are generally restored to normal.

<u>For Men</u>

There is no evidence that IBD affects male fertility.

However, for men as well as women, problems such as fatigue and poor body image can affect libido and sexual relationships and make it more difficult to conceive a child.

Abscesses and fistulae in the pelvic and anal regions may also cause some difficulties with erection and ejaculation.

Very rarely, men with IBD who have had a pouch operation, or have had both their colon and their rectum removed by surgery, may have difficulty having an erection. However, this problem is usually temporary or can be successfully treated with medication.

Can I improve my fertility?

For Women

It helps if you can get your IBD under control for at least 3 months before trying to conceive.

As your fertility may be being affected by factors other than your IBD, you may also find it helpful to follow some of the suggestions and tips usually given to couples wishing to conceive a child. For example:

Try to eat a healthy and balanced diet. If this is difficult because of your IBD, you could discuss with your doctor taking some supplements to ensure you get all the nutrients needed. Normal stores of iron, zinc and vitamin B6 are particularly important for fertility in both men and women.

For any woman, it is important to take folic acid supplements prior to conception and for the first twelve weeks of pregnancy, to reduce the risk of birth defects (neural tube defects). The usual recommendation for women without a family history of neural tube defects or medical complications is 500mcg / day. Both IBD and Sulfasalazine can decrease the folic acid in your body and folic acid 5mg is recommended throughout pregnancy.

Women can improve fertility by maintaining their weight in the normal healthy range, not smoking and avoiding alcohol during pregnancy.

Regular moderate exercise of around 30 minutes a day can help by improving energy, improving libido, maximising your fitness and keeping your weight in check.

For Men

Men can increase their likelihood of producing plenty of healthy sperm by not smoking, keeping alcohol drinking within guideline limits (not more than 2 standard drinks per day), exercising moderately and avoiding stress.

What if I am taking IBD drugs when I conceive?

It is not usually necessary to change the medicines you take for IBD before you try to conceive.

The only exceptions to this are:

1. Sulfasalazine (Salazopyrin)

Sulfasalazine leads to reversible male infertility. This effect is temporary and fertility should return to normal levels within two to three months of stopping the medication.

There are several good alternatives to sulfasalazine, such as mesalazine, olsalazine or balsalazide, which can usually be used instead. These have the same beneficial effects on IBD control but do not usually affect fertility.

2. Methotrexate

Methotrexate increases the risk of birth defects when taken by either men or women

thus these drugs should be stopped after discussion with your IBD treatment team before planning pregnancy, and a safer alternative prescribed.

The most important way of improving your chances of having a healthy baby is to keep the disease under control before and during pregnancy. So if your current medication is working well and is NOT methotrexate, it is usually better not to change your medication

Will my pregnancy be normal?

If your IBD is in remission at the beginning of your pregnancy, your chances of delivering a healthy baby are almost the same as a woman without IBD.

If your disease is active at the beginning of the pregnancy, or you suffer flare-ups during pregnancy, there is a risk of the baby being affected. It is twice as likely that your baby will be premature and will have a low birth weight. This is still a small risk, and the baby is likely to be healthy.

In most cases, the risk of the baby being small or delivered early is related to the disease activity itself, rather than to the medicines you are taking. So, if you are pregnant and your IBD is active, it is best to visit your doctor as soon as possible to discuss how to get your IBD under control.

Should I keep taking my IBD medicines during pregnancy?

It is important to keep your IBD under control while you are pregnant. Active inflammatory diseases do more harm to your growing baby than most IBD medicines.

Many people are afraid to take medications during pregnancy, and this is understandable. This fear is often increased by the TGA classification of medication safety in pregnancy, which is often based on animal studies or theoretical concerns, and this classification system is unlikely to be used in Australia in the future.

The guide IBD doctors use to care for pregnant patients is that of expert agencies such as ECCO (European Crohn's and Colitis Organisation) which classifies medications as safe, probably safe or harmful based on post marketing studies on real patients, and expert experience with these drugs. It has

been found that many IBD drugs are safer in real world experience than their “official” ratings, and ECCO guidelines take into account the fact that active disease during pregnancy is more dangerous than most of the medications.

How do IBD drug treatments affect pregnancy?

The majority of drug treatments for IBD are safer for your baby than active disease. However, there are some exceptions, as shown below.

If you are trying to start a family, or if you are already pregnant, do discuss this and your drug treatment with your doctor or IBD team as early as possible.

It is better to avoid disease flares while trying to conceive and while pregnant, so most doctors will recommend continuing with your medication, unless there are clear reasons not to. If the drugs you are on are not thought to be safe, there is usually a good alternative.

<u>5ASAs</u>

Sulfasalazine (Salazopyrine)

Mesalazine (Mesavant, Pentasa, Salofalk, Mesasal)

Olsalazine (Dipentum)

Balsalazide (Colazide)

5-ASAs have been taken by women during pregnancy for many years and are safe. Sulfasalazine has not been shown to affect fertility in women or to be linked to any birth defects if taken by women. There is very little transfer of these drugs across the placenta to the baby. They can be used as maintenance

therapy and during a flare. If you are taking sulfasalazine you are advised to take folic acid supplements (5mg daily). Mesalazine, which is a 5ASA drug without the sulpha component, is also safe.

Methotrexate (eg Methoblastin®)

This immunosuppressive drug sometimes prescribed for IBD, should NOT be taken by either men or women when trying to conceive as there is a risk of birth defects. You should avoid pregnancy if either partner has taken methotrexate within the last three months – or as advised by your doctor. This medication causes birth defects and increases the risk of miscarriage. If you become pregnant whilst taking methotrexate, do not take any more doses and see your doctor urgently.

Corticosteroids

- Prednisolone, (Panafcortelone®, Predsolone®, Solone®)
- Budesonide (Enterocort®, Cortiment®)
- Hydrocortisone (given intravenously in hospital)

These medicines may be used in pregnancy, but the need to use them indicates poorly controlled IBD and so, if you are on steroids long term (or frequently) you should discuss a better IBD management plan with your treatment team, ideally BEFORE you conceive. There are some studies suggesting that first trimester use of corticosteroids may increase the risk of oral clefts but other studies have not supported this finding. If there is a risk it is likely to be very small. The background risk of oral clefts in any pregnancy is 1-2 in 1000 births and this may be increased to 3-6 in 1000 with corticosteroid use.

Rectal steroid preparations (enemas and suppositories) may also be used right through pregnancy if required.

Thiopurines (Azathioprine (eg Imuran®), 6-mercaptopurine (6MP) (eg Puri-Nethol®)

These are immunosuppressive drugs used to maintain IBD control if 5ASA drugs alone are insufficient and are prescribed for about 40% of people with IBD. The aim of these drugs is to make the body's immune system less responsive. This has the effect of reducing inflammation in IBD (as inflammation is part of the immune system's processes). However, a less-responsive immune system may make a person slightly more susceptible to infections, especially if you are not having regular blood test monitoring on these drugs.

These immunosuppressive drugs have not been shown to affect fertility or pregnancy, so doctors advise continuing with azathioprine or 6-MP, rather than risking a flare up of the IBD.

The clinical experience of pregnancy outcomes with these drugs is now very large, and it is clear that the risks of active IBD are greater than the risks of taking these drugs for both mother and baby.

Therefore, IBD doctors will advise the continued use of azathioprine and 6-MP during pregnancy, as it is deemed that there is more risk to the baby if the mother becomes unwell.

Allopurinol (Zyloprim®)

Some people need to take this medication with azathioprine or 6 MP. As yet we do not have enough information from studies to recommend continuing allopurinol during pregnancy, and it may be unsafe, so it is best to discuss this with your doctor prior to conception. Your doctor will likely stop the allopurinol and find another medication to treat your IBD during pregnancy, or continue azathioprine without allopurinol.

Biologics - Anti-TNFα Therapy

Infliximab (Remicade®, Inflectra®)

Adalimumab (Humira®)

These drugs affect the immune process and are used in CD, when other drugs have not worked. As they are more costly, the PBS currently restricts them to people whose IBD is not controlled by 5ASA's and / or thiopurines and / or corticosteroids.

The clinical experience available so far across thousands of exposed pregnancies suggests that these drugs are safe to use in pregnancy.

The evidence currently available is that pregnancy outcomes for women, who are taking these drugs during pregnancy are similar to women with IBD not exposed to Anti-TNFs, and to the general population.

Infliximab and Adalimumab do cross the placenta into the baby during the last trimester. Infliximab has been detected in cord blood, and in infants up to 12 months of age, if exposed in the last trimester of pregnancy. For this reason, if the mother is not at high risk of a flare, some doctors avoid using infliximab and adalimumab during the last trimester.

If the newborn has been exposed to Anti-TNFs in the last trimester of pregnancy, LIVE vaccines should be avoided for at least the first 12 months of life, unless the baby has a blood test to document a zero level of the Anti-TNFα drug in his or her system.

Most vaccines scheduled for babies are not live; Rotavirus is an important exception and should be withheld if Infliximab (Remicade, Inflectra) or Adalimumab (Humira) has been administered in the last trimester. Some "travel" vaccines are also "live" vaccines and should not be given to babies under 12 months of age if mother has been administered anti-TNF's in pregnancy.

<u>Cyclosporin</u>

This is a very strong immunosuppressant drug which is rarely used now in IBD (only to prevent emergency Colectomy) and has a significant rate of serious side effects. However, it has not been associated with specific harm to an unborn baby. This treatment would not be suggested unless you had

a very severe (acute) colitis not responding to intravenous steroids. Cyclosporin in this situation is given to try to avoid the need for emergency surgery to remove the bowel, in which case its use may be justified. This is a rare scenario and would be discussed with you prior to using this drug.

Antibiotics

Amoxicillin

Metronidazole

Ciprofloxacin

These are often used in IBD to treat abscesses or perianal disease, which can be uncomfortable, especially during later stages of pregnancy. They appear relatively safe to use if needed. Studies have not shown an increased risk of negative pregnancy outcomes such as spontaneous abortion, prematurity, low birth weight or malformations.

Drugs for symptom relief of IBD in Pregnancy

Antiemetics

Metaclopramide and Vitamin B6 have been reported to be safe.

Antidiarrhoeals

Loperamide is considered safe.

Cholestyramine is considered safe

Diphenoxylate (Lomotil): If this is needed, discuss with your doctor.

Pain relief

Paracetamol is acceptable for use as directed on the packaging, but discuss pain with your IBD doctor if you need regular analgesia, as it suggests your IBD may not be well controlled.

Paracetamol is the safest choice for mild to moderate pain, or a high temperature.

Codeine is considered safe, although often has a constipating effect. If taken in high, regular doses toward the end of pregnancy, discuss with your doctor.

What about nutritional therapy?

Some people with Crohn's take special liquid feeds called elemental or polymeric diets as treatment. These diets may be safely used during pregnancy to treat active disease or as a nutritional supplement. They should ALWAYS be supervised by a professional dietitian and discussed with your IBD treatment team. Exclusion diets are not recommended for pregnant women without medical supervision as they can put you and your baby at risk of nutrient deficiencies.

What investigations for my IBD can I have during pregnancy?

If your disease flares during pregnancy you may need further investigations. It is important to make your doctor aware of your pregnancy before any procedure, as it may be possible to delay it until after delivery. Generally flexible sigmoidoscopy, rectal biopsy, ultrasound, MRI (without gadolinium contrast), endoscopy and in some instances colonoscopy can be carried out during pregnancy. The safest time for these investigations is during the second trimester, but tests are sometimes needed more urgently to keep the mother healthy, and are relatively safe at other times. Investigations which involve x-rays and radiation should normally be avoided by pregnant women unless absolutely essential. This includes CT scans.

What about surgery while I am pregnant?

Surgery is very rarely indicated during pregnancy, but very occasionally there are situations when an operation is the only option. In these cases, the risk to the baby is less than if the operation is not performed.

How can I increase the likelihood of having a healthy baby?

You can increase the likelihood of having a healthy baby in a number of the following ways:

Maintaining remission

For women with IBD, the most important message is that if your disease is under control then the baby is more likely to be healthy. Therefore it is important to take your medicines as directed to ensure that you are as well as possible before conception. It is also important to consult your doctor at an early stage if you fail to gain weight as expected or think you have a flare of IBD.

Diet

For any woman during pregnancy a balanced and varied diet with sufficient calories, vitamins and minerals is important for the growth of their baby. Having IBD, the increased nutritional demands of pregnancy may mean you may need to supplement your diet, particularly if you are underweight or have active disease. It is best to seek the advice of a dietician.

If you are taking corticosteroids like prednisolone, calcium and vitamin D supplements are important to prevent bone loss: The recommendation is 1500 mg of calcium and 800 IU of Vitamin D daily.

If you have Crohn's Disease and have had surgery to remove the terminal ileum (the end of the small intestine), you may need regular injections of Vitamin B12 to prevent anaemia.

Iron deficiency is quite common in IBD and iron supplements are often necessary to meet the increased demands of pregnancy. Check with your specialist before taking any supplements.

Fish oil supplements are quite often used by people with IBD. Research shows that for women with IBD who may be at increased risk of preterm birth and miscarriage, these supplements are not harmful and may be of some benefit. Research is ongoing.

Exercise

Regular exercise can help to keep you healthy. Gentle exercises such as walking, yoga and swimming are recommended.

Smoking

It is important for any woman not to smoke during pregnancy, as smoking harms the baby and leads to low birth weight with a higher risk of deformity and miscarriage. It also increases risks of blood clots during pregnancy and other complications.

The risk is even greater for women with IBD as smoking increases the activity of Crohn's and increases the need for surgery and medication.

The effects of smoking with UC are inconclusive; it certainly causes the same direct damage to the baby as in any non-IBD pregnancy but it may also reduce the severity of UC disease activity. On balance it is widely accepted that the damage caused by smoking is far more than any possible reduction in disease activity.

Alcohol

Drinking excess alcohol during pregnancy can seriously harm your baby's development. It is best to avoid alcohol during pregnancy.

Will pregnancy make my IBD worse?

Pregnancy has little effect on either UC or Crohn's. Overall about one third of women will have a relapse while they are pregnant, and this is similar to non-pregnant women with IBD over that period of time. Women with UC are slightly more likely to flare than non pregnant women.

A recent European study of women with IBD found that the rate of relapse decreased in the years following pregnancy. This suggests that pregnancy may sometimes have a positive effect on the disease process.

If IBD becomes active during a pregnancy there is no evidence to suggest that it will do so again in future pregnancies.

Similarly, if a pregnancy occurs without an episode of IBD, this is no assurance that the disease will remain inactive in subsequent pregnancies.

What sort of delivery should I have?

The type of delivery is usually decided upon by the Obstetricians, whilst also taking into account IBD issues.

In most cases, a normal vaginal delivery is suitable.

A caesarean section is often recommended if you have active perianal Crohn's disease, or a pouch (ileal pouch anal anastomosis).

