Linköping University Medical Dissertation No. 1865

Fertility in Inflammatory Bowel Disease

LINKÖPING UNIVERSITY

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To Olle, Gustav, Knut and Andreas

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I. Druvefors E, Landerholm K, Hammar U, Myrelid P, Andersson RE. Impaired fertility in women with inflammatory bowel disease: a national cohort study from Sweden. *Journal of Crohns Colitis*. 2021;15:383–90. Published under CC-BY license.

II. Druvefors E, Andersson RE, Hammar U, Landerholm K, Myrelid P. Minor impact on fertility in men with inflammatory bowel disease: a national cohort study from Sweden. *Alimentary Pharmacology and Therapeutics*. 2022;56:292–300. Published under CC-BY license.

III. Druvefors E, Myrelid P, Andersson RE, Landerholm K. Female and male fertility after colectomy and reconstructive surgery in inflammatory bowel disease: a national cohort study from Sweden. *Journal of Crohns and Colitis*. Online ahead of print. Published under CC-BY license.

IV. Druvefors E, Landerholm K, Andersson RE, Sydsjö G, Myrelid P. Reasons for reduced fertility after colectomy in women with ulcerative colitis. *Manuscript*.

ABSTRACT

Inflammatory bowel diseases (IBD) often present in adolescence or early adulthood and is thus frequently diagnosed in men and women in their reproductive age. Previous population-based studies of fertility in patients with IBD are scarce.

From the Swedish National Patient Register (NPR) all patients diagnosed with IBD of fertile age between 1964–2014 were identified. Statistics Sweden identified a matched reference cohort (ratio 1:5) from the general population matched for sex, age and place of birth. Children born were identified through the Medical Birth Register and the Swedish Multigeneration Register. For subgroup analyses information about medication was collected through Medical Drug Register and information about socioeconomic status from Longitudinal Integrated Database for Health Insurance and Labour Market Studies. From the SWedish Inflammatory Bowel disease quality REGister (SWIBREG) a cohort of women with UC who underwent colectomy 2000–2020 was identified. Demographic data from SWIBREG and information from a study specific questionnaire regarding reproductive history and voluntary childlessness were analysed.

From the NPR 27,331 women and 29,104 men with IBD were identified, corresponding to 272,793 matched individuals.

The fertility rate in women with IBD was 1.52 (standard deviation [SD] 1.22) births per 1000 person-years, compared with 1.62 (SD 1.28) (p <0.001) in the matched reference cohort. Fertility was negatively affected mainly in women with Crohn's disease (CD) and IBD-unclassified (IBD-U) and to a lesser extent in ulcerative colitis (UC). Disease activity, bowel resections and, in the case of CD, also perianal disease further adversely affected fertility. For women with UC and IBD-U, but not for women with CD, fertility improved throughout the study period. Contraceptive use was higher in female IBD patients, both before and after the diagnosis.

In total 2,989 women underwent colectomy during the study period. Reconstruction with ileal pouch anal anastomosis (IPAA) and ileorectal anastomosis (IRA) was used to about the same extent in UC and IBD-U, although this was rare in CD. Compared with the matched reference cohort, women with IBD had lower fertility overall after colectomy (HR 0.65, CI 0.61–0.69), with least impact for operations that left the rectum intact (HR 0.79, CI 0.70–0.90). When the comparison was made within the group of

patients undergoing colectomy, fertility in female patients remained nearly unaffected after IRA in all subtypes of IBD, but was impaired after IPAA, especially in UC (HR 0.67 CI 0.50–0.88), and after completion proctectomy in all subtypes of IBD (CD 0.61 CI 0.38–0.96), UC HR 0.65, CI 0.49–0.85 and IBD-U0.68, 0.55–0.85).

The survey regarding reproductive behavior after colectomy was completed by 214 (73%) out of 294 eligible women identified in SWIBREG. The desire to have children was negatively affected by disease onset in 59% of the women, colectomy in 44% and by reconstruction in 37%. Altogether, 39% women with UC estimated that they chose to have fewer children in the end because of the disease, but only 10% expressed that the disease made them completely restrain from having children. On the contrary 37% of the women reported that they had experienced difficulties to conceive and 19% expressed that they could not conceive at all. Of the women undergoing reconstruction post colectomy, 37% reported that the choice of reconstruction method was influenced by their desire to have children. Difficulty conceiving was more commonly reported after reconstruction with IPAA (odds ratio [OR] 5.54) than IRA (OR 2.57).

Men with IBD also had lower fertility rate compared with the matched reference population, although the impact on parity was limited; 1.28 (SD 1.27) versus 1.35 (SD 1.31) ($p < 0.001$). Fertility in men was nevertheless impaired in all IBD subtypes. The disease severity measured as order of hospital admissions (UC and IBD-U), intensity of medical treatment (CD), and bowel surgery (IBD-U) were further associated with impaired fertility in men. In the 3,771 men undergoing colectomy during the study period, fertility was only marginally (HR 0.89, CI 0.85–0.94) impaired, regardless of reconstruction.

In conclusion, women with IBD have only slightly reduced fertility rates compared with the matched reference population with some exceptions. In non-surgically treated patients, the impact was most pronounced in female patients with CD. Women post colectomy have a particularly marked impact on fertility independent of IBD subtype. Bowel reconstruction with IPAA and proctectomy had a pronounced negative impact on fertility, while fertility was not further affected after IRA. More than half of the women with UC post colectomy reported that developing UC has affected their desire to have children, but difficulty to conceiving is also commonly reported. The impact of IBD in men was only minor.

ABBREVIATIONS

ACTH	adrenocorticotropic hormone
AFRR	adjusted fertility rate ratio
AMH	anti Müllerian hormone
ASA	aminoaalicylic acid
ATC-code	anatomical therapeutic chemical code
CD	Crohn´s disease
CDEIS	Crohn's disease endoscopic index of severity
CI	confidence interval
CI	continent ileostomy (Kock pouch)
CRC	colorectal cancer
CRP	C-reactive protein
CUTE	colitis of uncertain type or etiology
EIM	extraintestinal manifestation
GI	gastrointestinal
GWAS	genome-wide association studies
HBI	Harvey Bradshaw index
HLA	human leukocyte antigen
HR	hazard ratio
IBD	inflammatory bowel disease
IBD-U	inflammatory bowel disease unclassified
IC	indeterminate colitis
ICD	international classification of disease
ICMART	international committee for monitoring assisted reproductive technologies
IL	interleukin
IPAA	ileal pouch–anal anastomosis
IFN	interferon
IRA	ileorectal anastomosis
JAK	janus kinas
LIFT	ligation of inter-sphincteric tract
LISA	longitudinal integrated database for health insurance and labour market studies
MAPK	mitogen-activated protein kinase

ABBREVATIONS

MBR	medical birth register
MGR	multi-generation register
OR	odds ratio
NOD	nucleotide-binding oligomerisation domain
NOMESCO	Nordic medico-statistical committee
NPR	national patient register
PDR	prescribed drug register
PDE	phosphodiesterase
PROMs	patient reported outcome measures
S1P	sphingosine-1-phosphate
SCB	statistics Sweden
SD	standard deviation
SES	socioeconomic status
SES-CD	simplified endoscopic activity score for Crohn's disease
SHS	short health scale
SILS	single incision laparoscopic surgery
SNP	single nucleotide polymorphism
SWIBREG	Swedish inflammatory bowel disease registry
Th-cell	T helper cell
TNF	tumor necrosis factor
TPR	total population register
UC	ulcerative colitis
UCEIS	ulcerative colitis endoscopic index of severity
WCE	wireless capsule endoscopy
WHO	world health organisation

BACKGROUND

The inflammatory bowel diseases (IBD) are heterogenic inflammatory conditions, characterised by a chronic inflammation of the intestinal mucosa. The disease is usually relapsing, with intervening periods of low or no disease activity. The pathogenesis is incompletely understood, but both heredity and environment are important[1]. The most common IBD subtypes are ulcerative colitis (UC) and Crohn's disease (CD). These subtypes have partly different histopathological findings and clinical presentation, but some features are shared by both IBD types.

HISTORY OF INFLAMMATORY BOWEL DISEASE

Chronic diarrhoea was reported by physicians in ancient Greece, including Hippocrates[2, 3]. First reports of patients with a disease picture that more clearly resembles UC came from United Kingdom during the latter part of 18th and 19th centuries, with patients suffering from long lasting, bloody diarrhoea and fever[3-5]. Autopsy revealed transmural intestinal inflammation. The number of patients with a similar clinical picture increased in Great Britain and reports also appeared in other parts of Europe and the United States. The disease was often serious, with many patients dying from perforation of the colon, peritonitis, hemorrhage, sepsis and pulmonary embolism. By the 1920s UC was a well-known medical condition[6]. In the 1930s and 1940s, surgical procedures were being standardised and different medical fields like pathology, radiology and psychiatry contributed to the understanding of UC. Early etiological speculation included allergy and psychogenic disorder[7, 8]. Later, an infectious disease was speculated to be the cause of the disease. The favourable response to treatment with adrenocorticotropic hormone (ACTH) and adrenal steroids gave rise to the theory of an underlying immunological cause in the 1950s[9] and the involvement of autoimmunity in the pathogenesis was reported 1959[10].

The first preserved description of CD is in an autopsy report from the beginning of the 17th century, where the ulcerated caecum was found to be contracted and invaginated into ileum in a boy suffering from abdominal pain and diarrhoea. Similar findings were reported on a few occasions over the next few centuries. In 1913 Dalziel linked the clinical picture of 13 patient's with the finding of chronic interstitial ileitis[11]. In the 1920s

hyperplastic, granulomatous lesions of the intestine was associated with fever, abdominal pain, diarrhoea and weight loss in young patients[8]. The distinction between CD and UC was made in 1932. In 1936 Burrill Crohn *et al* described patients with combined ileitis and right-sided colitis giving, and the disease became eponymous[12]. Early speculations as to the cause of the disease included infections, abdominal trauma, allergies, and impaired vascular or lymphatic circulation[7].

IBD used to be frequently fatal, but in the modern era are chronic controllable disorders in the majority of patients. Despite the many efforts to determine the aetiology, IBD is still not fully understood today.

EPIDEMIOLOGY

The first studies of epidemiology in IBD came in the 1950s and the first population-based studies were published in the 1970s[3]. There is a geographical variation in the incidence pattern of IBD, with the highest incidence rates reported in Europe, Oceania and North America[13, 14]. However, the incidence is increasing rapidly in many Asian countries, as well as in other newly industrialised countries[15]. During the 20th century most published studies demonstrated rising incidence also in Europe, while at the turn of the 21st many European countries have reported IBD incidence to have stabilised and in some regions even decline[15-17]. Within Europe, the incidence of IBD is characterised by a north-south and an east-west gradient, with higher incidence of UC and CD in Northern and Western Europe compared with Southern and Eastern Europe[18]. In high endemic regions like Northern Europe the incidence of UC is 11.4 per 100,000 and the incidence of CD is 6.3 per 100,000[19]. The highest IBD incidence ever reported is found in the Faroe Islands at 74 per 100,000 person-years from 2010–2014, driven mainly by the high incidence of UC[20]. In Sweden the incidence ratio for IBD is 29 per 100,000 (UC 16.9, CD 8.1 and IBD-unclassified [IBD-U] 5.2), giving a lifetime risk of IBD of 2,5%[17].