It is also worth considering that vaginal delivery avoids surgery and its possible risks, including an increased risk of clots in the legs and lungs (venous thromboembolism).

What about my ileostomy?

Most women with ileostomies have a normal pregnancy and vaginal delivery. Sometimes a caesarean section may be necessary. Occasionally a stoma can move during pregnancy and cause discomfort. It will usually return to normal after the delivery. You may also find there is an increase in output during the third trimester, but this will resolve after the birth.

What about my pouch?

If you have an ileoanal pouch you may find you pass stools more frequently and have reduced control of your bowel in the third trimester. This should return to normal after the delivery.

An ileoanal pouch is often considered an indication for caesarean section delivery, as potential damage to the anal sphincter during a difficult vaginal delivery may increase the chance of incontinence. This can be discussed with your obstetrician, however, and some women still choose a vaginal delivery.

I want to breastfeed. Will my medicines do any harm to the baby?

Breast milk is the normal food for your baby and breastfeeding has many benefits for both you and your baby, including promoting the development of a healthy immune system and possibly reducing the risk of a child developing IBD in later life.

Most medicines are safe to use while you are breastfeeding. The amount of medicine in your breast milk is usually small and not enough to cause any problems for your baby.

Be aware that the product information from drug companies about safety in breastfeeding may be overly cautious and is often different from current expert medical advice.

Many medicines used for IBD are safe in breastfeeding but it is best to check with the team involved in your care. You can also get advice about the safety of medicines in breastfeeding from the Medicines Information Service at the Women's and Children's Hospital, (08) 8161 7222.

Medications considered SAFE whilst Breastfeeding:

Corticosteroids: Based on a large amount of clinical experience, corticosteroids are considered by doctors to be safe whilst breast-feeding. Research has shown that only small amounts pass into the breast milk. If you are on 40mg or more a day, you can reduce the effects of corticosteroids on your baby by waiting to breastfeed until 4 hours after taking a dose.

5-ASAs & Thiopurines (Azathioprine & 6-MP): extremely small amounts of the active drug are present in breast milk and there is no evidence of harm in children of mothers who have breastfed on the drug. Thus the benefits of breast feeding are regarded as outweighing any risk. If you have any concerns you should discuss these with your doctor.

Biologics – The structure of these drugs means that they are not well absorbed in the gut, which is why they are given by injection. Even the tiny amount of drug in mature breastmilk reaching the infant gut is not well absorbed by the baby. This means breastfeeding is safe when taking either infliximab or adalimumab.

Antidiarrheals: Loperamide is safe to use in breastfeeding. Only small amounts pass into the breast milk and it is unlikely to affect the infant.

Antibiotics: Most antibiotics (such as penicillins) are safe to use whilst breastfeeding as only small amounts pass into the breast milk. It is best to check each antibiotic with your doctor or the WCH Medicines Information Service.

Cyclosporin: May be used in breastfeeding. Most studies have reported low levels in breast milk, but the infant should be monitored for immunosuppressive effects. This medication is rarely required and needs to be supervised by a doctor.

<u>Medications considered NOT SAFE whilst breastfeeding:</u>

Methotrexate and some antibiotics such as tetracyclines in long courses should be avoided whilst breastfeeding. Please discuss this with your doctor as there are usually safe alternatives to these medications which will allow you to breastfeed.

What are the chances of my child having IBD?

Whilst a parent with IBD is slightly more likely to have a child who develops IBD, there is approximately a 95% chance that the child will not develop IBD. If one parent has the disease, the chances of a child developing IBD at some point in their life is around 5%. This risk seems to be slightly higher with Crohn's than UC. If both parents have IBD the risk of a child developing IBD in their lifetime can increase to 35%, but again they are still twice as likely (65%) not to develop IBD ever. The causes of IBD are still incompletely understood and even with genetic predisposition, other additional factors are needed to trigger the disease.

Remember:

- IBD pregnancies have the best outcome if planned for and if women conceive during remission
- Flares of IBD during pregnancy give a greater risk of harm to mother and baby than most IBD treatments
- Most IBD medications are safe to continue during pregnancy and breastfeeding, but it is important to discuss this with your doctor before pregnancy or as soon as you recognise you are pregnant
- Birth defects are NOT increased by IBD medications except for methotrexate
- Stopping your medication during pregnancy without expert advice may harm your baby

So, when you are ready to plan a pregnancy, the most important thing you can do for your baby is to see your IBD specialist to ensure your disease is well controlled with safe medications.

Here is a list of online resources to help you get the right information about this important topic. The best sources of information about IBD medications in pregnancy are your IBD treatment team and the Medicines Information Service at the Women's and Children's Hospital.

If you have any questions or wish to discuss this further, please call:

Royal Adelaide Hospital IBD Service

Flinders Medical Centre IBD Service 82043942

Medicines Information Service at the Women's and Children's Hospital, (08) 8161 7222.

INFORMATION FOR YOUR GP

Overall fertility and pregnancy outcomes are good in women with inflammatory bowel disease

The greatest threat to pregnancy outcome is from active disease at conception and during pregnancy

IBD medications are considered safe in pregnancy except for methotrexate, and should be continued unless an IBD specialist advises otherwise

Specialist IBD units exist in the major teaching hospitals in South Australia, such as Flinders Medical Centre and the Royal Adelaide Hospital, and are always available and willing to provide advice to GPs and patients about the management of IBD during pregnancy (please see contact numbers above).

When an IBD patient is planning conception, it is ideal to arrange consultation with his or her IBD physician as early as possible to ensure disease is well controlled with medications considered safe.

Electronic prescribing programs used by GPs often prompt pop up warnings when IBD medications such as mesalazine as prescribed, citing concerns about these medications in pregnancy. These pop up warnings are based on outdated data which do not take into consideration the negative effect of disease activity during pregnancy. The FDA in the US has changed their pregnancy category system in recognition of this problem, in that categories A,B,C,D and X are now not used in product labelling. The TGA in Australia is also reconsidering this approach.

Consensus statements based on extensive international data agree that most IBD medications are safe during conception and pregnancy (except for methotrexate), and that most medications should be continued. (ECCO guidelines and Toronto consensus statement)

These guidelines are recognised as the standard of care in Australia and internationally.

Please do not hesitate to contact the information sources below for further information and support in managing IBD patients:

Royal Adelaide Hospital IBD Service

Flinders Medical Centre IBD Service 82043942

Medicines Information Service at the Women's and Children's Hospital, (08) 8161 7222.

Appendix B – Fertility / Pregnancy Questionnaire for Patients with Inflammatory Bowel Disease

Quality of Life, Body Image, Sexual Function and Pregnancy in Inflammatory Bowel Disease: A survey of patients in the reproductive years.

Part A

A1	How old are you?	…….years

A2	What is your sex?	❑ male ❑ female

A3	What type of Inflammatory Bowel Disease (IBD) do you have?	❑ Crohn's Disease ❑ Ulcerative Colitis ❑ Indeterminate Colitis ❑ Unsure

A4	How old were you when you first had symptoms of IBD?	…….years

A5	How old were you when a doctor first diagnosed you with IBD?	…….years

A6	What is your relationship status?	❑ Have a current partner/spouse

		❑ Never had a partner/spouse ❑ Previously had a partner/s/spouse/s

A7	Do you think your IBD has ever affected your relationship status?	❑ Yes ❑ No
A8	If yes please comment in what way : …… …… …… ……	

A9	Do you think your disease has ever affected your Quality of Life?	❑ Yes ❑ No
A10	If yes please comment in what way : …….. …… …….. ……..	

A11	Have you ever had any surgery for IBD?	❑ Yes ❑ No
A12	If yes, please specify which : …… …… ……	

This next question is only applicable if you have Ulcerative Colitis

A13	Have you ever had surgery for the formation of a pouch?	❑ Yes ❑ No	A14	**If yes** what age were you when the surgery performed? ……..

A15	Have you ever had any other sort of surgery, ie not for IBD?	❑ Yes ❑ No	A16	**If yes** please specify which: …… …… ……

PART B SEXUALITY

B1	Do you feel having IBD causes problems with your body image? ***Please note that "body image" is a person's perception of his or her physical appearance***	❑ Yes ❑ No
B2	**If yes** please comment in what way : …… …… ……	

Some of the following questions are personal so we remind you that you need only answer if you feel comfortable to do so

B3	Have you ever been sexually active?	❑ Yes ❑ No
B4	**If yes**, do you mind telling us what is your approximate frequency of sexual activity?	❑ more than weekly ❑ weekly ❑ once a month ❑ every few months ❑ twice a year or less

B5	If you feel comfortable to do so would you please state your sexual preference / sexual orientation	❑ heterosexual ❑ homosexual ❑ bisexual ❑ No comment

B6	Do you feel your IBD affects your libido ? ***Please note that libido refers to the level of interest in sexual activity***	❑ No ❑ Yes decreases it ❑ Yes increases it
B7	If you feel comfortable to do so would you make a comment?.....	

B8	Do you feel your IBD affects your frequency of sexual activity?	❑ No ❑ Yes decreases it ❑ Yes increases it

		❑ Not applicable
B9	If you feel comfortable to do so would you make a comment?..... …… ……	
B10	Do you feel your IBD medications change your libido and/or level of sexual activity?	❑ No ❑ Yes decreases it ❑ Yes increases it
B11	If you feel comfortable to do so would you make a comment?..... …… …….	
B12	Do you sometimes avoid taking your IBD medications due to the effect they have on your libido and/or sexual activity?	❑ very frequently ❑ frequently ❑ sometimes ❑ rarely ❑ never
B13	If you feel comfortable to do so would you make a comment?..... …… ……	
B14		❑ No

	Do you feel there has been a decrease in your level of sexual activity since the onset of symptoms of your disease?	❑ Yes ❑ Not Applicable
B15	**If yes** : was this decrease due to :	❑ decreased libido ❑ concern about how your partner would react to your IBD ❑ medical advice ❑ feeling unwell ❑ other reason - please specify:……
B16	If you feel comfortable to do so, would you make a comment?..... …… ……	

PART C FERTILITY

C1	How many children have you had?	……..

C2	What age were you when each of your children were born?	❑ Not applicable	(c2b) Child 1: ……	(c2c) Child 2: ……	(c2d) Child 3: ……	(c2e) Child 4: ……	(c2f) Child 5: ……	(c2g) Child 6: ……
Office use only: age at symptoms = …../age at diagnosis =…….								

C3	If you have never had any children is this because:	☐ Not Applicable ☐ choice made but not to do with having IBD ☐ choice made because of having IBD ☐ tried to have children but not successful ☐ other – please specify:…… …… …… …… ……

C4	How does the number of children you have compare with the number of children you wanted to have or planned to have?	❑ same or never thought about it ❑ more ❑ fewer

C5	If the number is fewer can you say why?..... …… ……

C6	Have you ever had any difficulty conceiving? ***Please note we say that difficulty to conceive = 12 months unprotected sexual activity without success***	❑ Yes ❑ No ❑ Not applicable (never tried to conceive a child)

C7	Have you ever feared a lack of fertility due to having IBD?	❑ Yes ❑ No ❑ Not applicable (never wanted to have children)

C8	Have you ever seen a doctor regarding fertility problems?	❑ Yes ❑ No ❑ Not applicable (never tried to conceive a child)
C9	**If yes** and you feel comfortable to do so please state why:…… …… ……	

C10	Have you ever been advised by a doctor that your ovaries and/or fallopian tubes have been affected by intestinal inflammation?	❑ Yes ❑ No ❑ Not applicable ie for males

C11	Have you ever had a laparoscopy for fertility problems?	❑ Yes ❑ No ❑ Not applicable ie for males
C12	**If yes** and if you feel comfortable to do so please state the results:…….. …… ……	

C13	Have you ever had any pelvic adhesions?	❑ Yes ❑ No/unsure ❑ Not applicable ie for males

The following 2 questions are particularly personal so only answer them if you feel comfortable to do so

C14	Have you or your partner ever had any terminations?	❑ Yes ❑ No
C15	If yes, can you tell us if your IBD had anything to do with your decision and, if so, in what way?..... …… …… ……	

PART D PREGNANCY

In this question we are asking about all pregnancies even if they didn't result in the birth of a baby

D1	If **female** how many pregnancies have you had? OR If **male** how many pregnancies have you been responsible for?	……

If your answer above is "0" please go straight to question D49

This Question is only applicable for those who answered yes to QA13"Have you ever had surgery for the formation of a pouch?"

D2	Of the total number of pregnancies how many were ***after*** you had surgery for formation of a pouch?	……

	D3 **What were the outcomes of each pregnancy?** ***Please note perinatal problems means any health issue for the baby from birth to about 2 months old(including premature babies).*** *please circle answer*	D4 If you had perinatal problems, miscarriage or stillbirth can you give details of any cause or explanation for this?
Pregnancy 1	D3a) Healthy baby/ perinatal problems/ Miscarriage/ termination/ stillbirth	D4a)
Pregnancy 2	D3b) Healthy baby/ perinatal problems/ Miscarriage/ termination/ stillbirth	D4b)
Pregnancy 3	D3c) Healthy baby/ perinatal problems/ Miscarriage/ termination/ stillbirth	D4c)
Pregnancy 4	D3d) Healthy baby/ perinatal problems/ Miscarriage/ termination/ stillbirth	D4d)
Pregnancy 5	D3e) Healthy baby/ perinatal problems/ Miscarriage/ termination/ stillbirth	D4e)

Pregnancy 6	D3f) Healthy baby/ perinatal problems/ Miscarriage/ termination/ stillbirth	D4f)

Please note extra pages are attached at the end of this questionnaire if you have had more than 6 pregnancies

D7-D18 Can you describe the severity of your IBD during each pregnancy? If you did not yet have IBD for any pregnancy please cross through the whole box.

Please note pre-pregnancy = 6 months before conception and post-pregnancy = 6 months after delivery

Pregnancy 1 *Outcome=*	Severity of IBD(tick)	Needed admission for IBD?	If needed admission did you have surgery for IBD?	If you had surgery please specify which:
Pre-pregnancy *Applies to males & females*	D7 a) ❑ Mild ❑ Moderate ❑Severe	D8 a) ❑ Yes ❑ No	D9 a) ❑ Yes ❑ No	D10 a) ……. ……. …….
During pregnancy *Females only*	D11 a) ❑ Mild ❑ Moderate ❑ Severe	D12 a) ❑ Yes ❑ No	D13 a) ❑ Yes ❑ No	D14 a) ……. ……. …….
Post pregnancy *Females only*	D15 a) ❑ Mild ❑ Moderate ❑ Severe	D16 a) ❑ Yes ❑ No	D17 a) ❑ Yes ❑ No	D18 a) ……. ……. …….

Pregnancy 2 *Outcome=*	Severity of IBD(tick)	Needed admission for IBD?	If needed admission did you have surgery for IBD?	If you had surgery please specify which:
Pre-pregnancy *Applies to males & females*	D7 b) ❑ Mild ❑ Moderate ❑ Severe	D8 b) ❑ Yes ❑ No	D9 b) ❑ Yes ❑ No	D10 b) ……. ……. …….
During pregnancy *Females only*	D11 b) ❑ Mild ❑ Moderate ❑ Severe	D12 b) ❑ Yes ❑ No	D13 b) ❑ Yes ❑ No	D14 b) ……. ……. …….
Post pregnancy	D15 b)	D16 b)	D17 b)	D18 b)

Females only	❑ Mild ❑ Moderate ❑ Severe	❑ Yes ❑ No	❑ Yes ❑ No	…… ……

D7-D18contd: Can you describe the severity of your IBD during each pregnancy? If you did not yet have IBD for any pregnancy please cross through the whole box.

Please note pre-pregnancy = 6 months before conception and post-pregnancy = 6 months after delivery

Pregnancy 3 ***Outcome=***	Severity of IBD(tick)	Needed admission for IBD?	If needed admission did you have surgery for IBD?	If you had surgery please specify which:
Pre-pregnancy ***Applies to males & females***	D7c) ❑ Mild ❑ Moderate ❑Severe	D8c) ❑ Yes ❑ No	D9c) ❑ Yes ❑ No	D10c) …… …… ……
During pregnancy ***Females only***	D11c) ❑ Mild ❑ Moderate ❑ Severe	D12c) ❑ Yes ❑ No	D13c) ❑ Yes ❑ No	D14c) …… …… ……
Post pregnancy ***Females only***	D15c) ❑ Mild ❑ Moderate ❑ Severe	D16c) ❑ Yes ❑ No	D17c) ❑ Yes ❑ No	D18c) …… …… ……

Pregnancy 4 ***Outcome=***	Severity of IBD(tick)	Needed admission for IBD?	If needed admission did you have surgery for IBD?	If you had surgery please specify which:
Pre-pregnancy ***Applies to males & females***	D7d) ❑ Mild ❑ Moderate ❑ Severe	D8d) ❑ Yes ❑ No	D9d) ❑ Yes ❑ No	D10d) …… …… ……
During pregnancy	D11d)	D12d)	D13d)	D14d) ……

Females only	❑ Mild ❑ Moderate ❑ Severe	❑ Yes ❑ No	❑ Yes ❑ No	…… ……
Post pregnancy ***Females only***	D15d) ❑ Mild ❑ Moderate ❑ Severe	D16d) ❑ Yes ❑ No	D17d) ❑ Yes ❑ No	D18d) …… ……

Please note extra pages are attached at the end of this questionnaire if you have had more than 4 pregnancies

D19-48 What **IBD Medications** were taken in the time surrounding each pregnancy? **If you did not yet have IBD for any pregnancy please cross through the whole box.**

The answers to the following questions may be a little difficult to recall but will be really helpful – just answer to the best of your memory. Remember, there are no right or wrong answers. Please tick the circles for your answers.

Pregnancy 1 ***Outcome=***	**5-ASA** Eg Mesalazine Sulphasalazine Olsalazine	**Steroids** Eg prednisolone, Hydrocortisone, Predsol enema budesonide	**MTX** methotrexate	**6-MP** (Mercaptopurine)	**Azathioprine** (Imuran,thioprine, Azahexal, azamun, azapin)	**Anti-diarrhoeals** Eg lomotil Immodium Gastrostop Codeine	**Antibiotics** Eg Metronidazole Ciprofloxacin	**Cyclosporin**	**Infliximab**	**Other,** specify
Pre-pregnancy ***Applies to males & females***	D19a) ○ Yes ○ No	D20a) ○ Yes ○ No	D21a) ○ Yes ○ No	D22a) ○ Yes ○ No	D23a) ○ Yes ○ No	D24a) ○ Yes ○ No	D25a) ○ Yes ○ No	D26a) ○ Yes ○ No	D27a) ○ Yes ○ No	D28a)
During pregnancy ***Females only***	D29a) ○ Yes ○ No	D30a) ○ Yes ○ No	D31a) ○ Yes ○ No	D32a) ○ Yes ○ No	D33a) ○ Yes ○ No	D34a) ○ Yes ○ No	D35a) ○ Yes ○ No	D36a) ○ Yes ○ No	D37a) ○ Yes ○ No	D38a)
Post pregnancy ***Females only***	D39a) ○ Yes ○ No	D40a) ○ Yes ○ No	D41a) ○ Yes ○ No	D42a) ○ Yes ○ No	D43a) ○ Yes ○ No	D44a) ○ Yes ○ No	D45a) ○ Yes ○ No	D46a) ○ Yes ○ No	D47a) ○ Yes ○ No	D48a)
Pregnancy 2 ***Outcome=***	**5-ASA** Eg Mesalazine Sulphasalazine Olsalazine	**Steroids** Eg prednisolone, Hydrocortisone, Predsol enema budesonide	**MTX** methotrexate	**6-MP** (Mercaptopurine)	**Azathioprine** (Imuran,thioprine, Azahexal, azamun, azapin)	**Anti-diarrhoeals** Eg Eg lomotil Immodium Gastrostop Codeine	**Antibiotics** Eg Metronidazole Ciprofloxacin	**Cyclosporin**	**Infliximab**	**Other,** specify
Pre-pregnancy ***Applies to males & females***	D19b) ○ Yes ○ No	D20b) ○ Yes ○ No	D21b) ○ Yes ○ No	D22b) ○ Yes ○ No	D23b) ○ Yes ○ No	D24b) ○ Yes ○ No	D25b) ○ Yes ○ No	D26b) ○ Yes ○ No	D27b) ○ Yes ○ No	D28b)

During pregnancy *Females only*	D29b) ○ Yes ○ No	D30b) ○ Yes ○ No	D31b) ○ Yes ○ No	D32b) ○ Yes ○ No	D33b) ○ Yes ○ No	D34b) ○ Yes ○ No	D35b) ○ Yes ○ No	D36b) ○ Yes ○ No	D37b) ○ Yes ○ No	D38b)
Post pregnancy *Females only*	D39b) ○ Yes ○ No	D40b) ○ Yes ○ No	D41b) ○ Yes ○ No	D42b) ○ Yes ○ No	D43b) ○ Yes ○ No	D44b) ○ Yes ○ No	D45b) ○ Yes ○ No	D46b) ○ Yes ○ No	D47b) ○ Yes ○ No	D48b)

D19-48 continued:What **IBD Medications** were taken in the time surrounding each pregnancy? **If you did not yet have IBD for any pregnancy please cross through the whole box**

***The answers to the following questions may be a little difficult to recall but will be really helpful – just answer to the best of your memory. Remember, there are no right or wrong answers. Please tick the circles for your answers*.**

Pregnancy 3 ***Outcome=***	**5-ASA** Eg Mesalazine Sulphasalazine Olsalazine	**Steroids** Eg prednisolone, Hydrocortisone, Predsol enema budesonide	**MTX** methotrexate	**6-MP** (Mercaptopurine)	**Azathioprine** (Imuran,thioprine, Azahexal, azamun, azapin)	**Anti-diarrhoeals** Eg lomotil Immodium Gastrostop Codeine	**Antibiotics** Eg Metronidazole Ciprofloxacin	**Cyclosporin**	**Infliximab**	**Other**, specify
Pre-pregnancy	D19c)	D20c)	D21c)	D22c)	D23c)	D24c)	D25c)	D26c)	D27c)	D28C)
Applies to males & females	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	
During pregnancy	D29c)	D30c)	D31c)	D32c)	D33c)	D34c)	D35c)	D36c)	D37c)	D38c)
Females only	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	
Post pregnancy	D39c)	D40c)	D41c)	D42c)	D43c)	D44c)	D45c)	D46c)	D47c)	D48c)
Females only	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	
Pregnancy 4 ***Outcome=***	**5-ASA** Eg Mesalazine Sulphasalazine Olsalazine	**Steroids** Eg prednisolone, Hydrocortisone, Predsol enema budesonide	**MTX** methotrexate	**6-MP** (Mercaptopurine)	**Azathioprine** (Imuran,thioprine, Azahexal, azamun, azapin)	**Anti-diarrhoeals** Eg lomotil Immodium Gastrostop Codeine	**Antibiotics** Eg Metronidazole Ciprofloxacin	Cyclosporin	**Infliximab**	**Other,** specify
Pre-pregnancy	D19d)	D20d)	D21d)	D22d)	D23d)	D24d)	D25d)	D26d)	D27d)	D28d)
Applies to males & females	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	
During pregnancy	D29d)	D30d)	D31d)	D32d)	D33d)	D34d)	D35d)	D36d)	D37d)	D38d)
Females only	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	
Post pregnancy	D39d)	D40d)	D41d)	D42d)	D43d)	D44d)	D45d)	D46d)	D47d)	D48d)
Females only	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	

Please note extra pages are attached to the end of this questionnaire if you have had more than 4 pregnancies

D49	Have you ever had concerns about the effect of taking **IBD medications** during pregnancy or around the time of conception?	❑ Yes ❑ No
D50	Can you explain to us why you did or did not have concerns?..... …… ……	

D51	Did you ever change your IBD medications because of wanting yourself or your partner to become pregnant?	❑ Yes ❑ No
D52	If yes, was this because…….	❑ advised by Gastroenterologist ❑ advised by GP ❑ advised by Gynaecologist/other doctor ❑ other reason, please describe:…….. …… …… …… ……

The next question applies to females only

D53	Did you ever change your medications because of being pregnant?	❑Yes ❑No
D54	If yes, was this because:	❑ advised by Gastroenterologist ❑ advised by GP ❑ advised by Gynaecologist/other doctor ❑ other reason, please describe :…… …… ……

The next 3 questions apply only to females who have breastfed their baby

D55	Did you ever change your IBD medications while you were breastfeeding?	❑ Yes ❑ No ❑ Not Applicable
D56	If yes , was this because:	❑ advised by Gastroenterologist ❑ advised by GP ❑ advised by Gynaecologist/other doctor ❑ other reason, please see next question
D57	If you changed your IBD medications while breastfeeding for another reason , can you say why?..... …… …… ……	

The remaining questions apply to males and females

D58	How would you rate your current compliance with taking your IBD medications?	❑ most of the time take them correctly ❑ take them correctly some of the time ❑ don't usually take them correctly ❑ take them rarely or not at all
D59	If your answer is "don't usually take them correctly "there can be valid reasons for this; Can you say why?..... …… …… ……	

D60	How do you rate your compliance with taking your IBD medications now compared with when you /your partner was pregnant or trying to conceive?	❑ Same ❑ Better ❑ Worse
D61	If your answer is "better" or "worse", can you say why?..... …… …… ……	

D62

We are now at the end of the Questionnaire. As this study is intended to cover your own perspective as a person living with IBD, is there any other information relating to Quality of Life, Body Image, Sexual Function or Pregnancy that you would like to share with us?

Thank you very much for your contribution in completing this questionnaire.

There are extra sheets following should you need the extra space for Questions D3, D4 ,D7-18 and D19-48

EXTRA SHEETS

	D3 **What were the outcomes of each pregnancy?** ***Please note perinatal problems means any health issue for the baby from birth to about 2 months old(including premature babies).*** *please circle answer*	D4 If you had perinatal problems, miscarriage or stillbirth can you give details of any cause or explanation for this?
Pregnancy 7	D3g) Healthy baby/ perinatal problems/ Miscarriage/ termination/ stillbirth	D4g)
Pregnancy 8	D3h) Healthy baby/ perinatal problems/ Miscarriage/ termination/ stillbirth	D4h)

D7-18 Can **you describe the severity of your IBD during each pregnancy?** ***Please note pre-pregnancy = 6 months before conception and post-pregnancy = 6 months after delivery***

Pregnancy 5	Severity of IBD(tick)	Needed admission for IBD?	If needed admission did you have surgery for IBD?	If you had surgery please specify which:
Pre-pregnancy ***Applies to males & females***	D7 e) ❑ Mild ❑ Moderate ❑Severe	D8 e) ❑ Yes ❑ No	D9 e) ❑ Yes ❑ No	D10 e) …… …… ……
During pregnancy ***Females only***	D11 e) ❑ Mild ❑ Moderate ❑ Severe	D12 e) ❑ Yes ❑ No	D13 e) ❑ Yes ❑ No	D14 e) …… …… ……
Post pregnancy ***Females only***	D15 e) ❑ Mild ❑ Moderate ❑ Severe	D16 e) ❑ Yes ❑ No	D17 e) ❑ Yes ❑ No	D18 e) …… …… ……

Pregnancy 6	Severity of IBD(tick)	Needed admission for IBD?	If needed admission did you have surgery for IBD?	If you had surgery please specify which:
Pre-pregnancy ***Applies to males & females***	D7 f) ❑ Mild ❑ Moderate ❑ Severe	D8 f) ❑ Yes ❑ No	D9 f) ❑ Yes ❑ No	D10 f) …… …… ……
During pregnancy ***Females only***	D11 f) ❑ Mild ❑ Moderate ❑ Severe	D12 f) ❑ Yes ❑ No	D13 f) ❑ Yes ❑ No	D14 f) …… …… ……
Post pregnancy ***Females only***	D15 f) ❑ Mild ❑ Moderate ❑ Severe	D16 f) ❑ Yes ❑ No	D17 f) ❑ Yes ❑ No	D18 f) …… ……

EXTRA SHEETS

D7-18 **Can you describe the severity of your IBD during each pregnancy?** ***Please note pre-pregnancy = 6 months before conception and post-pregnancy = 6 months after delivery***

Pregnancy 7	Severity of IBD(tick)	Needed admission for IBD?	If needed admission did you have surgery for IBD?	If you had surgery please specify which:
Pre-pregnancy ***Applies to males & females***	D7 g) ❑ Mild ❑ Moderate ❑Severe	D8 g) ❑ Yes ❑ No	D9 g) ❑ Yes ❑ No	D10 g) …… …… ……
During pregnancy ***Females only***	D11 g) ❑ Mild ❑ Moderate ❑ Severe	D12 g) ❑ Yes ❑ No	D13 g) ❑ Yes ❑ No	D14 g) …… …… ……
Post pregnancy ***Females only***	D15 g) ❑ Mild ❑ Moderate ❑ Severe	D16 g) ❑ Yes ❑ No	D17 g) ❑ Yes ❑ No	D18 g) …… …… ……

Pregnancy 8	Severity of IBD(tick)	Needed admission for IBD?	If needed admission did you have surgery for IBD?	If you had surgery please specify which:
Pre-pregnancy ***Applies to males & females***	D7 h) ❑ Mild ❑ Moderate ❑ Severe	D8 h) ❑ Yes ❑ No	D9h) ❑ Yes ❑ No	D10 h) …… …… ……
During pregnancy ***Females only***	D11 h) ❑ Mild ❑ Moderate ❑ Severe	D12 h) ❑ Yes ❑ No	D13 h) ❑ Yes ❑ No	D14 h) …… …… ……
Post pregnancy ***Females only***	D15 h) ❑ Mild ❑ Moderate ❑ Severe	D16h) ❑ Yes ❑ No	D17 h) ❑ Yes ❑ No	D18 h) …… ……

EXTRA SHEETS

D19-48 What **IBD Medications** were taken in the time surrounding each pregnancy?