The onset of IBD usually occurs during the pre-adolescence, adolescence or during young adulthood, but children are increasingly being diagnosed with IBD[21, 22]. Approximately 25% of patients present before 20 years of age[23]. Although early onset is commonest, a bimodal onset is seen with a second incidence peak at age 60-80[16] and up to 20% of the IBD patients are diagnosed after 60 years of age[24]. CD is slightly more common in females compared with males in Europe and United States, while the opposite has been observed in Asia[25]. UC appears to be equally present in both sexes[15].

Since IBD are chronic diseases, the prevalence increases with time[16] rendering a geographical distribution similar to the incidence pattern of IBD[15]. The young mean age

of onset, the low mortality and the increasing average life expectancy causes the prevalence to increase rapidly. Overall, 0.3% of the European population is estimated to have been diagnosed with IBD, corresponding to a total of 2.5–3 million people[15]. In Sweden, over 65,000 individuals have a diagnosis of IBD[17, 26], of which 58% have UC, 28% CD and 14% IBD-U[17].

PATHOPHYSIOLOGY

The aetiology of IBD remains largely unknown, but the pathogenesis appears to be multifactorial (Figure 1). There is a tri-directional relationship between the microbiota, the intestinal epithelial cells and the mucosal immune system. Homeostasis between these factors is affected by genetic susceptibility and external environmental factors leading to an increase in the gut permeability and an abnormal immune response to luminal antigens, causing barrier dysfunction and chronic inflammation.

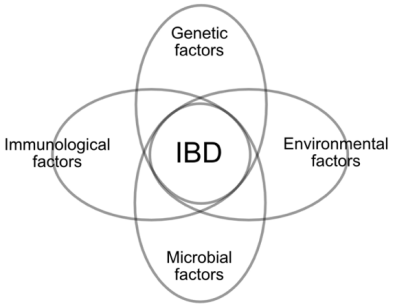

Figure 1. The multifactorial aetiology of IBD.

GENETIC FACTORS

At the beginning of the 20th century, there were already reports of familial clusters of IBD[27]. Later twin studies confirmed a genetic component[28-31]. Having a family member with IBD is the strongest known risk factor for IBD[32]. The genetic susceptibility seems to be stronger in CD than in UC[28-31, 33]. Around 5-16% of patients with IBD have a family history of IBD[33]. In monozygotic twins, the risk of developing CD is approximately 20-50% if one sibling is affected, the corresponding figure for UC is 14–19%[29-31]. The concordance rate in dizygotic twins is up to 7%. With two affected parents the risk of developing IBD for an offspring is over 30%[33].

Advances in genetic testing and analysing technologies have made it possible to carry out many genome-wide association studies (GWAS), which identify single nucleotide polymorphisms (SNPs)[34, 35]. GWAS have identified over 240 nonoverlapping genetic risk loci[36], of which around 30 genetic loci are shared between CD and UC[37, 38]. The genes and genetic loci affect several different pathways that play important roles in maintaining intestinal homeostasis. This includes barrier function, epithelial restitution, microbial defence, innate immune regulation, the generation of reactive oxygen species, autophagy,

regulation of adaptive immunity, endoplasmic reticulum stress and different metabolic pathways associated with cellular homeostasis[39, 40].

Nucleotide-binding oligomerisation domain 2 (NOD2) was the first gene found to be associated with CD[41]. Around one-third of the patients with CD have a mutation in this gene[37]. *NOD2* is a member of the cytosolic nod-like receptor family and control one of the two important systems that detect microbial invaders. *NOD2* activation can lead to secretion of proinflammatory cytokines, autophagy and can also activate the mitogen-activated protein kinase (MAPK) signalling pathway[38, 41]. Different mutations in the gene have been shown to cause a more severe phenotype or increased inflammatory cytokine responses[37, 42].

Moreover, GWAS have identified numerous SNPs in gene for IL-23R, highly associated with both UC and CD[43-45]. The gene for interleukin *IL23R* encodes a subunit of the receptor for the pro-inflammatory cytokine interleukin IL-23, which is a peptide involved in the production of Th17 cells[45]. Most risk-associated loci are shared across populations, but some loci show geographical heterogenicity. For example, variants of *NOD2* and *IL23R* are seen in most European patients, whereas these SNPs most often are absent in East Asian patients[46].

About 70% of IBD-associated loci overlap with loci associated with other complex immune diseases, such as psoriasis and ankylosing spondylitis[40]. The polymorphisms sometimes have opposite effects in different diseases[47], that is, a polymorphism in a genetic locus may be a risk factor for one autoimmune disease, but protective against another. Extraintestinal manifestations (EIMs) of IBD also share common loci with the underlaying, which may partly explain their co-occurrence. For example, some loci are associated with both UC and primary sclerosing cholangitis (PSC)[40, 48].

Genetic factors are the most important risk factors for the onset of IBD, but the contribution of each individual variant is very modest. Only a small proportion of genetically vulnerable patients will develop IBD. The strongest genetic effects have been demonstrated for IL23R, NOD2 and with certain human leukocyte antigen systems (HLA) with odds ranging from 1.4-3[36]. Overall, the genetic abnormalities account for only 20-25% of the heritability seen in IBD. This phenomenon is also seen in many other polygenetic diseases and it is proposed that that additional environmental factors and alterations in the gut microbiota and mucosal immune system are required for the development of IBD[37].

ENVIRONMENTAL FACTORS

Environmental factors include behaviours that increase risk at an individual level (such as diet and smoking), or they may modify the risk of populations of an entire region (such as with urbanisation). External environmental factors can contribute to gut dysbiosis, reducing microbiome diversity or introduce non-commensal microorganisms, altering the integrity of the epithelial barrier, and trigger an altered immune response. The incidence and prevalence of IBD have been observed to increase in different regions where industrialisation is increasing and occurs more commonly in urban versus rural regions. Moving to urban regions changes the risk profile over time, probably through lifestyle changes. Epidemiologic studies have identified several potential environmental factors that are associated with the risk of developing IBD.

Smoking

Smoking is associated with the development of IBD and the disease course. It has a divergent influence on the risk in UC and CD [49]. Current smokers have an increased risk of CD and decreased risk of UC compared with never smokers[49-51]. CD is 4 times more common among smokers and prevalence is also increased in ex-smokers[52]. Conversely, UC is relatively rare among smokers[51]. A dose-response relationship has been demonstrated[53], but no association was found between passive smoke inhalation as a child or prenatal maternal smoking and CD or UC[50]. Convincing causative explanations for the divergent influence of smoking on UC and CD have not been identified[50], but smoking is thought to influence IBD aetiology through epigenetic alterations affecting adaptive and immune response, autophagy, the gut microbiota composition and through immunosuppression[50]. Most studies report higher prevalence of ileal disease and lower prevalence of colonic involvement in smokers with CD, compared with non-smokers with CD[54].

For CD patients, smoking cessation is a crucial therapeutic strategy for IBD while smoking appears to decrease the risk for UC. Current smoking is associated with a more benign disease course, low hospitalisation rates, decreased need for steroids in UC, whilst quitting smoking before disease onset increased the risk of hospitalisation and colectomy[51, 55]. However, smoking has not been proven to alter the natural history of UC[56]. The role of smoking is strongly modified by genetic factors and ethnicity; no association between IBD and smoking is seen in Jewish and Asian patients[50].

Breastfeeding

Breastfeeding is one of the earliest environmental factors an infant is exposed to. Breastfeeding may protect against the development of IBD, the association is stronger in CD[54, 57]. The effect is seen both in early-onset IBD and in adult-onset IBD. Longer exposures were associated with decreased risk[50]. The protective effect was greater in Asian compared with European individuals[54, 55]. The protective effect may be mediated by improved development of the innate mucosal immunity through effects on the microbiome[50]. Breastfeeding may also be protective against other immune-mediated diseases[54].

Physical Activity

Physical training has been suggested to be protective against the onset of IBD and is inversely correlated with systemic low-level inflammation[58]. Some studies suggest that very physically active individuals are likely to be protected from developing CD, but not from UC[50]. However, data in this area are inconsistent[58].

Hygiene

The literature suggests that decreased microbial exposure in childhood and improved hygiene in general plays an important role in the development of IBD[59]. From a biological point of view, the lack of exposure to infectious antigenic stimuli in childhood can decrease microbiota diversity, which in turn will favour a pro-inflammatory T helper type 2-mediated (Th2) immune response in contrast to the dominant Th1–mediated response in environments with lower standard regarding hygiene[50]. Living near farm animals, home sharing, bed sharing, having pets and having two or more siblings and lack of access to hot water had a protective role in IBD[60]. The strength of the evidence supporting these different findings varies[59]. Overall, urban living was associated with CD and, to a lesser extent UC[61].

Appendectomy

Previous appendectomy with confirmed appendicitis, particularly at a young age, is associated with a protective effect (reduction of 13–26%) on the development of UC across different geographical regions and populations[61-63]. Appendectomy for appendicitis after onset of UC appears to be associated with worse disease course and the risk for subsequent colectomy is increased[64]. There is only a modest association with the development of CD[50].

Oral contraceptives

The use of oral contraceptives is associated with a 30% increased risk of developing IBD[65]. Longer exposures were associated with increased risk. The association between oral contraceptive use and UC is limited to women with a history of smoking[50]. No association between usage of progesterone-only contraception and IBD has been seen, suggesting that it is the oestrogen component of contraception that may drive IBD pathogenesis[66].

Antibiotics

Previous exposure to antibiotics is associated with increased risk of subsequent development of IBD[67]. The association between the use of antibiotics during the first year of life and the development of childhood IBD was strongest[50]. Antibiotics can alter the composition of the human gut microbiota. This association is stronger in CD than in UC, as antibiotics amplifies the dysbiosis seen in CD[50]. Any type of antibiotics, except for narrow-spectrum penicillin's, increased the risk of IBD. The highest risk was seen after the use of broad-spectrum antibiotic[67]. A dose-response relationship was detected in some studies[68].

Dietary Intake

Some studies have seen an association of IBD and dietary excess. Dietary components are implicated in mucosal dysbiosis, leading to low-grade persistent inflammation[69]. High intake of animal protein, sugars, sweets, oils and dietary fat, especially ω-6 fatty acids, and low in ω-3 fatty acids, have been implicated in increasing the risk of IBD, whereas high fibre, fruit and vegetable intake were associated with decreased risk of IBD[50, 70].

Infections

Gastric infection with *helicobacter pylori* is a associated with protective effect on IBD[71]. Conversely, intestinal infectious gastroenteritis with bacteria, viruses, parasites or fungi increases IBD risk by two- to threefold[50]. Gastrointestinal infections can also trigger or complicate an IBD flare[71].