The answers to the following questions may be a little difficult to recall but will be really helpful – just answer to the best of your memory. Remember, there are no right or wrong answers. Please tick the circles for your answers.

Pregnancy 5	**5-ASA** Eg Mesalazine Sulphasalazine Olsalazine	**Steroids** Eg prednisolone, Hydrocortisone, Predsol enema budesonide	**MTX** methotrexate	**6-MP** (Mercaptopurine)	**Azathioprine** (Imuran,thioprine, Azahexal, azamun, azapin)	**Anti-diarrhoeals** Eg lomotil Immodium Gastrostop Codeine	**Antibiotics** Eg Metronidazole Ciprofloxacin	**Cyclosporin**	**Infliximab**	**Other**, specify
Pre-pregnancy *Applies to males & females*	D19e) ○ Yes ○ No	D20e) ○ Yes ○ No	D21e) ○ Yes ○ No	D22e) ○ Yes ○ No	D23e) ○ Yes ○ No	D24e) ○ Yes ○ No	D25e) ○ Yes ○ No	D26e) ○ Yes ○ No	D27e) ○ Yes ○ No	D28e)
During pregnancy *Females only*	D29e) ○ Yes ○ No	D30e) ○ Yes ○ No	D31e) ○ Yes ○ No	D32e) ○ Yes ○ No	D33e) ○ Yes ○ No	D34e) ○ Yes ○ No	D35e) ○ Yes ○ No	D36e) ○ Yes ○ No	D37e) ○ Yes ○ No	D38e)
Post pregnancy *Females only*	D39e) ○ Yes ○ No ○	D40e) ○ Yes ○ No	D41e) ○ Yes ○ No	D42e) ○ Yes ○ No	D43e) ○ Yes ○ No	D44e) ○ Yes ○ No	D45e) ○ Yes ○ No	D46e) ○ Yes ○ No	D47e) ○ Yes ○ No	D48e)

Pregnancy 6	**5-ASA** Eg Mesalazine Sulphasalazine Olsalazine	**Steroids** Eg prednisolone, Hydrocortisone, Predsol enema budesonide	**MTX** methotrexate	**6-MP** (Mercaptopurine)	**Azathioprine** (Imuran,thioprine, Azahexal, azamun, azapin)	**Anti-diarrhoeals** Eg lomotil Immodium Gastrostop Codeine	**Antibiotics** Eg Metronidazole Ciprofloxacin	**Cyclosporin**	**Infliximab**	**Other**, specify:
Pre-pregnancy *Applies to males & females*	D19f) ○ Yes ○ No	D20f) ○ Yes ○ No	D21f) ○ Yes ○ No	D22f) ○ Yes ○ No	D23f) ○ Yes ○ No	D24f) ○ Yes ○ No	D25f) ○ Yes ○ No	D26f) ○ Yes ○ No	D27f) ○ Yes ○ No	D28f)
During pregnancy *Females only*	D29f) ○ Yes ○ No	D30f) ○ Yes ○ No	D31f) ○ Yes ○ No	D32f) ○ Yes ○ No	D33f) ○ Yes ○ No	D34f) ○ Yes ○ No	D35f) ○ Yes ○ No	D36f) ○ Yes ○ No	D37f) ○ Yes ○ No	D38f)
Post pregnancy *Females only*	D39f) ○ Yes ○ No	D40f) ○ Yes ○ No	D41f) ○ Yes ○ No	D42f) ○ Yes ○ No	D43f) ○ Yes ○ No	D44f) ○ Yes ○ No	D45f) ○ Yes ○ No	D46f) ○ Yes ○ No	D47f) ○ Yes ○ No ○	D48f)

EXTRA SHEETS

D19-48continued: What **IBD Medications** were taken in the time surrounding each pregnancy?

The answers to the following questions may be a little difficult to recall but will be really helpful – just answer to the best of your memory. Remember, there are no right or wrong answers. Please tick the circles for your answers

Pregnancy 7	**5-ASA** Eg Mesalazine Sulphasalazine Olsalazine	**Oral Steroids** Eg prednisolone, Hydrocortisone, Predsol enema budesonide	**MTX** methotrexate	**6-MP** (Mercaptopurine)	**Azathioprine** (Imuran,thioprine, Azahexal, azamun, azapin)	**Anti-diarrhoeals** Eg lomotil Immodium Gastrostop Codeine	**Antibiotics** Eg Metronidazole Ciprofloxacin	**Cyclosporin**	**Infliximab**	**Other**, specify
Pre-pregnancy *Applies to males & females*	D19g) ○ Yes ○ No	D20g) ○ Yes ○ No	D21g) ○ Yes ○ No	D22g) ○ Yes ○ No	D23g) ○ Yes ○ No	D24g) ○ Yes ○ No	D25g) ○ Yes ○ No	D26g) ○ Yes ○ No	D27g) ○ Yes ○ No	D28g)
During pregnancy *Females only*	D29g) ○ Yes ○ No	D30g) ○ Yes ○ No	D31g) ○ Yes ○ No	D32g) ○ Yes ○ No	D33g) ○ Yes ○ No	D34g) ○ Yes ○ No	D35g) ○ Yes ○ No	D36g) ○ Yes ○ No	D37g) ○ Yes ○ No	D38g)
Post pregnancy *Females only*	D39g) ○ Yes ○ No	D40g) ○ Yes ○ No	D41g) ○ Yes ○ No	D42g) ○ Yes ○ No	D43g) ○ Yes ○ No	D44g) ○ Yes ○ No	D45g) ○ Yes ○ No	D46g) ○ Yes ○ No	D47g) ○ Yes ○ No	D48g)
Pregnancy 8	**5-ASA** Eg Mesalazine Sulphasalazine Olsalazine	**Steroid**s Eg prednisolone, Hydrocortisone, Predsol enema budesonide	**MTX** methotrexate	**6-MP** (Mercaptopurine)	**Azathioprine** (Imuran,thioprine, Azahexal, azamun, azapin)	**Anti-diarrhoeals** Eg lomotil Immodium Gastrostop Codeine	**Antibiotics** Eg Metronidazole Ciprofloxacin	**Cyclosporin**	**Infliximab**	**Other**, specify:
Pre-pregnancy *Applies to males & females*	D19h) ○ Yes ○ No	D20h) ○ Yes ○ No	D21h) ○ Yes ○ No	D22h) ○ Yes ○ No	D23h) ○ Yes ○ No	D24h) ○ Yes ○ No	D25h) ○ Yes ○ No	D26h) ○ Yes ○ No	D27h) ○ Yes ○ No	D28h)
During pregnancy *Females only*	D29h) ○ Yes ○ No	D30h) ○ Yes ○ No	D31h) ○ Yes ○ No	D32h) ○ Yes ○ No	D33h) ○ Yes ○ No	D34h) ○ Yes ○ No	D35h) ○ Yes ○ No	D36h) ○ Yes ○ No	D37h) ○ Yes ○ No	D38h)
	D39h)	D40h)	D41h)	D42h)	D43h)	D44h)	D45h)	D46h)	D47h)	D48h)

Post pregnancy *Females only*	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	

Appendix C – Ethics Approval Fertility and Pregnancy Study

As discussed on the phone just now I can officially confirm that study 8/067 that you have outlined below was approved by the Southern Adelaide Human Research Ethics Committee in 2006. Dr Reme Mountifield's data relating to the project "Quality of life, body image, sexual function and pregnancy in inflammatory bowel disease: A survey of patients in the reproductive years" should be included in her dissertation as you have described.

Any further queries please don't hesitate to contact me.

Kind regards

Damian

Damian Creaser

Executive Officer

SAC HREC

Office for Research

Corporate Services

Southern Adelaide Local Health Network

Ward 6C, Room 219, Flinders Medical Centre

Tel: (08) 8204 6285

Email: damian.creaser@sa.gov.au

Appendix D - Participant Information Sheet

Quality of Life, Body Image, Sexual Function and Pregnancy in Inflammatory Bowel Disease: A survey of patients in the reproductive years.

This is a research project, and you do not have to be involved. If you do not wish to participate, your medical care will not be affected in any way.

You are invited to take part in a study exploring the possible effect of IBD on your general Quality of Life, Sexuality and Fertility. This study may provide sufferers of IBD, and the people who treat them, with helpful information about these poorly researched issues. You may have read about this study in the recent IBD newsletter.

PURPOSE OF THE STUDY

We believe that many people with IBD have issues related to sexual function and body image. We also suspect that fertility, family size and pregnancy are affected by the disease and its treatment. However, there is little evidence available that examines all these areas at once, so it can be difficult for your doctor to best advise you on these issues. Through this study we hope to gain knowledge from a patient point of view that can be used by the health care team to provide better care for their IBD patients. As we often only see patients when they are unwell, it is especially important for us to get a more complete overall picture of these issues from patients away from the hospital setting. We therefore are hopeful of getting responses to this survey from as many patients living with IBD as possible, regardless of how severe or mild your disease is, and how

often you have seen a doctor, or had troublesome symptoms. We are seeking this information to help with better managing care and advice for future patients with IBD.

WHAT IS INVOLVED?

Over 400 people on the IBD database who are aged 18-50 will be invited to participate in this study. If you choose to participate, you are invited to complete a questionnaire.

We have included the questionnaire with this information sheet.

Please fill in the questionnaire form.. You may choose to leave out an answer to any question.

There are no right or wrong answers. Simply tick the box that best suits your response or write your own answer. If you wish to discuss the questionnaire with anyone, feel free to do so. Our research nurse (the IBD Project Officer), Ruth Prosser can also be contacted if you want confidential assistance with completing the questionnaire.

Some questions are about:

your disease, such as when you were diagnosed,

your sexuality, such as whether having IBD affects your libido,

your fertility, such as how many children you have

We know some of the questions are personal so you can choose not to answer any question at any time.

The questionnaire should take approximately 30 minutes to complete.

If you do not wish to participate please complete the “opt –out” slip at the end of the invitation letter

Please return either the completed questionnaire or the “opt-out” slip to the research nurse in the enclosed reply paid envelope.

The research nurse will ring you if we have had no response from you within 4 weeks to see if you need another questionnaire posted out, or would like to arrange a time that is suitable for you to answer the questionnaire by phone.

That ends your involvement with the study.

BENEFITS OF PARTICIPATING IN THE STUDY

There may be no direct benefits to you associated with this study. However, by compiling the information provided from such a large number of people with IBD you can contribute to improving knowledge about sexual function, body image, fertility and general quality of life in IBD. This study is an opportunity for you to communicate information from a patient perspective to those who treat you.

There is no remuneration for participating in this study.

RISKS OF PARTICIPATING IN THE STUDY

As this is a simple survey we do not anticipate any risks to you from participating in this study. We believe the information you will provide to us will be worth the relatively short amount of time required to participate. If, however, you feel any emotional distress from completing the interview/questionnaire you can withdraw from the study at any time, and the research nurse will ensure that you receive appropriate support from your usual doctor as necessary.

PARTICIPATION IS VOLUNTARY

Your participation in the study is entirely voluntary. Due to the sensitive nature of information

sought in the study, we understand if you do not wish to answer some questions, or if you wish to withdraw from the study at any time.

If you decide not to participate in this study or if you withdraw, you may do this freely without prejudice to any treatment at Flinders Medical Centre or Repatriation General Hospital.

Confidentiality

Your personal information will be treated as strictly confidential. At the beginning of the study you will be given a code number. Only the research nurse, a project officer who works for the IBD Service, will know this number. The research nurse is not involved in your direct care so your privacy can be assured. All information collected during the study will be identified only by this number and you will remain anonymous. All information collected during the study will be kept on computer accessible by password and/or in a locked filing cabinet. Only the three Study Investigators listed below will have access to this information.

Publication of results

If you give us your permission by completing the questionnaire, we plan to publish the overall results (for all patients together) in a medical journal. This will be De-identified group data.

All records containing personal information will remain confidential and no information that could lead to your identification will be released.

FURTHER INFORMATION

Should you require further details about this project, either before, during or after the study, you may contact any of the Study Investigators:

The research nurse Ruth Prosser, Project Officer for the IBD Service on telephone 8204 5402

The Principal Investigator Dr Jane Andrews at the Repatriation General Hospital on telephone 8275 1764 or by email : jane.andrews@rgh.sa.gov.au

Co-Investigator Dr Peter Bampton at Flinders Medical Centre on telephone 8204 4964

WHO HAS REVIEWED THIS STUDY?

This study has been reviewed by the Flinders Clinical Research Ethics Committee. Should you wish to discuss the project with someone not directly involved, in particular in relation to matters concerning policies, your rights as a participant, or should you wish to make a confidential complaint, you may contact the Executive Officer, Research Ethics Committees, Ms. Carol Hakof on telephone 8204 4507.