MICROBIAL FACTORS

The whole human gut microbiome consists of approximately 1150 bacterial species, with each individual host having roughly 160 species[72]. The composition of the human microbiome is unique in each individual. It is established within the first weeks of life and then usually remains remarkably stable thereafter[73, 74]. The gut microbiota is

necessary for intestinal homeostasis and important for the maturation of the immune system, and its symbiotic relationship of tolerance and protective immunity. The gut microbiota can be influenced by diet, probiotics, prebiotics, antibiotics, exogenous enzymes, faecal microbiota transplantation, infections, and other environmental factors[74]. The intestinal microbiota is the major environmental driver of IBD. Some studies have also suggested alterations in the virome and mycobiome may also have a role in the pathogenesis[75].

Most intestinal bacteria belong to four phyla: *Firmicutes, Bacteroidetes, Proteobacteriae,* and Actinobacteriae. In healthy adults the two first phyla predominate[75, 76]. A significantly reduced biodiversity of the faecal microbiome is seen in IBD patients compared with that in healthy controls[77, 78] and the microbiota in IBD patients is also more unstable than that in healthy individual[76, 79]. Particularly in CD the intestinal microbiota is strongly suspected to play a role in initiating and triggering the immune system, leading to chronic inflammation. This is further supported by the finding that diversion of faecal stream prevents postoperative recurrence of ileal CD[80]. In healthy intestine, the *Firmicutes* and *Bacteroidetes* phylae predominate, whereas the microbiota in CD is characterised by a relative lack of *Firmicutes* and *Bacteroidetes*, and an over-representation of *enterobacteria*[76]. For example, a decrease in the abundance and biodiversity of *faecalibacterium prausnitzii* are seen in different intestinal disorders, including IBD. The finding is most evident in CD, particularly in patients with ileal involvement[81]. In UC, a reduction in *Clostridium species* and an increase in *Escherichia coli* is seen. The phenomenon of reduced diversity is not specific for IBD; a corresponding microbial shift is seen diabetes type II. It is also not clear whether the differences of reduced diversity is attributable to IBD is a cause of the disease, or a result of inflammation[71, 75].

IBD appears to result from abnormal host immune responses to the intestinal microbiota. The microbial community associated with the development of IBD may initiate damage the intestinal barrier via immune cells[82]. Animal studies have revealed that the intestinal microbiota play both proinflammatory and anti-inflammatory roles in the onset of IBD. In most animal models, the intestinal microbiota is essential for driving pathogenesis[75]. The same clear findings has been difficult to demonstrate humans[76].

IMMUNOLOGICAL FACTORS

The intestinal immune system is divided into innate- and adaptive immunity. The innate immunity includes the general barrier function of the intestine, while the adaptive immunity is pathogen specific.

Innate immunity in IBD

The innate immunity includes the acid pH in the stomach which limits microbial growth, the intestinal mucosa, antibacterial proteins, and innate immune cells with associated cytokines and molecules[37]. The first line of defence of the mucosal immune system is the mucous layer and the epithelial barrier of the intestine, representing a physical and chemical barrier encountered by the intestinal bacteria, pathogens and the food antigens[83]. The immunological dysregulation in IBD is characterised by epithelial damage with abnormal mucus production and defective repair, possibly caused by environmental factors and infections[84, 85]. It is not known if the increased intestinal permeability seen in IBD is a primary defect or a consequence of inflammation[86]. Polymorphisms have been detected in genes encoding junctional proteins and defective expression of antimicrobial peptides, implying barrier dysfunction is a primary mechanism[85]. Increased intestinal permeability is found in nearly one quarter of asymptomatic first-degree relatives of IBD patients. Some studies have reported similar figures in spouses of IBD patients, making it difficult to judge whether these alterations are due to genetic or environmental factors[33, 87].

Several types of innate immune cells have been shown to contribute to IBD pathogenesis[85]. Macrophages, dendritic cells, neutrophils, natural killer cells and innate lymphoid cells interact and produce cytokines, chemokines and antimicrobial agents to trigger inflammation. This leads to phagocytosis, antigen presentation and activation of the adaptive immune system[88]. Macrophages and mucosal dendritic cells show an increased expression of chemokine receptors (such as Toll-like receptors and NOD-like receptors). This promotes inflammation by inducing production of pro-inflammatory cytokines and while anti-inflammatory pathways are down-regulated[85]. They also act as antigen-presenting cells. Neutrophils impair the epithelial barrier function and release of multiple inflammatory mediators[89].

The pro-inflammatory cytokine tumour necrosis factor (TNF) is responsible for amplifying and maintaining the chronic inflammation in IBD by promoting transcription of other pro-inflammatory cytokines, up-regulating adhesion molecules in the endothelium and activating phagocytic activity of macrophages[90]. The family of innate lymphoid cells also participate in the pathogenesis of chronic intestinal inflammation, with an altered abundance and distribution. Innate lymphoid cells regulate their responses via secretion of cytokines and bridge the innate and adaptive immune systems[88, 91].

Adaptive immunity in IBD

Adaptive immunity us usually initiated if the innate immunity cannot evade the stimulation of a pathogen. The induction is slow and it usually takes several days to activation[37]. The adaptive immune system plays a central role in the progression of the chronic inflammatory events seen in IBD[85]. The initiation occurs when the gut-associated lymphoid tissue or in the mesenteric lymph nodes presents antigen to T-cells. Depending on type of antigen presented, the naive T-cells differentiate into different subsets, like for example effector-, regulatory-, and memory T-cells with up-regulated receptors, such as chemokine receptors and integrins. These receptors can bind to cellular adhesion molecules expressed on endothelial cells of the blood vessels, thereby allowing migration of leukocytes to the inflamed intestine[88].

The immune imbalance of Th1 and Th2 subsets has been shown to play an important role in IBD progression[85]. It has been suggested that CD is a Th1/Th17-mediated disease, while UC is associated with a Th2-type-like response[92]. Th1-cells are activated in responses to intracellular pathogens, and Th1-type cytokines can disrupt gut epithelial barrier function. Abnormal Th1 response is associated with intestinal inflammation. Th17 cells play an important role in protecting hos against extracellular bacterial and fungal infections in the mucosa. The intestinal mucosa and lamina propria of IBD patients contain much higher levels of Th17 cells, which are important in driving inflammation in IBD. Th2-cells have a role in eliminating helminth and extracellular microbes, but cytokines from Th2 cells also inhibit the development of Th1-cells and consequently enhance the innate immune response through the activation of macrophages[88].

PATHOLOGICAL FINDINGS

Although CD and UC share similar characteristics, they differ in terms of the location and nature of the inflammatory changes.

HISTOPATHOLOGICAL FINDINGS IN UC

UC is characterised by inflammation localised to the large intestine, involving the distal part of the colon, including rectum, extending proximally to an extent that varies between patients[93]. The inflammation is limited to the mucosa, is classically diffuse and continuous with proximally decreasing severity. The transition between adjacent involved and healthy mucosa is often sharp. The mucosa has a fragile, granular appearance which can progress to mucosal denudation or deep penetration[94]. Initially

superficial ulcers may reach the muscularis mucosae in severe or longstanding disease[95]. Extensive ulceration with spared mucosal islands may give rise to inflammatory pseudopolyps. Various types of pseudopolyps exist, all are originating from the mucosa and occur after repeated periods of inflammation and ulceration associated with excessive healing process generating hyperplastia[96].

Some macroscopic distribution patterns need to be recognised to avoid a misdiagnosis of CD[97]. The rectum may be spared in children (30%), in adults with fulminant colitis (13%), in patients with PSC (50%), or in patients receiving topical or systemic treatment (44%)[93, 98, 99]. Backwash ileitis has been reported in up to 20% of patients with extensive colitis[98, 100]. The finding of a caecal patch, namely discontinuous involvement of the caecum in patients with left sided colitis, has also been described[98, 101]. Another therapy-related finding is patchiness, which gives discontinuous rather than continuous inflammation[94].

No single histological feature is phatogmonic of UC[102], but the diagnosis is based on a pattern of distinctive findings. Typical microscopic features can be classified into four main categories; mucosal architecture, lamina propria cellularity, neutrophil granulocyte infiltration and epithelial abnormality[98]. The appearance of the mucosal architecture is often typical with irregular crypt architecture and crypt abscesses. The distorted crypt architecture increases with the duration of disease. Moreover, the inflammation in UC has superficial epithelial features including flattening, focal cell loss, erosions, and ulcers. Reduced number of goblet cells are seen, but not diagnostic as this may also be seen in CD as well. Paneth cell metaplasia, inflammatory polyps, hypertrophy of the muscularis mucosae, and submucosal fibrosis are features of chronicity. The inflammatory infiltrate in untreated disease is limited to the mucosa. The number of eosinophils is variable, but their coexistence with basal plasmocytosis makes UC likely. Granulomas are generally not observed[94].

HISTOPATHOLOGICAL FINDINGS IN CD

CD can affect any part of the gastrointestinal tract, from mouth to anus, although the area around the ileocaecal valve is the most common location (50%). The localisation usually remains stable over time[94], with approximately one fifth of the patients presenting with isolated colonic CD (20%)[103] and one third with small-bowel limited disease (30%)[104, 105]. There is evidence suggesting ileal and colonic CD could be different disease entities[106]. Upper gastro-intestinal involvement (0.5–4%)[107] refers disease occurrence in the esophagus, stomach, duodenum or jejunum, either isolated or together with other localisations[108].

CD is characterised by transmural inflammation involving both mucosal and submucosal layers of the intestines, eventually causing development of fibrosis and subsequent stenosis of the intestines. The inflammation shows a discontinuous pattern, with diseased segments frequently separated by areas of uninvolved bowel, so-called skip lesions. The serosal surface is often hyperemic and may be covered with inflammatory exudate. In longstanding disease, serosal adhesions may occur. The earliest grossly visible mucosal lesions are small aphthous ulcers that typically develop along the mesenteric margin of the bowel wall. As these ulcers coalesce, they become deeper and wider giving rise to classic cobblestone appearance[93]. Inflammatory pseudopolyps can also occur. Fistulae are frequently seen in the small bowel, but can also occur in the colon. The bowel wall becomes thickened and increasingly rigid as a consequence of the transmural nature of the inflammation with fibrosis and fibromuscular proliferation[93]. On macroscopic examination of a resection specimen adipose tissue expands towards the antimesenteric surface, a finding termed fat wrapping or creeping fat[94].

A variety of microscopic features support the diagnosis of CD. The findings with highest diagnostic value are discontinuous chronic inflammation, focal crypt architectural distortion and granulomas not related to crypt injury[94].