Appendix E - CCP Know Questionnaire

Please answer the questions without any help. Circle only one answer for each question

Inheritance

1. Inflammatory Bowel Disease

- Will always pass from a parent to a child
- Will never pass from a parent to a child
- Is more likely to affect a child if mother or father are suffering from it
- Does not run in families
- Don't know

2. The risk of passing on Inflammatory bowel disease to a child

- Is zero
- Can be exactly determined by genetic testing
- Is less than 10 %
- Can be reduced by medication

Fertility

3. Men with Inflammatory Bowel Disease

- Usually do not have problems with fertility
- Should avoid all medication when trying for a baby
- Should not have children with women suffering from Inflammatory Bowel Disease
- Should not father children after the age of 40
- Don't know

Disease Activity

4. What is most important when trying for a baby?

- Women should come off all drugs when pregnant
- Inflammatory Bowel Disease should be well controlled before becoming pregnant
- There is no need for women to discuss it with her doctor before becoming pregnant
- Women with Crohns disease should not stop smoking
- Don't know

5. Women with Inflammatory Bowel Disease

- Should delay trying for a baby until their disease has been controlled by medication
- Will never experience flares of their disease during pregnancy
- Will always experience a flare during pregnancy
- Often need surgery during pregnancy
- Don't know

6. Active Inflammatory Bowel Disease during pregnancy

- Does not affect the chance of having a healthy baby
- Does not cause birth defects
- Should be put up with to protect the unborn from drug effects
- Should be treated with some types of drugs to protect the pregnancy

Drugs

7. Pregnant women with Inflammatory Bowel Disease

- Should avoid all drugs
- Should continue some medications

- Should use herbal medicines only
- Do not need to discuss drugs with their doctor
- Don't know

8. Infliximab and Adalimumab

- Are generally seen a s "probably safe " in pregnancy
- Cause serious harm to babies
- Do not work in pregnant women

9. The drug methotrexate

- Does not cause birth defects
- Is safe in pregnancy when taken as a tablet
- Should always be stopped 3-6 months before trying for a baby
- Does not need to be stopped in males who are taking it when they are trying for a baby
- Don't know

10. During pregnancy Mesalazine (this includes tablets like Asacol, Mezavant, pentasa, salofalk etc)

- Should not be taken a s a suppository or enema
- Should be avoided at all costs
- Does not work
- Is safe and should be continued
- Don't know

11. During pregnancy Azathioprine or 6-Mercaptopurine

- Cause serious harm to babies
- Do not work
- Can be continued

- Are considered unsafe
- Don't know

12. Mode of delivery

- Women with Inflammatory Bowel Disease
- Should never have a caesarean section
- Must have a caesarean section
- And peri-anal disease (abscesses or fistulae around and outside the back passage) are advised against having a caesarean section
- Can have a vaginal delivery in most cases

13. Peri-anal disease (abscesses or fistulae around and outside the back passage) that occurs after a normal vaginal delivery

- is common in ulcerative colitis
- response well to creams
- is more likely if a woman has suffered from it previously
- is never seen in women with Crohns disease
- don't know

<u>Pregnancy outcomes</u>

14. Women suffering from Inflammatory Bowel Disease

- Usually have bigger and heavier babies than other women
- Often give birth a bit early
- Often give birth a bit late
- Always have their baby on time even when Crohns disease flares
- Don't know

15. Birth defects in babies of mothers with Inflammatory Bowel Disease

- Are a common problem
- Occur slightly more often than in babies of mothers without Inflammatory Bowel Disease
- Are usually due to drug side effects
- Can be prevented by vaccinations

- Don’t know

16. The chances of having a healthy baby for mothers suffering from Inflammatory Bowel Disease

- Are less than 50%
- Are very good
- Depend on the method of delivery
- Can be improved by avoiding medication
- Don’t know

17. Breastfeeding

- Mothers suffering from Inflammatory Bowel Disease
- Should not breast feed to avoid passing the disease onto their child
- never experience a flare of disease when breastfeeding
- may have tiny amounts of medication in their breast milk
- do not need to discuss breast feeding with their midwife or doctor
- don’t know

END OF SURVEY THANK YOU

Appendix F – Ethics Approval "The Effect of Patient Education regarding Knowledge of Fertility and Pregnancy in Inflammatory Bowel Disease"

Southern Adelaide Clinical

Human Research Ethics Committee

30 April 2013

Dear Dr Mountifield

This is a formal correspondence from the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC). Whilst this official title of the committee has changed the committee is still properly constituted under AHEC requirements with the registration number EC00188. This committee operates in accordance with the "National Statement on Ethical Conduct in Human Research (2007)." This department only uses email correspondence for all documents unless prior arrangements have been made with the manager.

Application Number: 221.13

Title: The effect of patient education regarding knowledge of fertility and pregnancy

in Inflammatory Bowel Disease

Chief investigator: Dr Reme Mountifield

The Issue: The Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC) have reviewed and approved the above application. Your project may now commence. The approval extends to the following documents/changes:

- Low and negligible risk application dated 22 April 2013
- CCPKnow Questionnaire

Approval Period: 30 April 2013 to 29 April 2013

Please retain a copy of this approval for your records.

TERMS AND CONDITIONS OF ETHICAL APPROVAL

Final ethical approval is granted subject to the researcher agreeing to meet the following terms and conditions.

As part of the Institution's responsibilities in monitoring research and complying with audit requirements, it is essential that researchers adhere to the conditions below.

Researchers have a significant responsibility to comply with the National Statement 5.5. in providing the SAC HREC with the required information and reporting as detailed below:

1. Compliance with the National Statement on Ethical Conduct in Human Research (2007) & the

Australian Code for the Responsible Conduct of Research (2007).

2. To immediately report to SAC HREC anything that may change the ethical or scientific integrity of

the project.

3. Report Significant Adverse events (SAE's) as per SAE requirements available at our website.

4. Submit an annual report on each anniversary of the date of final approval and in the correct

template from the SAC HREC website.

5. Confidentiality of research participants MUST be maintained at all times.

6. A copy of the signed consent form must be given to the participant unless the project is an audit.

7. Any reports or publications derived from the research should be submitted to the Committee at

the completion of the project.

8. All requests for access to medical records at any SAHS site must be accompanied by this approval

email.

9. To regularly review the SAC HREC website and comply with all submission requirements, as they

change from time to time.

10. The researchers agree to use electronic format for all correspondence with this department.

11. Researchers are reminded that all advertisements/flyers need to be approved by the committee,

and that no promotion of a study can commence until final ethics and executive approval has been obtained. In addition, all media contract should be coordinated through the FMC media unit.

Yours sincerely

Petrina Kasperski

Executive Officer

SAC HREC

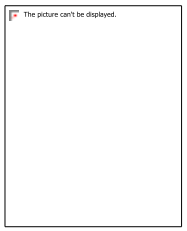
Appendix G – Patient questionnaires: “Anxiety, Perception of Cancer Risk and Quality of Life in Patients with Inflammatory Bowel Disease at Increased Risk for Colorectal Cancer”

Patient Questionnaires

Anxiety, Perception of Cancer Risk and Quality of Life in Patients with Inflammatory Bowel Disease (IBD)

at

Increased risk for Colorectal Cancer”



Questionnaire Part 1. Demographic Details Survey

As colorectal cancer screening is likely to involve people of all different backgrounds, we (the researchers) would like to obtain some background information from you. Please answer the following questions.

Currently, how old are you? _____yrs

Gender ☐ Female ☐ Male

What is your country of origin?_____

What is the main language that you speak at home?_____

What is your current occupational (job) status?

- ☐ Working full-time
- ☐ Working part-time
- ☐ Not working at present
- ☐ Retired

Do you currently own/lease a car?

- ☐ Yes
- ☐ No

In terms of housing, do you:

☐ Own your own home

☐ Currently pay a mortgage

☐ Currently rent

☐ None of the above (please specify)_____

Questionnaire Part 1 continued. *Demographic Details Survey*

What is your highest education qualification?

☐ Nil qualifications

☐ High School Certificate

☐ Diploma

☐ Bachelor

☐ Post Graduate

☐ Masters

☐ Doctorate of Philosophy

☐ Other (please specify)

_____

What is your current marital status?

Single

☐ Defacto

☐

☐

☐

Married

Separated

Divorced

Widowed

Questionnaire Part 1 continued. *Demographic Details Survey*

Over the last 3 months, have you experienced any of the following bowel problems? (if yes, please tick the relevant box)*

Constipation	Diarrhoea
☐ Not at all	☐ Not at all
☐ Sometimes	☐ Sometimes
☐ Frequently	☐ Frequently

Wind (Flatulence)	Abdominal Pain

Not at all Not at all

Sometimes Sometimes

Frequently Frequently

Incontinence Blood

☐ Not at all ☐ Not at all

☐ Sometimes ☐ Sometimes

☐ Frequently ☐ Frequently

Hemorrhoids

- Not at all
- Sometimes
- Frequently

*** Please note, if you are experiencing any or some of these symptoms and are at all concerned about it, please consult your General Practitioner.**

Questionnaire Part 2 **: Risk Perception**

The following questions ask about your perceptions of your risk for colorectal cancer. You may not know the answer and there is NO 'correct' answer. We'd just like your impression. Don't spend too long thinking about it (please circle the answer which pertains to you).

1. ***Risk Likelihood:*** What is the likelihood that ***you*** might suffer from colorectal cancer if you do NOT participate in screening?

Extremely Unlikely	Very Unlikely	More unlikely than likely	More likely than unlikely	Very Likely	Extremely Likely

2. ***What do you think your chance is of developing colorectal cancer in your lifetime?*** Please choose a number between 0% (no chance of colorectal cancer) and 100% (definitely will get colorectal cancer) : _____***%***

3. ***Risk Susceptibility:*** How much more likely are you to suffer from colorectal cancer than the average person of the same gender and age?

Very much more likely	Considerably more likely	A little more likely	Same likelihood	A little less likely	Considerably less likely	Very much less likely

4. ***Risk Severity:*** How serious would it be if you were to suffer from colorectal cancer?

Catastrophic	Extremely Serious	Very Serious	Quite Serious	Only a little serious	Not at all Serious

Questionnaire Part 2 continued **: Risk Perception**

5. ***Self Efficacy for CRC Screening/Surveillance*** I am confident that I can participate in colorectal cancer screening/surveillance sufficiently to alter my risk of colorectal cancer

Strongly Disagree	Disagree	Disagree a little	Agree a little	Agree	Strongly Agree

6. ***I know I will find it very difficult to participate in ongoing screening for*** colorectal cancer

Strongly Disagree	Disagree	Disagree a little	Agree a little	Agree	Strongly Agree

7. ***Response Efficacy for CRC Screening/Surveillance*** Following the screening recommendations of the medical profession will reduce my risk for colorectal cancer.

Strongly Disagree	Disagree	Disagree a little	Agree a little	Agree	Strongly Agree

Questionnaire Part 2 continued **: Risk Perception**

8. **No *matter what I do with screening, my risk for dying from*** colorectal cancer ***will stay the same***.

Strongly Disagree	Disagree	Disagree a little	Agree a little	Agree	Strongly Agree

9. ***Stage of Readiness for Screening/Surveillance Participation*** Do you currently participate in a screening/surveillance program so as to avoid colorectal cancer? (Please circle the response that best reflects your current situation)

No, and I do not intend to in the next 5 years

No, but I intend to in the next 5 years.

No, but I intend to in the next year.

Yes, and I have been for the last year.

Yes, and I have been for more than 5 years.

No, but I have done so in the past .

Questionnaire Part 3 Short-Form 36 (SF-36)

For each of the following questions, please mark an ☒ in the one box that best describes your answer. Please feel free to use the space at the end

for any additional comments you wish to make.

1. In general, would you say your health is:

(Please mark one box only)

Excellent	☐
Very Good	☐
Good	☐
Fair	☐

Poor ☐

2. ***Compared to one year ago,*** how would you rate your health in general now?

(Please mark one box only)

Much better now than one year ago ☐

Somewhat better now than one year ago ☐

About the same as one year ago ☐

Somewhat worse now than one year ago ☐

Much worse now than one year ago ☐

Questionnaire Part 3 continued Short-Form 36 (SF-36)

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(Please mark one box on each line)

		limited a lot ➘	limited a little ➘	not limited ➘
a.	***Vigorous Activities***, such as running, lifting heavy objects, participating in strenuous sports	☐	☐	☐
b.	***Moderate Activities***, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐	☐	☐
c.	Lifting or carrying groceries	☐	☐	☐

d.	Climbing ***several*** flights of stairs	☐	☐	☐
e.	Climbing ***one*** flight of stairs	☐	☐	☐
f.	Bending, kneeling, or stooping	☐	☐	☐
g.	Walking ***more than a mile (1.6 Kms)***	☐	☐	☐
h.	Walking ***half a mile (0.8 Kms)***	☐	☐	☐
i.	Walking ***100 yards (457 metres)***	☐	☐	☐
j.	Bathing or dressing yourself	☐	☐	☐

Questionnaire Part 3 continued Short-Form 36 (SF-36)

4. During the ***past 4 weeks,*** have you had any of the following problems with your work or other regular daily activities ***as a result of your physical health****?*

(Please answer YES or NO to each question)

		YES ↓	**NO** ↓
a.	Cut down on the ***amount of time*** you spent on work or other activities	☐	☐
b.	***Accomplished less*** than you would like	☐	☐
c.	Were limited in the ***kind*** of work or other activities	☐	☐
d.	Had ***difficulty*** performing the work or other activities (for example, it took extra effort)	☐	☐

5. During the ***past 4 weeks,*** have you had any of the following problems with your work or other regular daily activities ***as a result of any emotional problems*** (such as feeling depressed or anxious)?

(Please answer YES or NO to each question)

		YES ↓	**NO** ↓
a.	Cut down on the ***amount of time*** you spent on work or other activities	☐	☐
b.	***Accomplished less*** than you would like	☐	☐
c.	Didn't do work or other activities as ***carefully*** as usual	☐	☐

6. During the *past 4 weeks,* to what *extent* has your *physical health or emotional problems* interfered with your normal social activities with family, friends, neighbours, or groups?

(Please mark one box only)

Not at all ☐

Slightly ☐

Moderately ☐

Quite a bit ☐

Extremely ☐

7. How much *bodily* pain have you had during the *past 4 weeks*?

(Please mark one box only)

None ☐

Very Mild ☐

Mild ☐

Moderate ☐

Severe ☐

Very Severe ☐

During the *past 4 weeks*, how much did *pain* interfere with your normal work (including both work outside the home and housework)?

(Please mark one box only)

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

9. These questions are about how you feel and how things have been with you *during the past 4 weeks*. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the *past 4 weeks*……*(Please mark one box on each line)*		All of the time ↓	Most of the time ↓	A good bit of the time ↓	Some of the time ↓	A little of the time ↓	None of the time ↓
a.	Did you feel full of life?	☐	☐	☐	☐	☐	☐
b.	Have you been a very nervous person?	☐	☐	☐	☐	☐	☐
c.	Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐
d.	Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
e.	Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
f.	Have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐
g.	Did you feel worn out?	☐	☐	☐	☐	☐	☐
h.	Have you been a happy person?	☐	☐	☐	☐	☐	☐
i.	Did you feel tired?	☐	☐	☐	☐	☐	☐

j.	Has your health *limited your social activities* (Like visiting close friends or relatives)?	☐	☐	☐	☐	☐	☐

Questionnaire Part 3 continued Short-Form 36 (SF-36)

10. How TRUE or FALSE is *each* of the following statements for you?

(Please mark one box on each line)

		Definitely true ➘	Mostly true ➘	Not sure ➘	Mostly false ➘	Definitely false ➘
a.	I seem to get ill more easily than other people	☐	☐	☐	☐	☐
b.	I am as healthy as anybody I know	☐	☐	☐	☐	☐
c.	I expect my health to get worse	☐	☐	☐	☐	☐

d.	My health is excellent	☐	☐	☐	☐	☐

Any Additional Comments you wish to make:

Questionnaire Part 4 Spielberger Scale – 5 sample questions approved to reproduce in appendix by copyright

Parts A and B

A number of statements that people have used to describe themselves are given blow. Read each statement and then circle the appropriate value to indicate how you feel RIGHT NOW, that is, AT THIS MOMENT. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to BEST describe your PRESENT FEELINGS. (further questions as per Spielberger Scale in Part B for how patient GENERALLY feels)

		Not at all	***Somewhat***	***Moderately so***	***Very much so***
1	I feel calm	1	2	3	4
2	I am in a questioning mood	1	2	3	4

3	I am furious	1	2	3	4
4	I feel strong	1	2	3	4
5	I am tense	1	2	3	4

***Part 5* :** Multi-dimensional Health Locus of Control

Instructions: Each item below is a belief statement about your health with which you may agree or disagree. Beside each statement is a scale which ranges from strongly disagree (1) to strongly agree (6). For each item we would like you to circle the number that represents the extent to which you agree or disagree with that statement. The more you agree with a statement, the higher will be the number you circle. The more you disagree with a statement, the lower will be the number you circle. Please make sure that you answer **EVERY ITEM** and that you circle **ONLY ONE** number per item. This is a measure of your personal beliefs; obviously, there are no right or wrong answers.