PHENOTYPIC CLASSIFICATION OF IBD

Several classification schemes have been described to classify the severity of IBD. The schemes can be used to guide treatment, discern risk of complications as well as facilitate epidemiological studies. The Rome classification in 1991 proposed by the International Working Party suggested a classification system of CD based on anatomical distribution, operative history and clinical behaviour[109]. This was subsequently revised in Vienna at the World Congress of Gastroenterology in 1998[110] and further refined in 2005 in Montreal[111]. The Paris classification was developed as a modification of Montreal in order to describe the change in disease location and behavior over time, and also to capture growth failure seen in paediatric IBD[112]. The current clinical classification systems are still probably too simplistic, as IBD is very heterogenous[113] and an audit is ongoing.

CLASSIFICATION OF UC

Neither the Rome nor the Vienna Working Parties addressed subclassification of UC. In the Montreal classification UC is classified depending on disease extent and severity of an individual relapse (Table 1). The disease extent (E) of UC is defined into three subgroups with respect to the extent of inflammation within the colon (proctitis, distal

UC, or pancolitis). The endoscopic appearance may underestimate the true extent, and this should be confirmed histologically[102]. The severity (S) of relapse in UC is grouped into four disease activity/severity categories (clinical remission, mild, moderate and severe UC)[111].

Establishing the extent of the inflammation in a patient with UC is important for prognosis, as the likelihood of colectomy is dependent on disease extent. Disease extent can change over time[114]. Around half of all patients with proctitis or proctosigmoiditis at diagnosis, will develop more extensive disease[115, 116], but the extent of inflammation can also regress. However, the classification of the colitis for an individual describes the maximal extent ever observed[114].

Table 1. Montreal classification of UC and CD[111].

UC-classification		CD-classification	
Severity	S0: remission	**Age at diagnosis**	A1: <17 years
	S1: mild symptoms		A2: 17–40 years
	S2: moderate symptoms		A3: > 40 years
	S3: severe symptoms		
Extensy	E1: ulcerative proctitis	**Location, endoscopic or macroscopic estimation**	L1: terminal ileal
	E2. Left-sided UC; distal colitis		L2: colon
	E3: extensive UC, pancolitis		L3: ileocolonic
			L4: isolated upper GI
		Behaviour over time	B1: non structuring, non-penetrating
			B2: stricturing
			B3: penetrating
			P: perianal disease

In CD, *L4* is a modifier which can be added when concomitant upper GI disease is present, and *p* is a modifier which can be added when concomitant perianal disease is present.

CLASSIFICATION OF CD

In the Montreal classification scheme, CD patients are classified according to age of onset of disease, (A), disease location (L), and disease behaviour (B) as the predominant phenotypic elements (Table 1)[111, 114]. Disease location (L) is defined into four subgroups, including ileal, colonic, ileocolonic and disease isolated to upper GI. The three different types of behavior (B) classifications include inflammatory CD, fibrostenotic CD, and penetrating[111]. These three types of disease behaviours can be seen in the same patient as the disease progress. A patient is initially diagnosed with inflammatory disease, can over time develop fibrostenotic disease and finally proceed to an obstruction, with perforation proximal to the obstruction and abscess formation. When such abscesses spontaneously drains into an adjacent structures or organs, fistula formation results[102].

IBD-UNCLASSIFIED

UC and CD represent the major phenotypic forms of IBD, but it is sometimes difficult to differentiate between two entities[117]. Analysis of multiple biopsies allows a correct diagnosis of IBD in 66–75% of newly diagnosed patients. Additional endoscopic and clinical data allow a final diagnosis in about 90%[118]. Uncertainty about the diagnosis tends to decrease over the disease course[119]. However, in some IBD patients, endoscopic and histological assessments cannot distinguish between UC and CD[102]. Uncertainty regarding the type of IBD is more frequent in patients with severe inflammatory activity[118] and paediatric patients [102, 120].

The term indeterminate colitis (IC) was introduced in 1978 as a diagnosis following colectomy among IBD patients whose histopathology showed overlapping features of CD and UC[121]. The term IC has been used inconsistently over the years, but is nowadays reserved for patients without a definitive diagnosis even after complete histological analysis of a colectomy specimen[111]. In resected specimen the term colitis of uncertain type or aetiology (CUTE) is used synonymously[122]. The term inflammatory bowel disease unclassified (IBD-U) was introduced in the Montreal classification[111]. IBD-U is used when endoscopic and histological findings are not adequate to differentiate between UC and CD[111, 122] to define the presurgical patient with evidence of clinical and endoscopic chronic IBD, with no definitive indications of CD or UC[111, 117]. The clinical course of patients with IBD-U is often more severe when compared with classical UC[123]. Surgical and medical treatment can be demanding, as these patients often require more intensive medical treatment[123]. Type of surgery must be seriously considered. From its origin as a post colectomy pathological diagnosis, this IBD subtype remains a poorly understood disease entity with no definitive histological or clinical features in either children or adults[117, 124, 125].

CLASSIFICATION OF IBD SUBTYPES IN REGISTER STUDIES

It is not always straightforward in clinical practice to decide whether patients with IBD have UC or CD. For a patient with IBD, a correct diagnosis is crucial in order to tailor an optimal treatment. The diagnostic difficulties however also compose problems enrolling patients into scientific studies, as it is difficult to ensure that the right patient group is studied. This may be due to difficulties to establish the correct diagnosis and varying disease expression over time, but also due to incorrect reporting to the register[126, 127]. Consequently, the registered diagnosis in patients' charts may vary over time. In the Swedish NPR, the diagnosis changed for 18% of the patients during a follow-up shorter than 4 years[128].

Several schemes have been proposed to categorise patients with inconsistent coding in the registers. Classification based on first diagnosis code assigned or most frequent coding used are commonly used strategies. Some epidemiological researchers have additionally chosen only to report the outcome for UC and CD patients. The use of the term IBD-U in register-based studies are commonly identifies a mix of patients diagnosed with IBD-U and IC. It can also be used for patients with inconsistent IBD-diagnosis and for patients with contradictory coding. For example a patient with a diagnosis of UC in the register, with additional coding for small bowel involvement or perianal disease, could be labeled IBD-U in order to minimise misclassification and keep the UC and CD cohorts as consistent as possible[128].

SYMPTOMS

IBD symptoms vary, depending on the severity of inflammation and where the inflammation occurs, but do not always correlate to disease activity and severity. There is a significant overlap of symptoms between CD and UC[129]. The most common IBD symptoms are diarrhoea and fatigue[130].

SYMPTOMS OF UC

Diarrhoea is the most common symptom in UC, it is characteristically bloody[129]. Typically, patients with UC experience periods of relapse and remission[102]. Symptoms can include urgency, incontinence, fatigue, increased frequency of bowel movements, mucus discharge, nocturnal defecations, and abdominal discomfort[131]. Pain in the lower left part of the abdomen is common. Patients with pancolitis often suffer from tenesmus, nocturnal defecation, rectal urgency, and abdominal pain, while patients with isolated proctitis more often experience symptoms such as rectal bleeding, tenesmus, urgency and sometimes paradoxical constipation[131].

Up to 15% of patients initially present with severe disease[132], with symptoms such as high fever, tachycardia and weight loss. Up to 90% will have one or more relapses after the first attack. Early relapse or active disease in the first 2 years after onset is associated with a worse disease course[102, 133, 134].

Physical examination may reveal signs of anaemia, abdominal tenderness, and blood on rectal palpation. Abdominal distention and tympany on percussion may indicate colonic dilatation. Patients may have anal fissures or skin tags due to irritation from diarrhoea, but the presence of anal or perianal fistulas strongly indicates CD[131].

SYMPTOMS OF CD

CD most often presents insidiously, but can present as an acute toxic illness[135]. The two most common presenting symptoms are fatigue and abdominal pain, classically pain in the lower right abdomen[129]. The location of the inflammation determines the clinical picture. Ileocaecal CD typically causes diarrhea, cramping, abdominal pain and weight loss. CD in small bowel usually gives a similar clinical picture, and may additionally cause malnutrition. Isolated colonic CD causes less frequently weight loss, whereas diarrhoea, rectal bleeding, perirectal abscess, fistula and perirectal ulcers are commonly seen[103]. Diarrhoea with blood is not as common as with UC[102]. Involvement of both small bowel and colon is also frequently seen[103]. The least common form of CD is involvement of the gastroduodenal region, which may cause anorexia, nausea and vomiting[129, 135, 136].

The most common complication of CD is blockage of the intestine due to inflammation which results in thickening of the bowel wall. Fistulas, abscesses, and strictures with associated symptoms are common as the disease precedes. Problems related to malnutrition, or the presence of nutritional deficiencies, are seen as a result of poor absorption. Perianal and extra-intestinal manifestations are common. Abdominal examination findings include tenderness, distention, and masses[136, 137]. Perianal findings such as fistulae, abscesses increase the likelihood of CD[135].

EXTRAINTESTINAL MANIFESTATIONS OF IBD

Involvement of organs outside the gastrointestinal tract are usually termed extraintestinal manifestations (EIM) and should be differentiated from extraintestinal complications of IBD [138, 139]. Up to half of IBD patients will have one or more EIM[140], and up to 25% have several EIMs[141]. EIMs may occur before or after the diagnosis of IBD[138]. Up to 26% of cases have their first EIM before IBD is diagnosed[141]. Some EIMs are synchronous with flares of the underlying IBD but others can be independent of the IBD activity. Sometimes the EIMs respond to the treatment of the intestinal inflammation, but frequently require specific treatments[138, 142]. The EIMs can be divided based on affected organ system (Figure 2). Almost any

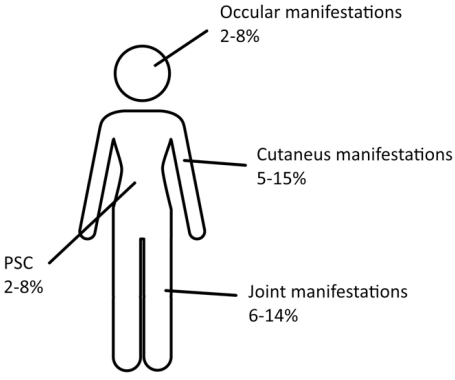

Figure 2. Occurence and distribution of EIMs in IBD.

part of the body can be affected, but involvement of joints, skin, eyes and liver are the most common. EIMs in general are more common in CD, than in UC[94].

JOINT MANIFESTATIONS

Arthritis is by far the most common EIM. The prevalence of arthritis has been reported to range from 6% to 46% depending on the clinical and radiologic criteria used. IBD-associated arthritis can affect both the peripheral joints and the axial joints[138], it is less commonly deforming than rheumatoid arthritis. Arthritis is more common in patients with colonic disease than those with small bowel involvement, but is still more common in CD than in UC[143].

CUTANEOUS MANIFESTATIONS

Cutaneous EIMs have been reported in 5%–15% of patients with IBD[144] Most common cutaneous EIMs include erythema nodosum and pyoderma gangrenosum[138, 143]. Other skin lesions include psoriasis and oral aphthous stomatitis. Erythema nodosum is characterised by red painful swollen nodules in the subcutaneous fat, that usually will respond to systemic steroid administration. Pyoderma gangrenosum is characterised by extremely painful ulcerating lesions that frequently occur at sites of repeated trauma ,such as near surgical incisions or around intestinal stomas[138]. As the pyoderma deteriorates with any type of surgical manipulation or debridement, these lesions are best treated by nonoperative strategies[143].

OCULAR MANIFESTATIONS

Ocular manifestations include uveitis, iritis, and episcleritis[145]. 2%–7% of patients with IBD experience ocular manifestations[138].

PRIMARY SCLEROSING CHOLANGITIS

PSC is estimated to affect approximately 2–8% of patients with IBD, less frequently in patients with CD than UC[146, 147]. In 60–80% of patients with PSC, an underlying IBD can be diagnosed either before or after the PSC diagnosis[148]. PSC is characterised by infiltration of lymphocytes in the intrahepatic and extrahepatic biliary tree, followed by an inflammatory process that triggers fibrosis, which ultimately can lead to strictures of the small or large bile ducts[138]. This confers a significant risk of end-stage liver disease, malignancy and mortality. PSC is associated with a 10-fold increased risk of the development of colorectal cancer (CRC) in patients with IBD[149, 150]. Besides endoscopic dilatation of bile duct strictures, the treatment options for patients with PSC are

limited[138, 151]. The median survival time without liver transplantation for patients with PSC is reported to be 10–12 years[150].

OTHER EXTRAINTESTINAL MANIFESTATIONS

Other EIMs include hepatitis, arterial manifestations with increased risk of heart failure, acute myocardial infarction and cerebral vascular insults, thromboembolism, pancreatitis, and pneumonitis[138, 147].

DIAGNOSIS

A single reference standard for the diagnosis of IBD does not exist. The diagnosis of UC and CD is based on a combination of clinical features, biochemical tests, stool investigations, endoscopic examination, histological investigations, and cross-sectional imaging[102, 152]. The investigation process differs greatly. A patient with ulcerative proctitis is often primarily examined with stool sample and flexible endoscopy, while the patient with ileocaecal CD may present with acute abdominal pain and the primarily examination after blood sampling is cross-sectional imaging.

BIOCHEMICAL TESTS

There are no specific blood tests available for diagnosis of IBD[94], those used have low specificity. At diagnosis all patients should have full blood count, inflammatory markers, electrolytes, liver function tests, and stool sample for microbiological analysis[98, 152].

Blood samples can be used for assessment of disease activity, predicting disease course, monitoring disease activity and response to therapy. Signs of inflammation in blood laboratory tests are seen in most newly manifested CD cases but can be completely absent in left-sided UC. Elevated acute phase reactant proteins (such as C-reactive protein, CRP) broadly correlate with clinical severity. Patients with long-lasting inflammation in IBD are often anemic secondary to vitamin B12 deficiency and autoimmune haemolysis. Thrombocytosis and leucocytosis due to inflammation are common[152]. Low serum protein and albumin suggest severe protein loss or malabsorption. Liver function tests, including cholestasis parameters, should be assessed regularly to identify hepatotoxicity as a drug side effect and patients with PSC[98].

Stool examination to exclude an infectious aetiology should be repeated during each relapse and before immunosuppressive therapies are initiated[98]. Faecal calprotectin is the most sensitive marker of intestinal inflammation in IBD, related to endoscopic activity.

Calprotectin can be used for screening purposes, to differentiate from non-inflammatory gastrointestinal conditions, as well as in the monitoring of known IBD[152, 153], but lacks specificity to discriminate between IBD and other causes of intestinal inflammation[152].

ENDOSCOPIC PROCEDURES

Endoscopic examination is a mainstay in the diagnosis of IBD. Often, a proctosigmoidoscopy is performed as initial examination when bowel symptoms predominate the clinical picture, but an initial diagnostic colonoscopy should intubate the terminal ileum and include systematic biopsies from each anatomic segment[98]. A minimum of two biopsies from the inflamed regions should be obtained[152]. Histological examination should ideally be performed before initiation of treatment because drugs can induce changes in morphology[93]. Endoscopic sampling is required also during follow-up to assess the therapeutic effect, and for cancer prevention[102].

Endoscopic appearance, distribution and shape of lesions helps to differentiate UC from CD[94]. Histopathology can frequently distinguish IBD from non-IBD, however microscopic differentiation between UC and CD can be more challenging. In general, upper endoscopy is not recommended as a screening procedure, unless clinical suspicion for involvement of the upper GI tract exists[102]. Device-assisted endoscopy such as balloon-assisted enteroscopy can visualise the small bowel mucosa beyond the reach of ileocolonoscopy, allowing tissue biopsy for histological assessment[154].

CAPSULE ENDOSCOPY

Around 5% of CD patients suffer from involvement of the upper GI tract and up to 20% of patients have isolated proximal small bowel disease beyond the reach of an ileocolonoscopy[102]. With wireless capsule endoscopy (WCE) patients swallow a capsule that contains a video chip, transmitter, and small battery. The ingested capsule transmits serial photographs of the mucosa of the upper GI tract to a portable device carried by the patient. WCE is superior for diagnosis of small bowel lesions in non-stricturing CD[154]. Disadvantages of WCE include the inability to take biopsies, the risk of the capsule obstructing in stricturing disease, the time-consuming for analysis of images, and the high cost of this single-use device. Precedent examination with patency capsule can be performed to reduce the risk for capsule obstructing. All patients with IBD-U at diagnosis should be considered for WCE[152].

IMAGING PROCEDURES

Luminal barium fluoroscopic techniques have been the mainstay of radiological imaging in CD, but have largely been replaced by cross-sectional imaging techniques, which may evaluate both luminal and extraluminal disease[102]. There are no consistent differences in accuracy for CD diagnosis between computed tomography enterography (CTE), magnetic resonance enterography (MRE) or small bowel ultrasound (SBUS), with sensitivity and specificity around 85–95%[152, 155-158]. Radiological signs of disease activity include increases in bowel wall thickness and vascularity, contrast enhancement, T2 and diffusion weighted imaging signal (for MRE), and identification of ulceration and acute extraluminal complications[157].

CLINICAL AND ENDOSCOPIC DISEASE ACTIVITY

The clinical severity of UC is often evaluated with the Truelove and Witts Severity Index, based on the daily number of stools, fecal blood, pulse, body temperature, hemoglobin, and erythrocyte sedimentation rate or CRP[159].

Endoscopic remission is an important therapeutic endpoint in the management of patients with IBD. Endoscopic improvement is associated with reduced risk of relapse, hospitalisation, dysplasia, cancer, and need for surgery[152, 160]. There is wide variation in interpretation of disease activity[102]. The Mayo Score for UC is widely used in clinical trials and may be applied to clinical practice. It includes a measure of stool frequency, rectal bleeding, a physician's global assessment and a measure of mucosal inflammation at endoscopy[161]. Mayo Score is easy and practical but is suboptimal in providing an accurate depiction of segmental healing and at measuring a substantial but incomplete response[160]. The partial Mayo score uses the non-invasive components of the full score and correlates well to patient perceptions of response to therapy[162]. The Ulcerative Colitis Endoscopic Index of Severity (UCEIS) has been developed to improve reliability of the endoscopic assessment of UC[163].

In CD, the Crohn's disease activity index (CDAI)[164] has long been used in clinical trials for evaluating the severity of the disease, but it suffers from several limitations[102]. The Harvey Bradshaw Index (HBI) relies on clinical parameters only, heavily weighted by diarrhoea[165]. An HBI score ≤4 is often used to define clinical remission. There are several endoscopic scoring systems which are used regularly in clinical trials. The two most frequently used are the Crohn's Disease Endoscopic Index of Severity (CDEIS) and the Simplified Endoscopic activity Score for Crohn's disease (SES-CD)[102]. Worth mentioning is also Rutgeerts score, or the postoperative endoscopic recurrence score,

which was designed to predict clinical recurrence risk in CD undergoing ileocolonic resection based on early endoscopic findings[166].

The Short Health Scale (SHS) can be used in both UC and CD to rate the impact of the disease of subjective health symptoms[167]. Patient reported outcome measures (PROMs) reflects the overall impact of disease on the individual[168, 169]. Digital health apps are increasingly used in the clinical care of IBD[170].

TREATMENT

There is no known medical cure for IBD. For a long time the only effective treatment available was intestinal resection[3]. Apart from digestive rest and specific diets, the medical alternatives during the first decades, were merely sedatives and antispasmodics. Treatment with steroids was introduced during the 1950s[159]. Immunomodulatory drugs were presented in the early 1980s, with widespread use in the 1990s. The first biologics was available 1998, with rapid continuing development since. The overall treatment goal in modern era is for the patient to be free of symptoms as well as inflammation.

MEDICAL TREATMENT

The choice of medical treatment is individually tailored, based on diagnosis, location of disease, degree of severity, co-morbidity, previous treatment response, other concurrent treatment, as well as the patient's age and conditions. To achieve the treatment goal, different drug classes may need to be combined. Most often, an initial intensive induction treatment is needed to induce remission, whereby the patient becomes symptom-free. The induction treatment is followed by maintenance treatment, the goal of which is to maintain remission, and avoid subsequent flares. Control of inflammation is required both to avoid chronic intestinal damage, and to keep patient symptom-free.

Steroids

Oral steroids have been used in the treatment of IBD treatment since the 1950s[159], and can effectively and safe induce remission when a flare occurs[171]. Steroids stimulate synthesis of anti-inflammatory proteins and have an indirect suppressive effect on the synthesis of inflammatory mediators such as interferon-γ (IFN-γ) and TNF-α[172]. Steroids cannot achieve mucosal healing and thereby are inefficient in affecting long term outcome[173]. Side-effects are common and can develop even after short-term and low-dose use. Common side-effects are osteoporosis, metabolic complications (glucose intolerance and diabetes mellitus), ocular effects (glaucoma), hypertension, venous

thromboembolism and serious opportunistic infections[174]. Second-generation oral steroids, such as budesonide, have better safety and tolerability profile than conventional steroids since target delivery of steroids to the site of inflammation potentially reduces systemic side effects[175].

Aminosalicylates

Aminosalicylates for IBD mainly include traditional sulfasalazine and other types of 5-aminosalicylic acid drugs. In the treatment of IBD, sulfasalazine is the prodrug, sulphapyridine is the carrier, and 5-aminosalicylic acid (5-ASA) is the active part responsible for the efficacy of sulfasalazine[173], while sulfapyridine accounts for many of its side effects. Aminosalicylates interfere with the metabolism of arachidonic acid, scavenging of reactive oxygen species, and has effects on the function of white blood cells and the production of cytokines[176]. ASA preparations are effective in mild to moderate UC for inducing and maintaining remission[177, 178]. 5-ASA maintenance therapy can also reduce the risk of CRC by 75% in UC patients[179, 180]. Oral 5-ASA is the standard therapy for mild to moderately active UC, those with incomplete response to oral 5-ASA should have topical therapy added[102, 181].