		Strongly Disagree	**Moderately Disagree**	**Slightly Disagree**	**Slightly Agree**	**Moderately Agree**	**Strongly Agree**
1	If my health worsens, it is my own behaviour which determines how soon I will feel better again.	1	2	3	4	5	6
2	As to my health, what will be, will be	1	2	3	4	5	6

3	If I see my doctor regularly, I am less likely to have problems with my health	1	2	3	4	5	6
4	Most things that affect my health happen to me by chance.	1	2	3	4	5	6
5	Whenever my health worsens, I should consult a medically trained professional.	1	2	3	4	5	6
6	I am directly responsible for my health getting better or worse	1	2	3	4	5	6
7	Other people play a big role in whether my health improves, stays the same, or gets worse.	1	2	3	4	5	6

Part 5

continued **:** Multi-dimensional Health Locus of Control

		Strongly Disagree	**Moderately Disagree**	**Slightly Disagree**	**Slightly Agree**	**Moderately Agree**	**Strongly Agree**
8	Whatever goes wrong with my health is my own fault.	1	2	3	4	5	6
9	In order for my health to improve, it is up to other people to see that the right things happen	1	2	3	4	5	6
10	Whatever improvement occurs with my health is largely a matter of good fortune.	1	2	3	4	5	6
11	The main thing which affects my health is what I myself do.	1	2	3	4	5	6

12	I deserve the credit when my health improves and the blame when it gets worse	1	2	3	4	5	6
13	Following doctor's orders to the letter is the best way to keep my health from getting any worse	1	2	3	4	5	6
14	If my health worsens, it's a matter of fate	1	2	3	4	5	6
15	If I am lucky, my health will get better.	1	2	3	4	5	6
16	If my health takes a turn for the worse, it is because I have not been taking proper care of myself	1	2	3	4	5	6
17	The type of help I receive from other people determines how soon my health improves.	1	2	3	4	5	6

Thank you for taking the time to fill in these questionnaires. Once completed, please return in the reply paid envelope .

Appendix H – Ethics Approval "Anxiety, Perception of Cancer Risk and Quality of Life in Patients with Inflammatory Bowel Disease at Increased risk of Colorectal Cancer"

Dear Dr Mountifield,

RE: Research Application314/08 - Anxiety, Perception of Cancer Risk and Quality of Life in Patients with Inflammatory Bowel Disease (IBD) at Increased risk for Colorectal Cancer.

Status: Final ethical approval granted

Period of Approval: 8 January 2009 to 8 January 2012.

Your application to the Flinders Clinical Research Ethics Committee was received and reviewed by the Committee out of session. I am pleased to notify you this study has received final approval and may commence.

This approval encompasses the following:

Ethics application including the participant information sheet

The anxiety study questionnaires

The invitation letter (appendix 1 to the email dated 6 January 2009)

The opt out letter (appendix 7 to the email dated 6 January 2009)

The email from john Markic advising that the study will be indemnified dated 6 January 2009

Please note final ethical approval is granted subject to the following conditions:

Compliance with the National Statement on Ethical Conduct in Human Research (2007) & the Australian Code for the Responsible Conduct of Research (2007).

To immediately report to FCREC anything that may change the ethical or scientific integrity of the project.

To regularly review the FCREC website and comply with all submission requirements as they change from time to time.

Submit an annual report on each anniversary of the date of final approval and in the correct template from the FCREC website.

Confidentiality of research participants MUST be maintained at all times.

A copy of the signed consent form must be given to the participant.

Any reports or publications derived from the research should be submitted to the Committee at the completion of the project.

Report Significant Adverse events (SAE's) as per SAE requirements available at our website.

A copy of this email should be printed and kept on file for your records.

Yours sincerely,

Dr Harry Randhawa MB BS, LLB/LP

Acting Executive Officer for the Flinders Clinical Research Ethics Committee and Clinical Drug Trials Committee

Manager - Human Research and Ethics Department

Southern Adelaide Health Service

Room 2A 221

Flinders Medical Centre Bedford Park SA 5042

T: 08 8204 6453 or M: 0422 687 087 or Fax: 8204 4586

Harry.Randhawa@sa.gov.au

Appendix I – Participant Information Sheet: Anxiety, Perception of Cancer Risk and Quality of Life in Patients with Inflammatory Bowel Disease at Increased Risk for Colorectal Cancer

PARTICIPANT INFORMATION SHEET

Anxiety, Perception of Cancer Risk and Quality of Life in Patients with Inflammatory Bowel Disease (IBD) at Increased risk for Colorectal Cancer

Researchers:

Dr Reme Mountifield (Trial coordinator and PhD student))

Associate Professor Peter Bampton (Trial coordinator and supervisor of PhD)

Ruth Prosser (Research Team member)

Dr Amanda Moseley (Research Team member)

We wish to invite you to participate in a research study, as you have inflammatory bowel disease (IBD) and may or may not be are enrolled for colorectal cancer screening by regular colonoscopy via the Flinders Medical Centre database. This study seeks to explore whether being in a screening program affects Quality of life, emotional well being, and perception of risk of colorectal cancer. You do not have to be involved, your help would be purely voluntary and the decision is entirely up to you. Whether you choose to be involved or not, your medical care will not be affected in any way.

Aims of the project

To explore the effect of colonoscopic screening for colorectal cancer in IBD patients on quality of life and emotional wellbeing.

Summary of procedures

Participating in the research involves completing 5 questionnaires and returning to us in a reply paid envelope. The questionnaires will be identified with a specific code. This means all the information is confidential (so you cannot be identified)

You will have any colonoscopy procedures as usual.

Commitments

The questionnaire should take less than 30 minutes to complete. Along with questions looking at your feelings, quality of life and your understanding of the risk of colorectal cancer, we will ask some background questions about you as well.

By completing these questionnaires and sending them back in the reply paid envelope, you will be consenting to participate in this study.

Benefits

You will not receive any payment for your participation, but we hope important information will be obtained from this study which may help us provide better care to IBD patients in the future.

Your participation in this study is entirely voluntary and you have the right to withdraw at any time without giving a reason. If you decide not to participate in the study, or if you withdraw from the study you may do so freely, without affecting the standard care of treatment you receive.

Confidentiality

All records containing personal information will remain confidential and no information which could lead to your identification will be released, except as required by law.

It is intended that the results of this research will be published in a scientific journal. You will not be identified in the journal.

Should you require further details about this project, either before or after the study, you may contact:

Dr Reme Mountifield or Assoc Prof Peter Bampton, Gastroenterology Dept Flinders Medical Centre, Ph 8204 4693

Should you not wish to participate, please return the “opt out” letter in the enclosed self-addressed envelope so that we know not to contact you about the study again.

Complaints

This study has been reviewed by the Flinders Clinical Research Ethics Committee. If you wish to discuss the study with someone not directly involved, in particular in relation to policies, your rights as a participant, or should you wish to make a confidential complaint, you may contact David Van der Hoek FCREC, at the Flinders Medical Centre (8204 4507) or email research.ethics@fmc.sa.gov.au.

Appendix J – Invitation and Opt Out Letters: Anxiety, Perception of Cancer Risk and Quality of Life in Patients with Inflammatory Bowel Disease at Increased Risk for Colorectal Cancer

Re: A RESEARCH PROJECT

"Anxiety, Perception of Cancer Risk and Quality of Life in Patients with Inflammatory Bowel Disease (IBD) at Increased risk for Colorectal Cancer"

We are writing to you as a person who has had IBD for at least 8 years and is enrolled in the colonoscopic screening program via Flinders Medical Centre, or you may have IBD but not yet be eligible for colorectal cancer screening.

We would like to invite you to participate in a research study which will explore quality of life, levels of anxiety and perception of risk of colorectal cancer in people who participate in this method of screening for colorectal cancer.

I have enclosed the following:

Participant Information Sheet – this explains all about the study in detail

Questionnaire

Reply-paid envelope

Opt-out letter – Please sign and return this letter if you do not wish to be contacted further about the study.

Please contact myself or Dr Reme Mountifield (Study Co-ordinator) on 8204 4693 or 8204 6720 if you have any questions or concerns.

Yours Sincerely,

Associate Professor Peter Bampton

Gastroenterologist, Flinders Medical Centre

'Opt Out' Letter

"Anxiety, Perception of Cancer Risk and Quality of Life in Patients with Inflammatory Bowel Disease at Increased Risk for Colorectal Cancer"

Dear Associate Professor Bampton and Colleagues,

Thank you for the invitation to participate in your study.

I do not wish to participate in this study, and would prefer not to be contacted about this study again. I am aware that this decision will not affect in any way my future treatment at Flinders Medical Centre.

Yours sincerely,

Please Sign _____

_____

Please print your name

Appendix K – Patient Questionnaire: A Research Project Exploring Patients' Views on Health Care in Inflammatory Bowel Disease

Confidential Inflammatory Bowel Disease Survey

A Research Project Exploring Patients' Views on Health Care in Inflammatory Bowel Disease

This research aims to understand the kinds of issues you might face when seeing health care providers for your Inflammatory Bowel Disease (IBD) . Please do not spend too much time on any one question as your first response is usually the best.

Please write the first 2 letters of your first name__ and surname__

Date of Birth

Disease Type (please circle)1. Crohn's Disease 2. Ulcerative Colitis 3. Indeterminate Colitis

Are you of Aboriginal or Torres Strait Islander descent? Yes / No

We would like to ask you questions about you and your IBD in 5 areas: Medicine Use, Alternative Therapies, What you think about health care in IBD, your Quality of Life and Personality and Emotional wellbeing.

Thank you for your help with this important research.

Section A – Medicine Use

Most people miss doses of their medication at times. In this section we would like to ask some questions to explore this. In response to each of the statements below please circle the response which you think most accurately describes your own experience in taking your medications for IBD.

A5. I alter the dose of at least one of my medications

Never / Rarely / Sometimes / Often / Very Often

A6. Do you ever forget to take your IBD medication?

Yes / No

A7. I stop taking at least one of my medications

Never / Rarely / Sometimes / Often / Very Often

A8. Do you ever have problems remembering to take your IBD medication?

Yes / No

A9. I take less than prescribed of my IBD medication without telling my doctor

Never / Rarely / Sometimes / Often / Very Often

A10. I take more than instructed of my IBD medication without telling my doctor

Never / Rarely / Sometimes / Often / Very Often

If you decide to miss medication doses, please state the main reason for this

Medication cost 2. Concern about side effects 3. Don't think they work 4. Don't like using enemas 5. Haven't received enough information about medications 6. Do not feel satisfied with doctor's explanation for medication use 7. Other (Please list in the space provided)

A11. When you feel better, do you sometimes stop taking your IBD medication?

Yes / No

A12. Sometimes if you feel worse when you take your IBD medication, do you stop taking it?

Yes / No

A13. For which medication are you most likely to miss doses?

A14. How often do you change the dose of your medication without consulting your doctor?

Never / Rarely / Sometimes / Often / Very Often

A15. How well do you feel your medication works to control your IBD?

Not at all / A little / Neutral / Quite Well / Very Well

A16. Do you believe what your doctor tells you about the medication?

Never / Rarely / Sometimes / Often / Very Often

Please give details

A17. How many times daily are you expected to take tablets or enemas?

A18. What is the total number of tablets and enemas you are required to take each day?

A19. Do you have easy access to a health professional who can answer your questions about IBD and IBD medications?

Never / Rarely / Sometimes / Often / Very Often

If not, would this help? 1.Yes 2.No 3. Not applicable

A20. Would you prefer to make contact with your IBD doctor by:

Phone 2. Email 3. SMS 4. In person 5. Other If other, please list

A21. Would an interview with a pharmacist help to manage your IBD medication?

Definitely not / Not likely / Unsure / Would help / Definitely would help

A22. Do you think a blood test to show how often you miss doses would help you to take your medications as prescribed?

Definitely not / Not likely / Unsure / Would help / Definitely would help

A23. Do you take other medications beside those for IBD? (eg for asthma, blood pressure etc)

1.Yes 2.No 3.Unsure

A24. If yes, Are you more likely to miss IBD medication doses than doses of other medications?

1.Yes 2. No 3.Unsure

Section B – Alternative Therapies

Now we would like to ask some questions about your use of Complementary and Alternative Medicines

B1. How often do you use complementary of alternative therapies to treat IBD?

Never / Rarely / Sometimes / Often / Very Often

If so, what therapies have you tried? Chinese medicine, homeopathy, acupuncture, probiotics, Biswellia extracts, exercise, prayer, magnetism, other (Please list)

B2. Why did you try these therapies

B3. Was this on the advice of an alternative practitioner? 1. Yes 2.No

B4. How well do you think the treatment worked?

Not at all / Not a lot / Unsure / Well / Very Well

B5. Did you continue to use conventional IBD medications at the same time? 1 Yes 2. No

If so, did you discuss this with your doctor / pharmacist? 1. Yes 2. No

B6. How comfortable do you feel discussing IBD and treatments with your GP or specialist?

Very uncomfortable / Uncomfortable / Neutral / Comfortable / Very comfortable

B7.How comfortable do you feel discussing IBD and treatment s with an alternative practitioner?

Very uncomfortable / Uncomfortable / Neutral / Comfortable / Very comfortable

B8. Do you find the consultation experience less intimidating when seeing alternative practitioners compared with doctors?

Definitely not / Not really / Unsure / Somewhat / Definitely

If yes, please describe

B9. Do you feel more informed after consultations with the alternative practitioner compared with your doctor?

Definitely not / Not really / Unsure / Somewhat / Definitely

B10. Please describe who you preferred seeing (Alternative Practitioner vs doctor) and what differences you noticed between the two

B11. Did you alternative practitioner discourage you from using conventional therapy?

Definitely not / Not really / Unsure / Somewhat / Definitely

B12. Do your family or friends use alternative treatments?

Definitely not / Not really / Unsure / Somewhat / Definitely

B13. Have you noticed side effects of standard IBD medications?

Definitely not / Not really / Unsure / Somewhat / Definitely

B14. How many times a week do you eat take away food?