The use of aminosalicylates for CD is controversial, and no longer routinely used to treat most people with CD[182]. Side effects associated with 5-aminosalicylic acid drugs are generally mild and includes flatulence, nausea, abdominal pain, diarrhea, and headache. Renal toxicity may be seen. The side effects of sulfasalazine are worse and includes infertility (in men), hemolytic anemia, photosensitisation, and granulocytosis[173].

Immunomodulatory drugs

Immunomodulators, including thiopurines, methotrexate and calcineurin inhibitors, were introduced in the 1970s, with widespread use in the 1990s. All drugs in this class have both an immunomodulatory effect and an anti-proliferative effect. If long-time remission on immunomodulator drugs is achieved, continued use is recommended. Whilst remission is achieved first by combination therapy with biologicals, switching to monotherapy with biologicals is preferred. Introduction of immunomodulators have diminished UC-related hospitalisation and colectomy rates[183].

Thiopurines

Thiopurines (including azathioprine, 6-mercaptopurine and 6-thioguanine) control intestinal inflammation by inhibiting T-lymphocyte proliferation and activation, by incorporation of 6-thioguanine instead of guanine during DNA-replication[173].

Thiopurines are in general not effective in induction of remission, but may be effective in the maintenance of remission[102, 182]. Azathioprine has a similar therapeutic effect on CD and UC, which reduce hospitalisation, steroid use, and surgery rates of IBD patients[184-186]. Reported adverse side effects include bone marrow suppression[187], liver injury[188] and gastrointestinal intolerance[189]. Nausea is very common. Up to 39% of patients with IBD discontinue using thiopurines due to adverse reactions, most within three months of treatment[189].

Methotrexate

Low dose of methotrexate can inhibit the function of several enzymes related to DNA synthesis and downregulate a variety of inflammatory cytokines, thus inhibiting the proliferation of T-cells and inflammatory response[190]. Methotrexate is most often given as injections, as bioavailability is very variable, but oral administration is sometimes tried for convenience[102]. Clinical remission may be attained in CD[191], but methotrexate has not been proven to have efficacy in inducing remission in UC[192]. Adverse drug reactions are frequent, dose-independent reactions includes skin rash, fever, and pancreatitis, whereas dose-dependent events involves malaise, myelotoxicity and hepatotoxicity. Up to 15% of patients discontinue methotrexate use due to adverse reactions[173].

Calcineurin inhibitors

Calcineurin inhibitors, including cyclosporine A and tacrolimus, are potent immunosuppressive drugs. Inhibition of calcineurin results in profound suppression of T-cell and macrophage activation, thereby inhibiting the production of pro-inflammatory cytokines. Calcineurin inhibitors are of limited value in the maintenance of remission, but can effective induce remission in steroid-refractory and dependent UC and act as bridging agents until maintenance therapy with other agents becomes effective[193].

Biologics

Biologic therapy was developed towards the end of the 90s and refers to monoclonal antibodies against inflammatory immune mediators, including pro-inflammatory cytokine inhibitors and integrin antagonists. The use is expensive. Monoclonal antibodies need to be administered intravenously or subcutaneously since proteolytic gastrointestinal enzymes will destroy them. A better response rate to biologics among patients with CD treated early in the course of their disease has been suggested[194]. In UC data on disease duration and relationship with outcomes are more mixed.

Anti-TNF-α Therapy

TNF-α is a major pro-inflammatory cytokine early in the inflammatory cascade, involved in many biological activities, including cell proliferation, survival, and death. Overexpression of TNF-α can cause chronic inflammation, lead to autoimmune diseases, and tissue damage. TNF-α plays a key role in the immune-mediated pathogenesis of IBD[195]. The TNF-α inhibitors are antibodies against TNF-α, including infliximab, adalimumab, certolizumab and golimumab. These drugs are fast-acting and can induce and maintain remission. The treatment response is generally good. In CD, a high rate of fistula closure is seen[196].

Up to 30% of the patients are primary non-responders and up to 50% will lose clinical benefit within a year, requiring dose escalation, combination therapy or change of therapy[197]. The causal mechanism is probably multifactorial, proposed causes include the metabolism of the drug and development of anti-drug antibodies. Use of concomitant immunomodulators reduces the problem with development of antibodies[198].

About 20% of patients develop inconvenient infusion reactions and 2% of the patients experience delayed reactions, such as fever, myalgia, and arthralgia. All of these reactions can necessitate withdrawal of therapy. Use of TNF-α can cause other diseases due to the immunosuppressive effect, mostly infectious disorders[199].

Anti-Integrin Therapy

Integrins are cell surface glycoprotein receptors that binds to tissue specific adhesion molecules[173]. Anti-integrin drugs prevent migration of leukocytes to the intestinal mucosa that mediate the inflammatory process in IBD[200]. This strategy can also be effective preventing the recruitment of lymphocytes to the site of inflammation during the pathogenesis of EIMs of IBD[200, 201]. Anti-integrin drugs are an important alternative for those IBD patients who do not respond to an anti-TNF-α treatment. There are two anti-integrins available, namely natalizumab and vedolizumab. The use of natalizumab is limited due to its adverse effects, particularly progressive multifocal leukoencephalopathy[199, 200].

Vedolizumab acts selectively in the intestine and can induce and establish remission in IBD patients. It is used to treat moderate to severe UC and CD[173]. Due to its high selectivity, sparse adverse effects are seen[199]. Unfortunately, this means that the effect on EIMs is reduced, and even an increased risk of EIMs is noted[200]. Vedolizumab is mostly used in patients who have not responded to, or have lost response to, anti-TNF-α treatment. The effect of Vedolizumab may be greater than corresponding effect of anti-

TNF-α in the maintenance phase[199, 202], but the efficacy seems to be superior in IBD patients naive to anti-TNF-α therapy[203].

Other anti-Cytokine Therapies

IL-12 and IL-23 are important pro-inflammatory cytokines, mainly produced by antigen presenting-cells, suggested to participate in induction and maintenance of intestinal inflammation[173]. Anti-Cytokine Therapy, Ustekinumab, is a monoclonal antibody that binds to subunits of IL-12 and IL-23, thereby inhibit their binding to immune cells[204]. The induction phase requires intravenous administration but during the maintenance phase the administration is subcutaneous[199]. Ustekinumab is effective in both CD and UC[205], and can maintain long-term remission[206]. Risankizumab has recently been approved IBD, and guselkumab is under development[207].

Small molecules

Biomolecular drugs are complex polypeptide chains with up to tertiary structures and a net higher molecular weight (mean: 150 kDa), for example Janus kinas-inhibitors (JAK-inhibitors), sphingosine-1-phosphate (S1P) receptor modulators and phosphodiesterase (PDE) 4 inhibitors[207, 208].

SURGICAL TREATMENT

Approximately 20% of patients with UC will require surgery, whereas up to 80% of CD patients will undergo bowel surgery during their lifetime[209].

Bowel surgery in UC

Initially, surgical treatment of UC was sporadic and experimental. After 1930, surgical interventions for UC gradually became standardised[2]. The most common procedure in UC is colectomy (removal of the entire colon to the rectum) with deviation with an end ileostomy (Figure 3)[102, 210, 211]. Segmental resections are rarely performed because of the high probability that the disease will recur in the remaining colon. The colectomy could be performed laparoscopically or open, but a laparoscopic approach is likely to result in shorter length of hospital stay, less risk of incisional hernia, less adhesions, and reduced risk of infectious complications. Laparoscopic approach also facilitates possible subsequent surgey[102, 209, 212].

The colectomy rate in UC has varied over time and depending on therapy tradition. In early studies of UC, colectomy was performed only when complication occurred. In

1960s early colectomy in acute severe colitis was introduced. Together with the introduction of corticosteroid treatment, this reduced the mortality rate to less than 1 % from earlier 24%[102, 159].

The indication for elective colectomy today is chronic continuous UC refractory to immunosuppressive treatment, intolerable side effects of medication, high grade dysplasia, malignant transformation and in children and adolescents also delayed growth and/or puberty. Despite rescue therapy, a significant number of patients still go on to surgery in the acute situation[102]. Indications for emergency surgery include perforation, uncontrolled haemorrhage, fulminant disease, and toxic megacolon[102, 213]. Some data indicate worse outcomes for surgery since the introduction of biologics[214]. This may be because the use of biologics as rescue therapy after failure of corticosteroids creates a delay in surgery or selection of the most severely ill patients, given that patients responding to rescue therapy may represent a less severe end of the disease severity spectrum[102].

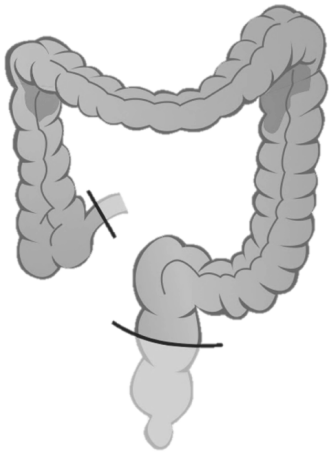

Figure 3. Colectomy is the most common surgical procedure in UC. Illustration reprinted with permission of © Typoform.

The 10-year colectomy rate is 19% for those with extensive colitis, 8% with left-sided colitis and 5% with proctitis[102]. Other risk factors for colectomy are male sex, young age and elevated inflammatory markers at diagnosis[116]. Backwash ileitis is also associated with more aggressive disease and with PSC[100]. Patients with extensive colitis have the highest risk of developing CRC[102, 215].

Restoration of intestinal continuity should not be undertaken in the acute setting, given the significant risk of complications in a patient who is likely to be clinically unwell, malnourished and on immunosuppressive medication[102]. Indications for completion proctectomy are severe rectal symptoms despite fecal deviation, concurrent PSC, or if endoscopic surveillance of rectum is impossible, or when dysplasia or even rectal cancer is evident[216, 217].

Bowel surgery in CD

Initially, CD surgery was performed as attempts to cure the patient. Radical resections to avoid recurrence was used, with wide margins of normal non-inflamed bowel on each

side of the affected part [218]. Today only grossly diseased tissue is resected, as it has been shown that the recurrence rate is not affected by the presence of microscopic disease at the surgical margins[219]. Moreover, such extensive resections exposes the patient to the risk of developing short bowel.

CD can present with acute complications such as free perforation, intestinal obstruction, hemorrhage and toxic megacolon. About 6–16% of cases with CD require emergency surgery[220]. Patients with active inflammation are often first given medical treatment. In cases of failure of the medical therapy, surgery is indicated. However, surgery can be a good alternative as first-line therapy for patients with for example, uncomplicated short sections of terminal ileal disease, and as a part of combination therapy with biologics[209, 221-223]. Other indications for intestinal resection in CD are complications such as intra-abdominal abscess, medically intractable fistula and dysplasia or cancer[220, 224]. In perforating CD, surgery should be considered at an early stage. In children growth retardation is a major indication for elective surgery[220].

Rates of surgery for CD appear to be declining[225, 226], but despite improvements in medical therapy, the rate of surgery in CD after 5–10 years is approximately 20–30 %[225, 227]. Clinical recurrence rates in the range of 10–30% are described the first year after surgery, the risk increases to 60% in the course of 10 years after the operation[228]. To avoid short bowel syndrome only limited resection of symptomatic bowel segment is performed[229].

The most common indication for surgery is long-standing ileitis or inflammatory ileitis refractory to medical treatment, often complicated by a distal ileal stenosis, hence the most common surgical procedure in CD is ileocaecal resection (Figure 4)[209, 224]. Endoscopic recurrence one year after ileo-colonic resection is observed in up to 80% of patients, while clinical recurrence is observed in about 20% of patients at two years and in up to 80% at 20 years[209].

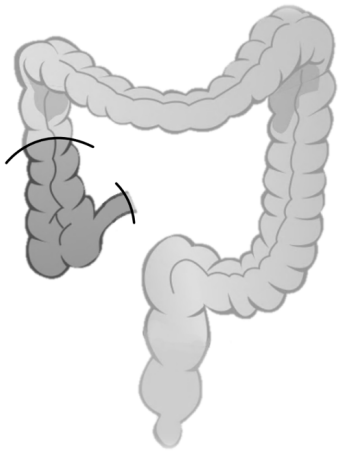

Figure 4. Ilecoceceal resection is the most common procedure in CD. Illustration reprinted with permission of © Typoform.

Many patients undergoing surgery at CD are treated with steroids. A temporary stoma should be considered if steroids cannot be withdrawn or reduced prior to surgery, either a primary anastomosis with protective stoma or no anastomosis and split stoma[230].

Primary anastomosis can safely be performed when the patients are treated with biologicals, provided other risk factors have been accounted for[230].

Different surgical techniques have evolved to reduce the risk of surgical relapse[224]. The most common anastomotic technique to postpone recurrence is the use of stapled side-to-side anastomosis, with lower rates of overall postoperative complications, clinical recurrences, and ultimately reoperations compared with end-to-end anastomoses (Figure 5)[230, 231]. The width of the anastomosis is likely the explanation. The so-called Kono-S anastomosis has lately been proposed as an additional alternative[232]. There is a constantly ongoing debate about novel ways of modifying the surgical technique to reduce the risk of recurrence, as including more of the mesentery in the resection[224, 233].

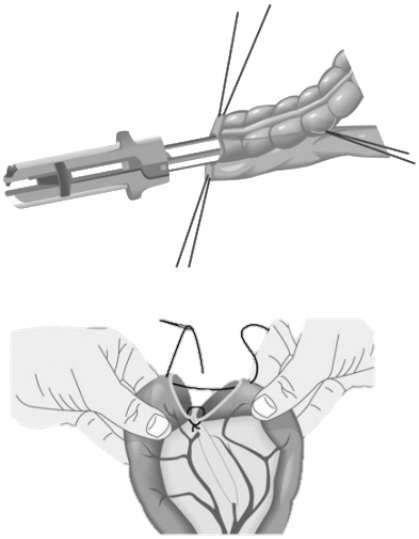

Figure 5. Stapled side-to-side anastomosis (top) and end-to-end anastomosis (bottom). Illustrations reprinted with permission of © Typoform.

The risk of short bowel syndrome has diminished dramatically due to awareness and better surgical techniques. In the absence of fistulising disease, cancer or inflammatory mass, balloon dilation and strictureplasty techniques can be alternatives to resection, as techniques to preserve bowel length and absorptive area, whilst alleviate bowel narrowing[102, 224, 234]. Endoscopic balloon dilatation was introduced in the 80s. It is often used for anastomotic strictures but can also be used for primary ileal strictures[220, 235]. The primary success rate is high, but the risk for re-dilation and eventually surgical resection is high[236, 237].

The strictureplasty techniques may be used both in primary strictures and at recurrent disease causing stenosis of an anastomosis in small bowel[220, 229, 237]. Strictureplasty has acceptable long-term outcomes, although it has a higher rate of recurrence than resection[220, 238]. The Heineke-Mikulicz strictureplasty is used in strictures shorter than 10 cm and the technique ad modum Finney is used in strictures between 10 and 25 cm (Figure 6). The Michelassi procedure are used for longer strictures (isoperistaltic enteroenterostomy)[220, 237, 239-241]. Strictureplasty is considered safe and effective regarding post operative complication and surgical recurrence[220, 237, 242]. Short bowel is likely rarely caused by the extent of CD, but rather by complications to surgery[224] and if multiple

small bowel strictures can be dealt with by a single resection in a patient with adequate bowel length, then it is preferable to avoid a complex multiple strictureplasty procedure[102]. The most important indication for the non-conventional strictureplasty techniques is extensive recurrent disease after prior resection surgery[224].

Strictureplasty is not recommended in colon, as there is a risk of missing colorectal malignancy[220, 243]. When a single colonic segment is involved, a segmental colon resection is appropriate procedure. It gives a better functional outcome and less risk of future short bowel syndrome[220, 230, 244]. When multiple colon segments are involved a subtotal colectomy is the preferred approach[224]. In an acute setting with severe refractory colitis, colectomy is the best alternative[224].

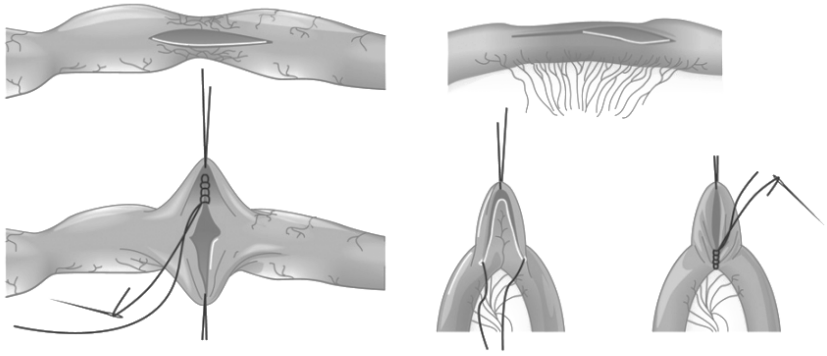

Figure 6. The Heinecke-Mikulicz strictureplasty (left) and Finney strictureplasty (right) Illustrations reprinted with permission of © Typoform.

Perianal CD

The occurrence of perianal fistulae in CD varies between 14% and 23%. The debut may precede intestinal symptoms but can also appear at the time of diagnosis or subsequently. The risk of perianal disease depends on disease location. In case of colonic disease with rectal involvement, the prevalence of fistulising anal disease is reported as high as 92%[220, 245-247]. Upon diagnosis of symptomatic perianal fistula in CD, the initial approach is examination under anaesthesia, drainage of abscesses, and placement of setons. The exception to routine insertion of setons are patients with rectovaginal fistulae, in whom setons may make faecal discharge per vaginum worse[102]. Definitive procedures for fistula management in perianal CD are removal of draining seton only, fistulotomy, ligation of inter-sphincteric tract (LIFT) procedure, and advancement flap[248]. Other less commonly performed procedures include fibrin glue, collagen plugs, collagen paste, and expanded allogeneic adipose-derived stem cells[102]. The reported efficacy of curative surgical options within the context of perianal CD is variable. Some procedures are effective in selected CD patients, but cryptoglandular fistulas have better

prognosis. Of note, healing and freedom of symptoms is not always equated[102, 220]. Creation of a defunctioning stoma may offer rapid improvement of perianal CD, however evidence is limited to expert opinion supported by several case series[102]. The mechanism likely relates to diversion of the faecal stream, which of itself seems to contains factors, probably microbial in origin, that promote rectal inflammation[249]. Faecal diversion improves symptoms in approximately two-thirds of patients, but bowel restoration is only successful in 17%[250]. For severe refractory disease, proctectomy is an effective treatment[251].

RESTORATION OF INTESTINAL CONTINUITY

The main objectives of surgical treatment for IBD are to alleviate symptoms and minimise cancer risk. At the same time, avoiding a permanent stoma, and to preserve good bowel function, urinary function, fertility and sexuality are important. A significant proportion of the patients with IBD eventually undergo a colectomy. Some patients are satisfied with keeping their ileostomy, but a permanent ileostomy may negatively impact body image and thus quality of life[252, 253]. Alternatives to the restoration of intestinal continuity have therefore been developed. Despite this, less than half of the patients with IBD treated with colectomy underwent any kind of reconstruction in Sweden and England[254, 255]. The ileal pouch anal anastomosis (IPAA) is considered the gold standard reconstruction after colectomy[256], wherein this procedure the rectum is removed and a pouch is created from the distal part of the ileum which is stapled or sutured to the anal canal[257]. Another option is the ileorectal anastomosis (IRA) where the rectum is left in place and the terminal ileum is stapled or handsewn to the top of the rectal remnant[258]. The IPAA and IRA are equally often performed in Sweden, in contrast to the rest of the world[254]. In patients who are unsuitable for either IPAA or IRA but who still wants to avoid a stoma, the Kock pouch may be an option[259].

Ileorectal anastomosis

Lilienthal first described IRA for patients with UC in the beginning of the 1900s[260] (Figure 7). The technique was used more extensively in the early 50s before IPAA was described[258]. IRA surgery can be performed at the same time as the colectomy, or as two step surgery. The construction of an IRA involves moderate surgical trauma and avoids pelvic floor dissection in particular[261]. It is associated with short operating time and minimal blood loss[262]. As the pelvic nerve damage is minimised IRA may be safer in order to avoid sexual and urinary dysfunction, as well as fertility problems[263]. Reports of incontinence, erectile dysfunction, reduced fertility, and dyspareunia are less common compared with IPAA[264]. Moreover, the functional outcome regarding stool frequency is

better in IRA compared with IPAA[262]. However, poor bowel function due to a rigid, noncompliant rectum and proctitis are problems seen after IRA formation in UC patients. The compliance of the rectum is likely the most important factor for the functional outcome post IRA. Therefore, patients with poor sphincter function, severe rectal disease, and non-distensible rectum should not be offered an IRA[264].

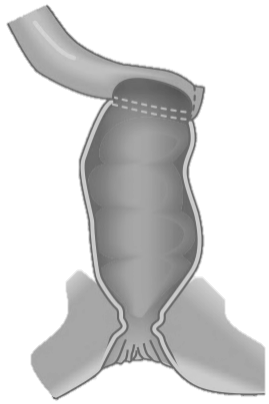

Figure 7. Ileorectal anastomosis can be used to restore intestinal continuity after colectomy. Illustration reprinted with permission of © Typoform.

A further disadvantage of IRA is the possible future risk of cancer in the remaining rectal tissue[265]. The rates of dysplasia and risk for cancer in patients with UC increase with time[217]. Age, IBD duration, PSC, dysplasia, and prior CRC are independently associated with a higher risk[266]. A cumulative incidence of rectal carcinoma of 1.6% at 10 years and at 5.6% at 20 years after IRA for UC in a population-based Swedish study of UC patients have been demonstrated[217]. In a multicentre retrospective study the overall cumulative incidence of rectal carcinoma was 3.2% at 10 years and at 7.3% at 20 years following IRA for UC[266]. Many of the cancers found in the remaining rectum may present with an advanced stage, possibly because of a more aggressive tumour biology making regular rectal surveillance with rectal biopsies imperative[263].