Never / Once / Twice / Three times / Four times / Five or more times

B15. Do you modify your diet for IBD or general health benefits?

Definitely not / Not really / Unsure / Somewhat / Definitely

B16. Please list the food components you avoid

B17. Do you treat water or food in any way before drinking / eating it? 1.Yes 2.No

B18. Do you exercise regularly? 1.Yes 2. No

B19. Are you vegetarian? 1.Yes 2. No

If yes please specify: 1.Lacto-ovo (milk & eggs) 2. Vegan (no milk and eggs)

B20. Do you smoke? 1. Yes 2 .No 3. Previously

Section C. How you receive health care for IBD

This section looks at the way you see the health care system and your doctor

C1. Who is your main care provider for IBD?

1.GP 2. Gastroenterologist 3. Surgeon 4. Other

If other, please list

C2. How many different doctors have you consulted about your IBD?

1/2/3/4/5/6/7/other

C3. Have you ever changed doctors because you were dissatisfied? Or sought a second opinion?

1.Yes 2.No

If yes, please give details

C4. Is the doctor you see most for IBD male or female? 1.Male 2.Female

C5. Please estimate your doctor's age group:

1.25-35 years 2. 35-45 years 3.45-55 years 4. 55-65 years 5. Other

C6. How would you rate your relationship with your doctor?

Poor / Not very good / Neutral / Good / Excellent

C7 Please rate your level of satisfaction with communication between yourself and your doctor

Poor / Not very good / Neutral / Good / Excellent

C8. Do you find it easier to communicate with your IBD nurse than the doctor? (if applicable)

Definitely not / Not really / Unsure / Somewhat / Definitely

C9. How often does your doctor ask about our feelings about IBD and psychological welfare?

Never / Rarely / Sometimes / Often / Very often

C10. If not, would that improve the relationship with your doctor?

Definitely not / Not really / Unsure / Somewhat / Definitely

C11. How much of what your IBD doctor says during appointments do you understand?

Nothing / Almost nothing / About half / Almost everything / Everything

C12. Do you feel embarrassed to ask questions of your doctor?

Definitely not / Not really / Unsure / Somewhat / Definitely

C13. How often do you miss appointments with your doctor?

Never / Rarely / Sometimes / Often / Very Often

C14. Please state your reasons for missing appointments

C15. Would you like to take more responsibility for management of your IBD?

Definitely not / Not really / Unsure / Somewhat / Definitely

C16.Would you prefer to attend regular check ups when your IBD is not active, or would you rather manage it yourself and see a doctor when you have a flare?

See doctor when IBD is stable and when flare 2. See doctor only with a flare

C17. Would you be more likely to attend outpatients if evening appointments were available?

Definitely not / Not really / Unsure / Somewhat / Definitely

C18. Please indicate your level of employment

Full time 2. Part time 3. Casual 4. Voluntary employment 5. Unemployed

C19. What is your occupation?

C20. Do you receive IBD treatment in the Public or Private system? 1. Public 2. Private

C21. If public hospital care, do you see the same doctor each visit?

Never / Rarely / Sometimes / Often / Very Often

Section D: Your Quality of Life, Personality and Emotional Wellbeing

This section helps us understand your personality and how IBD affects your quality of life

D1 How frequent have your bowel movements been during the last 2 weeks?

Very infrequent / Infrequent / Unsure / Frequent / Very frequent

D2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks?

Never / Rarely / Sometimes / Often / Very Often

D3. How much energy have you had or the last 2 weeks?

Very little / Little / Neutral / Enough / A lot

D4. How often during the last 2 weeks have you had to delay or cancel a social engagement?

Never / Rarely / Sometimes / Often / Very Often

D5. How often during the last 2 weeks have you been trouble by cramps in your abdomen?

Never / Rarely / Sometimes / Often / Very Often

D6. How often during the last 2 weeks have you felt generally unwell?

Never / Rarely / Sometimes / Often / Very Often

D7. Overall, in the last 2 weeks, how much of a problem have you had with passing a large amount of gas?

Never / Rarely / Sometimes / Often / Very Often

D8. How much of the time during the last 2 weeks have you been troubled by feeling nauseated or sick to your stomach?

Never / Rarely / Sometimes / Often / Very Often

D9. How satisfied, happy or pleased have you been with your personal life during the last 2 weeks?

Very unsatisfied / Unsatisfied / Neutral / Satisfied / Very satisfied

D10. Do you belong to an IBD Support group? 1. Yes 2. No

If no, do you have access to an IBD support group? 1. Yes 2. No

D11. How satisfied are you about the level of information you have about IBD?

Very unsatisfied / Unsatisfied / Neutral / Satisfied / Very satisfied

D12. How satisfied are you with your current relationship?

Very unsatisfied / Unsatisfied / Neutral / Satisfied / Very satisfied

D13. If you are having relationship problems, do you feel IBD contributes to your problems?

Definitely not / Not really / Unsure / Somewhat / Definitely

D14. Please describe the impact of IBD on your relationships

Please answer each of the following questions giving your immediate reaction.

Which best describes how you have been feeling over the past week:

(5 sample HADS questions reproduced to comply with copyright)

D16	I still enjoy the things I used to enjoy	Most of the time A lot of the time From time to time, occasionally Not at all	□ 1 □ 2 □ 3 □ 4
D17	I get a sort of frightened feeling as if something awful is about to happen	Most of the time A lot of the time From time to time, occasionally Not at all	□ 1 □ 2 □ 3 □ 4
D22	I feel as if I am slowed down	Most of the time A lot of the time From time to time, occasionally Not at all	□ 1 □ 2 □ 3 □ 4

D25	I feel restless as if I have to be on the move	Most of the time A lot of the time From time to time, occasionally Not at all	□ 1 □ 2 □ 3 □ 4
D27	I get sudden feelings of panic	Most of the time A lot of the time From time to time, occasionally Not at all	□ 1 □ 2 □ 3 □ 4

D29. Do you feel you have enough support from the people around you to cope with your IBD?

Definitely not / Not really / Unsure / Somewhat / Definitely

D30. Do you feel your IBD treatment is adequate?

Definitely not / Not really / Unsure / Somewhat / Definitely

D31. Have you ever been diagnosed with Irritable Bowel Syndrome? 1. Yes 2. No 3.Unsure

D32. Have you had counselling before? 1. Yes 2. No

D33. Have you ever seen a psychiatrist before? 1. Yes 2 .No

Have you ever seen a psychologist before? 1.Yes 2. No

D34. Have you ever taken antidepressant medication 1.Yes 2.No

If yes, please specify

If yes, did your mood improve?

Definitely not / Not really / Unsure / Somewhat / Definitely

D35. If yes, did your bowel symptoms improve?

Definitely not / Not really / Unsure / Somewhat / Definitely

D36. Who prescribed this medication?

Please circle whether you strongly disagree, moderately disagree, neither agree nor disagree, moderately agree or strongly agree with each of the following:

D37. When I cry I always know why

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

D38. Daydreaming is a waste of time

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

D39. I wish I were not so shy

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

D40. I am often confused about what emotion I am feeling

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

D41. I often daydream about the future

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

D42. I seem to make friends as easily as others do

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

D43. Knowing the answers to problems is more important than knowing the reasons for the answers

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

D44. It is difficult for me to find the right words for my feelings

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

D45. I like to let people know where I stand on things

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

D46. I have physical sensations that even doctors don't understand

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

D47. It's not enough for me that something gets the job done; I need to know why and how it works

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

D48. I'm able to discuss my feelings easily

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

D49. I prefer to analyse problems rather than just describe them

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

D50. When I'm upset, I don't know if I'm sad, frightened or angry

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

D51. I use my imagination a great deal

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

D52. I spend much time daydreaming whenever I have nothing else to do

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

D53. I am often puzzled by sensations in my body

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

D54. I daydream rarely

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

D55. I prefer to just let things happen rather than to understand why they turned out that way

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

D56. I have feelings that I can't quite identify

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

D57. Being in touch with emotions is essential

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

D58. I find it hard to describe how I feel about people

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

D59. People tell me to describe my feelings more

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

D60. One should look for deeper explanations

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

D61. I don't know what's going on inside me

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

D62. I often don't know why I'm angry

Strongly disagree / Moderately disagree / Neutral / Moderately agree / Strongly agree

Spielberger State Trait Personality Inventory

Part A and B (reproduction of 5 sample questions with copyright permission)

A number of statements that people have used to describe themselves are given below. Read each statement and then circle the appropriate value to indicate how you feel RIGHT NOW, that is, AT THIS MOMENT. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to best describe your PRESENT FEELINGS. (further questions as per Spielberger Scale in Part B for how patient GENERALLY feels)

	Part 1: RIGHT NOW (PRESENT)	Not at all	Somewhat	Moderately so	Very much so

1	I feel calm	1	2	3	4
2	I am in a questioning mood	1	2	3	4
3	I am furious	1	2	3	4
4	I feel strong	1	2	3	4
5	I am tense	1	2	3	4

Thank you for completing this questionnaire.

Your views are very important to our research and to the future care of people with Inflammatory Bowel Disease. If there is anything else you wish to say about the areas covered in this survey or other aspects of IBD health, please do so in the space below.

Appendix L – Ethics Approval: Exploring the interaction between health care delivery and patient behaviour in very different patient cohorts

Dear Dr Mountifield,

RE: Research Application 177/08: Exploring the interaction between health care delivery in inflammatory bowel disease and patient behaviour in very different patient cohorts.

Your response dated 28 October to the Flinders Clinical Research Ethics Committee was received and reviewed by the Committee. I am pleased to notify you this study has now received final approval and may commence.

This approval encompasses the following:

- Original NEAF submission;
- Updated Participant Information Sheet, received 28 October 2008;
- Participant Questionnaire;
- Revocation of Consent Form.

Period of Approval: 28 October 2008 to 28 October 2011.

Please note final ethical approval is granted subject to the following conditions:

1. Adherence to the principles outlined in the National Statement on Ethical Conduct in Human Research (NHMRC, 2007).

2. Researchers are required to immediately report to the FCREC anything which might warrant review of ethical approval of the project, including:

a. Adverse events

b. Proposed project amendments; and

c. New information or unforeseen events that may impact the ethical or scientific integrity of the project.

3. Projects are approved for 3 years only. A progress report must be provided annually. Extensions after 3 years will only be granted on the basis of a satisfactory progress report, and submission of any amendments to the project protocol or documentation, if applicable.

4. Confidentiality of research participants shall be maintained at all times.

5. A copy of the signed consent form must be provided to the participant.

6. A report and a copy of any published material should be forwarded to the Committee at the completion of the project.

A copy of this email should be printed and kept on file for your records.

Yours sincerely,

David Van der Hoek

Executive Officer

Flinders Clinical Research Ethics Committee

Clinical Drug Trials Committee

Ph: (08) 8204-4507

Fx: (08) 8204-4586

Web: http://www.flinders.sa.gov.au/research/pages/ethics/

Level 2, Room 2A/221

Flinders Medical Centre

Appendix M – Ethics Approval for involvement of Northern Territory participants in "Exploring the interaction between Health Care Delivery in Inflammatory Bowel Disease and patient behaviour in two very different patient cohorts"

menzies
school of health research

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Ph: 08 8922 8695 | Fax: 08 8922 8687 | Web: www.menzies.edu.au
ABN: 70 627 512 887

discovery for a healthy tomorrow

17 August, 2009

Associate Professor Peter Bampton
Department of Gastroenterology
Flinders Medical Centre
Bedford Park
Adelaide SA 5042

Dear Associate Professor Bampton and Dr Mountefield,

Re: 08/87 - Exploring the interaction between Health Care delivery in Inflammatory Bowel disease and patient behaviour in two very different patient cohorts.

The Human Research Ethics Committee of the NT Department of Health and Families and Menzies School of Health Research thanks you for taking the time to rework your application and submit for expedited review by the Fast Track Committee.

The Human Research Ethics Committee (HREC) of the NT Department of Health and Families and Menzies School of Health Research has considered and approved your application.

Full approval is now granted. The Committee is satisfied that the research proposal meets the requirements of the NH&MRC National Statement on Ethical Conduct in Human Research 2nd ed, 2007.

This approval will be ratified at the next meeting of the Human Research Ethics Committee to be held 21/10/2009. Please note that HREC approval applies only to research conducted after the date of this letter.

Approved Project timeline: 17/8/2009 to 1/3/2012

This approval is for a period of twelve (12) months. A project progress report is required on or before **17/8/2010**

Please note the terms under which ethical approval is granted:

1. The safe and ethical conduct of this project is entirely the responsibility of the investigators and their institution(s).
2. Researchers should report immediately anything which might affect continuing ethical acceptance of the project, including:
   a) adverse effects of the project on subjects and the steps taken to deal with these,
   b) other unforeseen events,
   c) new information that may invalidate the ethical integrity of the study,
   d) Proposed Changes in the project
3. Approval for a further twelve months will be granted if the HREC is satisfied that the conduct of the project has been consistent with the original protocol
4. Confidentiality of research participants should be maintained at all times as required by law

5. The Patient Information Sheet and the Consent Form shall be printed on the relevant site letterhead with full contact details
6. The Patient Information Sheet must provide a brief outline of the research activity including, risks and benefits, withdrawal options, contact details of the researchers and must also state that the Human Research Ethics Secretary can be contacted (telephone and email) for information concerning policies, rights of participants, concerns or complaints regarding the ethical conduct of the study.
7. The Committee must also be notified at the completion of the project.

Yours sincerely

Dr Gurmeet Singh
Deputy Chair

Human Research Ethics Committee
of NT Dept of Health & Families
and Menzies School of Health Research

Menzies School of Health Research
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Appendix N – Participant Information Sheet: A Research Project Exploring Patients' Views on Health Care in Inflammatory Bowel Disease

A Research Project Exploring Patients' Views on Health Care in Inflammatory Bowel Disease

"Exploring the interaction between Health Care

delivery in Inflammatory Bowel Disease and patient

behaviour in two very different patient cohorts"

Participant Information Sheet

What is the research about?

Inflammatory Bowel Disease (IBD) is a group of diseases including Crohn's Disease, Ulcerative Colitis and Indeterminate Colitis. It affects 1 in 200 Australians of both genders, all ages and from all walks of life. It affects the bowel and can cause abdominal pain, diarrhea, and rectal bleeding, but can also cause problems in skin, eyes, liver and joints. Patients with IBD need long term medication and often surgery.

Many patients with this disease find it difficult to take medication used to treat IBD, and many miss appointments with health care workers trained to treat the disease. There may be many reasons for this, but as treatments for IBD improve we would like the opportunity

to understand what patients don't like about their medication and about seeing IBD doctors and nurses.

The aim of this project is to explore the views of people with IBD on a range of topics related to the way health care is delivered, such as medication taking, use of alternative medicines, clinic appointments as well as your quality of life and psychological wellbeing.

Why do you want me to take part?

You have been invited to take part in the study because we are interested in the opinions of people with IBD. This kind of research requires careful collection of information from a large number of patients from different areas of Australia. If you have ever been diagnosed with IBD, you can help with this research.

This is a research project, and you do not have to be involved. If you do not wish to participate, your medical care will not be affected in any way.

What will being in the study mean for me?

If you agree to take part, being in the study will involve the following:

Reading this information sheet and signing the consent form

Completing a questionnaire about your experience of IBD including medication taking, alternative medicines, health care structure, quality of life and your emotional wellbeing.

Returning the questionnaire and Consent Form in the Reply Paid envelope (or in person)

We may access your previous medical records and pathology reports and will store information about you confidentially. These reports may come from another specialist, GP or hospital.

Your participation in this study is voluntary. You are free to decline to participate in any or all parts of the study. There may be no direct benefit to you from taking part in this study, but the results are likely to help other people who have Crohn's Disease in the future.

Will you collect tissue samples during the study?

No

Will I find out the results of the study?

The results will be submitted to medical journals for publication. As a participant, you may have been included in some of these studies but you will not be identified in any way. Results from the study are only reported in summary form. Participants' responses and names remain completely confidential and will never be identified in any report.

What if I do not want to participate?

Your participation is entirely voluntary and you have the right to withdraw at any time. If you decide not to participate in this study or if you withdraw, you may do this freely without prejudice to any treatment from any health care provider. If you do not want to be contacted again, you can phone one of the study coordinators (contact details below).

YOU CAN SAY NO and this will NOT affect your medical treatment in any way.

Can I withdraw from the study?

Your participation in the study is entirely voluntary and you have the right to withdraw from the study at any time without giving a reason. If you decide not to participate in the study, or if you withdraw from the study, you may do so freely, without affecting the standard care or treatment you will receive. The answers you have given will be destroyed if you wish.

How is my privacy protected?

All records containing personal information will remain confidential and no information which could lead to your identification will be released, except as required by law. We identify all information you give us by number rather than name. Your interview answers will be written on a sheet of paper that will have your number only, not your name. The interview answers will be kept in a locked filing cabinet. Your consent form will be kept in a separate locked filing cabinet. All records will be kept for a total of 30 years or until the completion of the project (whichever comes sooner).

Information collected about you during this study will be stored securely in a password protected computer database. Your identifying personal information (name, address and date of birth) will be retained on this database, in addition to details about your health, to allow accurate analysis and contact with you if necessary. Access to this information is restricted to members of the research team. Our staff members are trained to protect the privacy of participants, and have signed legal agreements not to disclose information. Any information that is obtained in connection with this study and identifies an individual will remain confidential and will only be used for the purpose of this research project. It will only be disclosed with your permission, except as required by law.

Expenses and Payments

You will not receive any payment for your participation in the study.

Who is conducting this research?

The formal title of this project is “Exploring the interaction between Health Care

delivery in Inflammatory Bowel Disease and patient behaviour in two very different patient cohorts.”

This study has been initiated by investigators from the Departments of Gastroenterology and Hepatology and Pharmacology at Flinders Medical Centre (FMC), where the principal investigators are Dr Réme Mountifield (FMC), Associate Professor Peter Bampton (FMC) , and Dr Jane Andrews of the Department of Gastroenterology and Hepatology at the Royal Adelaide Hospital. Other researchers such as Dr Anne Kidman, of Royal Darwin Hospital, and Ruth Prosser, of Flinders Medical Centre, are also involved.

Will more research be done in the future?

After we have finished this particular study we will keep the information and samples in de-identified form for 30 years. Any extra studies will first have to be approved by the Ethics Committee at the institution carrying out the study. Information given to researchers will be identified by a code only so it will not be possible for them to identify individual participants in any way. You will not receive any notice of future uses of the information.

What if I have questions?

If you have any questions, please contact one of the following:

Principal Investigators:

Dr Reme Mountifield 08 8204 4963

A/Prof Peter Bampton 08 8204 4964

Complaints

This study has been reviewed by the Flinders Clinical Research Ethics Committee and the Human Research Ethics Committee of the NT Dept of Health and Families and Menzies School of Health Research. If you wish to discuss the study with someone not directly involved, in particular in relation to policies, your rights as a participant, or should you wish to make a confidential complaint, you may contact the Executive Officer, FCREC, at the Flinders Medical Centre (8204 4507) or email research.ethics@fmc.sa.gov.au. If you are in Darwin, please contact Ph: 08 8922 7922.

Appendix O – Consent Form: A Research Project Exploring Patients' Views on Health Care in Inflammatory Bowel Disease

Southern Adelaide Health Service / Flinders University

CONSENT TO PARTICIPATION IN RESEARCH

I,

(first or given names) (last name)

request and give consent to my involvement in the research project

Exploring the interaction between Health Care

Delivery in Inflammatory Bowel Disease and Patient

Behaviour in two very different patient cohorts

I acknowledge the nature, purpose and contemplated effects of the research project, especially as far as they affect me, have been fully explained to my satisfaction by

(first or given name) (last name)

and my consent is given voluntarily.

I understand that I CAN SAY NO to the research

I acknowledge that the detail(s) of the following has/have been explained to me, including indications of risks; any discomfort involved; anticipation of length of time; and the frequency with which they will be performed:

1. I agree to complete a study questionnaire (as described) about my health and inflammatory disease and about my experience of its treatment.

2. I may be approached again to participate in future studies but I am under no obligation to do so.

3. The answers I give to questions may be stored for 10 years and analysed further but they will be anonymous (no one will know they are my answers).

I have understood and am satisfied with the explanations that I have been given.

I have been provided with a written information sheet.

I understand that my involvement in this research project may not be of any direct benefit to me and that I may withdraw my consent at any stage without affecting my rights or the responsibilities of the researchers in any respect.

I declare that I am over the age of 18 years.

I acknowledge that I have been informed that should I receive an injury as a result of taking part in this study, I may need to start legal action to determine whether I should be paid.

Signature of Research Participant : Date:

I, have described to

the research project and nature and effects of procedure(s) involved. In my opinion he/she understands the explanation and has freely given his/her consent.

Signature: Date:

Status in Project:

Appendix P – GESA Clinical Update Chapter: Pre Conception Counselling and Patient Perceptions of IBD and Pregnancy

Pre Conception Counselling and Patient Perceptions of IBD and Pregnancy

Pre conception counselling in this context is a realistic, evidence based discussion of risks specific to IBD in pregnancy, between specialist doctor or IBD Nurse, and an IBD patient and her family.

Why It is Important?

Australian and international data have demonstrated a knowledge "gap" between doctor and patient[20, 21, 157] whereby patients appear overly pessimistic regarding their chances of healthy conception and pregnancy. The main area of patient concern is the fear of detrimental effects of IBD medications on the developing fetus[21, 157] This leads to medication non adherence, a major cause of flares during pregnancy[266].

Current evidence suggests the biggest threat to pregnancy outcomes in IBD women is active disease, especially at conception[277]. Apart from Methotrexate, continued IBD maintenance medications are considered lower risk to pregnancy than uncontrolled disease, as detailed above.

Patient misperceptions about this risk ratio appear to influence reproductive decisions and contribute to voluntary childlessness in both male and female IBD patients[19].

Patients are unlikely to seek specific reproductive IBD counselling[20], thus the physician or nurse should initiate the discussion as part of routine long term IBD care.

Timing and content of counselling

Counselling can be divided into 3 stages depending on patient level of readiness for conception and suitability based on disease activity.

At diagnosis:

All patients should be informed that reproductive outcomes in IBD are good overall, but that conception and pregnancy require careful planning in conjunction with the IBD team. For best outcomes the disease must be well controlled, and most medications are safe in pregnancy, with the exception of methotrexate.

All patients should be advised to use effective contraception whilst their IBD is active, and referred to CCA and local IBD nurses where possible.

At the Remission visit:

When in remission and other long term health discussions are occurring, counselling should be more individualised. It is important that the major concepts are covered here as >30% of Australian pregnancies are unplanned.

Information for Men:

- Perinatal outcomes are the same same as healthy controls[278]
- No increase in congenital anomalies
- Fertility is impaired by sulfasalazine and methotrexate but this is reversible
- Ensure adequate contraception if taking Methotrexate as the effect on sperm in unknown.

Information for Women:

- Stable remission is the key to optimising pregnancy outcome
- Discuss safety of individual medications in pregnancy, and plan to continue during pregnancy (except Methotrexate)
- Discuss need for cessation of methotrexate at least 4 months prior to conception
- Ask about timing of pregnancy plans, and to be informed when conception is planned with 6 months' notice
- Recommend Folate (2-5mg od if taking sulfasalazine, 0.5mg od otherwise)
- Ensure effective contraception for now

At the conception planning visit:

Once patients wish to conceive a long visit to plan for pregnancy should be scheduled, ideally 6 months prior to planned conception, and should involve the patient's partner and other family members if possible. Counselling should be realistic and comprehensive, focussing on the improved pregnancy outcomes achieved when disease is well controlled.

For Men:

- Stop methotrexate and or sulfasalazine
- Ensure remission with another agent
- Optimise nutritional parameters

For Women:

- Provide information regarding all reproductive aspects of IBD (see list below)
- Encourage and allow time for questions
- Provide written information if possible, using plain language
- The goal of this appointment is a clear medication plan for pregnancy agreed on by doctor and patient – this has been shown to improve adherence if agreed pre conception[266].

IBD Pre Conception Counselling – Areas to cover

- Pregnancy outcomes in IBD
- Effect of disease activity on pregnancy outcome
- Effect of IBD medications on pregnancy
- Congenital Anomalies risk
- Inheritance of IBD
- Breast Feeding
- Fertility
- Delivery Mode
- Biologic specific management
- Plan for cessation or continuation final stages pregnancy
- Infant vaccination plan

In addition to patient education, the IBD physician must ensure that disease control and is optimized with safe medications and that patient and care team members are well prepared for pregnancy.

Physician's "To Do" list at the Conception Planning appointment:

- Stop Methotrexate
- Ensure folate supplementation (At least 2mg daily for patients taking sulfasalazine)
- Ensure clinical (and ideally endoscopic) remission using endoscopy, fecal calprotectin and imaging in addition to clinical assessment.
- Address smoking
- Bloods – check B12, Iron, folate, Vit D, albumin, fbe
- Optimise nutritional parameters
- Check thiopurine metabolites
- Document baseline weight
- Establish the Multidisciplinary team for this patient's pregnancy and refer to High Risk Pregnancy Clinic.
- Plan and agree upon pregnancy IBD medication to achieve uninterrupted "on message" care
- Write a detailed letter to the GP explaining need for controlled disease during pregnancy and giving contact details for queries

- Agree upon mode of communication between members of care team – Patient Hand Held Pregnancy record, case notes, electronic record

The time burden of detailed individualised pre conception counselling may be eased by the use of patient group education before family planning takes place. Australian data have demonstrated group education to be effective at addressing misperceptions and improving reproductive knowledge in IBD[22].

T**ake home messages for the patient:**

- Active disease is the major threat to good pregnancy outcomes
- Low risk medications preconception and during pregnancy are beneficial
- Very good outcomes are achievable with thorough and timely planning at the preconception stage

Appendix Q – GESA Clinical Update Chapter: IBD Investigations during Pregnancy

IBD investigations during Pregnancy

Careful preconception planning to ensure stable remission and to encourage IBD medication adherence during pregnancy will minimise the need for investigations during pregnancy.

Most women with stable IBD will not need Investigation during pregnancy. Those which can be deferred should be delayed until after delivery (eg surveillance colonoscopy). Semi urgent investigations are most safely performed in the second trimester[267].

Urgent Ix, however, is warranted where IBD management decisions will depend upon information obtained. Flares of disease where there is diagnostic uncertainty, the onset of potential IBD during pregnancy, or the development of complications such as toxic megacolon or haemorrhage may warrant urgent Ix to enable informed management decisions and optimise safety of mother and fetus.

Symptoms consistent with a patient's usual IBD flare should be treated as such as early as possible after exclusion of infection with a stool specimen, and do not usually require further investigation unless refractory or atypical.

Risk of IBD Investigations during pregnancy

Potential fetal risk from investigations must be weighed against potential benefit, and discussed carefully with the patient, her family and obstetric colleagues.

Radiologic Investigation:

Radiologic studies that do not use ionising radiation (ie Ultrasound and MRI) are ideal where possible[279]. Bowel ultrasound becomes technically difficult with increasing fetal size, however, and the safety of gadolinium use during MRI is unclear. Whilst some recommendations suggest avoidance of MRI during the first trimester[280, 281], a recent study found MRE without gadolinium safe and effective in diagnosing small bowel Crohn's during pregnancy[282].

Investigations which involve potential irradiation to the fetus (Xray, CT) need to be carefully discussed with the patient and involve a strong indication. The main risks of fetal irradiation increase with dose and include miscarriage and fetal death, childhood carcinogenesis and neurological effects. Although the risk is low, such tests should only be performed if the risk of misdiagnosis outweighs the risk from irradiation. The uterus should be shielded from radiation where possible. Iodinated contrast should be avoided where possible[283].

Endoscopic Investigation:

Gastroscopy and sigmoidoscopy are relatively safe in pregnancy[284, 285] although limited data exist for colonoscopy [286] [287]. The potential therapeutic or management determining benefit of endoscopy, however, should exceed fetal risk. Potential risks include maternal and fetal hypoxia, hypotension, respiratory depression, teratogenicity of medications, preterm delivery and IUFD but these events are rare[279] [288]. ASGE and ECCO recommend their use during pregnancy only when there is strong indication and the results change antenatal IBD management [267, 279]. Fecal calprotectin may be a viable alternative if the diagnostic question is whether or not active inflammation is present.

Bipolar electrocautery is relatively safe but should only be used with strong indication [279] (ie immediate haemostasis requirement), otherwise deferred until after pregnancy.

Procedures should be performed in the left pelvic tilt or left lateral position to avoid vena caval compression and maternal hypotension after the first trimester.

Obstetric and midwifery input is recommended to confirm fetal heart sounds pre and post procedure and fetal monitoring may be necessary during the procedure.

Medications during endoscopy

The minimum dose necessary to achieve patient anxiolysis but avoid maternal respiratory depression is suggested. Patients should undergo thorough counselling prior and the option of no sedation offered to pregnant women. Fentanyl is considered safe, although midazolam is more controversial [289]but probably safe [279]. Obstetric anaesthetic support may be necessary.

Bowel preparation

Poly ethylene glycol based preparations are low risk, but sodium phosphate preparations should be used with caution[290].

Summary

Investigations that will contribute to management decisions by allowing timely treatment of complications and active disease (where there is diagnostic uncertainty) are usually lower

risk than a “wait and watch” approach during pregnancy, but patients must be comprehensively counselled and high risk obstetricians involved in decision making.

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