IRA may be offered to both UC and CD patients. However, IRA is not a definitive operation for many patients with UC, as some patients will require a later completion proctectomy. The main cause of rectal removal is recurrent proctitis refractive to medical treatment[263]. Around 20% of UC patients with a grossly normal rectum at time of colectomy may develop proctitis[267]. Other reasons for completion proctectomy are rectal dysplasia or rectal cancer. The surgical options for patients requiring rectal resection are an IPAA, permanent ileostomy, or in selected cases a continent Kock pouch. In the majority of the patients IPAA can be accomplished after completion proctectomy, with no increased risk of failure[268].

Ileal pouch-anal anastomosis

The first reported case of the anastomosis of ileum to the anal sphincter complex was described as early as in the 1930s. The surgical method gradually developed over the years[269]. Restorative proctocolectomy with IPAA was however associated with severe

complications until Sir Alan Parks and John Nicholls further developed and described the procedure in the 1978[257]. It consists of the complete removal of the colon and rectum from the caecum down to the dentate line, and the consequent restoration of the continuity of the gastrointestinal tract with the creation of an ileal reservoir. The original description included a mucosectomy followed by a hand-sewn anastomosis between pouch and anus with formation of an S-shaped pouch[257].

In modern era, the reservoirs can be performed via hand-sewn, with or without mucosectomy, or via transanal stapling[270]. Studies that compared the stapled and hand-sewn anastomosis reported no significant differences in postoperative complications, but some studies have reported more incontinence problems in the handsewn group[271, 272]. The retained rectal stump in a stapled anastomosis should be minimal to minimise the risk of subsequent inflammation (cuffitis) and or dysplasia at the site of the rectal remnant[273].

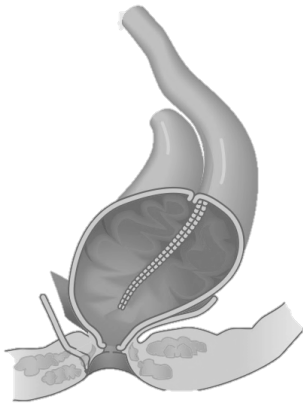

Figure 8. Ileal-pouch anal anastomosis. Illustration reprinted with permission of © Typoform.

Several shapes of the reservoir have been developed, the S-, the J-, K- and the W-reservoir[269, 272, 274]. Good pouch function depends mostly on patient's sphincter function, pouch volume and compliance[275]. No significant differences between the shapes of pouches regarding the postoperative complications have been found, but S-, K- and W-shaped pouches manifest lower frequency of defecation and thus less need for anti-diarrheal treatment[271, 274]. Most surgeons prefer the J-pouch, which can be formed by stapling and therefore is easier to construct and still confers good quality of life[272, 275]. The number of bowel movements however tends to be higher in J-pouches, because of a smaller pouch volume[273].

IPAA can be constructed in one step at the same session of the proctocolectomy, which may be safe for selected UC patients in the elective setting. High rates of complications are seen during periods of acute flares due to catabolism, low albumin, and steroid use are seen. Therefor IPAA is usually performed as a two-, modified two-, or three-staged procedure[212, 269, 272, 273]. The most common method in Sweden is a three-staged procedure with subtotal colectomy and end-ileostomy first. When the patient has recovered a proctectomy is performed with creation of the IPAA and a diverting loop-ileostomy. The diversion is closed after approximately 3 months.

As minimally invasive approaches have become more widely adopted, their use in IPAA has also become increasingly common. Laparoscopic approaches for IPAA have been described since the 1990s and have been demonstrated to be feasible and safe[276]. Surgical techniques have progressed rapidly to robot-assisted techniques[277, 278], single incision laparoscopic surgery (SILS)[279], transanal proctectomy[280], and natural orifice specimen extraction[281].

After total proctocolectomy in UC, IPAA is the procedure of choice in most countries[212]. It can also be performed secondary to an IRA with good outcome[268]. The advantages of IPAA include markedly decreased risk of UC-related neoplasia as the affected organ is excised and reduced or even no need of immunosuppressive medication. An IPAA also offers patients an unchanged body image with no stoma and a preserved anal route of defecation[282]. However, the patient satisfaction after IPAA surgery is dependent on their anorectal function and sexual function. CD is a relative contraindication to IPAA[283]. An IPAA may however be discussed in highly selected and motivated patients with CD, without small bowel disease and no existing or previous evidence of perineal involvement[220]. Even in highly selected patients with CD, pouch failure rates remain higher than in patients with UC[283].

Complications after IPAA

Although IPAA is associated with low mortality and good patient satisfaction[284], complications are common[285]. These can be separated into early or late[286]. Both early and late complications can ultimately lead to pouch failure.

Early complications are those occurring within 30 days after surgery. Most of the early complications do not differ from those seen after other major abdominal surgery. The most common early complications are pelvic sepsis, anastomotic leaks, small bowel obstruction, and pouch bleeding[285, 286]. Pelvic sepsis is the most serious early complication and may be due to suture line leaks or bacterial contamination of the surgical space during the operation[286]. A diverting ileostomy reduces not only the septic consequences of leakage but also the rate of leakage itself[270, 273]. Complications should be treated according to general surgical principles, but abscess adjacent to the IPAA could affect long term function and thus, rapid drainage is mandatory[287].

Late complications are often defined as complications evident after closure of the diverting loop ileostomy or after more than 90 days after IPAA surgery. Pouchitis is the most common late complication in patients with IBD[288], with an incidence that is increasing with time. Pouchitis is an acute or chronic inflammation of the ileal reservoir that causes symptoms such as increased stool frequency, urgency, crampy abdominal

pain, bleeding, and faecal incontinence[286]. The cause is poorly understood[288]. Diagnosis should be made on the basis of clinical, endoscopic, and histologic feature[289]. There are no medications with approved indications for pouchitis[288], but the mainstay of treatment for acute pouchitis is antibiotics[286, 288]. More traditional IBD treatments such as corticosteroids, biologics, small molecule drugs, and others can be considered for patients with chronic pouchitis[288]. Surgical management of pouchitis refractory to medical treatment is limited to defunctioning stoma or pouch excision[286, 290].

The other main late complication is fistulae. Pouch-vaginal fistulae are the most common, but fistulae may also occur between the pouch and perineum, pre-sacral space, or the skin. Treatment options vary from local repair to major surgical procedures[291]. Other late complications include the development of an anastomotic sinus, a chronic cavity in the pelvis, late strictures of the ileo-anal anastomosis, and small bowel obstruction[286].

Pouch failure

Failure of the pouch is defined as excision or permanent diversion of the pouch. Rates varies in different studies around 5-7% at 5 years and 8-10% at 10 years in patients with UC. When also including patients with CD and IBD-U the failure rate increases to 35% after 10 years[292].

IPAA-related complications are associated with pouch failure, of which pelvic sepsis appears to be the most important risk factor[293-295]. Other reasons are poor function and chronic pouchitis[296]. The main strategies to reduce the risk of pelvic sepsis has been optimisation of preoperative performance status, staged procedures[297, 298], minimally invasive techniques[299], diversion of the pouch[299], and adequate postoperative management with early detection and active treatment of anastomotic leaks[285, 300].

Continent ileostomy

A continent ileostomy (CI or Kock pouch) is a form of ileal pouch with a continent nipple valve that serves as an intra-abdominal reservoir for stool (Figure 9)[259, 301]. It was developed as an alternative to end ileostomy after proctocolectomy in 1969 by Nils Kock[259]. CI is a complex procedure that carries significant risk of postoperative complications as well as a frequent requirement for reoperation to repair nipple valve

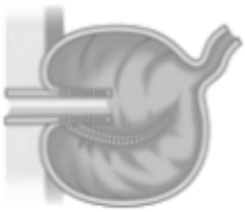

Figure 9. Kock pouch. Illustration reprinted with permission of © Typoform.

slippage[302]. After introduction of IPAA in the late 1970s its use has been limited, despite high patient satisfaction. Nowadays CI is preferred only for selected patients when IPAA is not technically feasible or advisable and in some cases when IPAA fails[303].

Comparing surgical reconstructive alternatives

IPAA is considered gold standard in the international surgical society, but IRA is an alternative option in Scandinavia and is gradually becoming accepted as an alternative option in Spain and UK[261]. In a recent French report no difference in fertility was seen after IRA compared with IPAA[304]. The study has several methodological weaknesses which makes the conclusion questionable. Randomisation is challenging in surgical trials. To date there are no trials comparing the main surgical options after colectomy[305]. An attempt on a randomised controlled trial comparing outcome after IPAA and IRA was made many years ago in Sweden, but after receiving standardised information patients insisted on choosing operation themselves. In order to circumvent this, the ongoing CRUISE study enrolls patients who choose their operation after receiving standardised, neutral information[305].

FERTILITY

There is conceptual confusion when it comes to the terminology of fertility. The word *fertility* is used differently in lay speech from different geographical regions. More problematic in a research context is that the terms are used differently in epidemiological/demographic research, compared with the research of reproductive medicine[306]. This inconsistency partly stems from the variety of disciplines that generate infertility measurements[307].

DEFINITION

Colloquially, fertility most often indicate to reproductive performance, i.e. the number of children born[308]. Likewise in demographic and epidemiologic context, fertility refers to the actual production of offspring, rather than the physical capability to reproduce which is termed fecundity[308-310]. The terminology in the field of epidemiology is influenced by the fact that data are collected from registers, where parameters such as births and deaths mostly are used[308]. While fertility can be measured, fecundity cannot. In the 1920s the concept of fecundability was developed, defined as the likelihood of conceiving during a normal menstrual cycle with sexual relations and no contraception[311]. Fecundability measures the degree of fecundity. Fecundability depends on the timing and frequency of coitus, as well as on other biological parameters[308]. Similarly, the definition of infertility

relies on a restricted time period in population-based studies, while sterility is a permanent state of infertility[310]. In its demographic meaning fecundity is limited to the biological ability to reproduce, while fertility beyond fecundity is dependent on several demographic, socio-economic and anthropometric factors[312]. Such factors are for example stress, emotional and reproductive health, willingness, availability of a potential mating partner, and preventive measures being taken[313].

The terms and definitions are used differently in fertility care and reproductive medicine. In 2006 the International Committee for Monitoring Assisted Reproductive Technologies (ICMART) published a first glossary of some terms and definitions related to fertility issues[314]. In 2009 ICMART together with World Health Organisation (WHO) published a revised and expanded version[315]. A revision was published in 2017[316]. ICMART defines fertility is the capacity to establish a clinical pregnancy, fecundity is defined as the capacity to have a live birth. Fecundability is the probability of a pregnancy, during a single menstrual cycle in a woman with adequate exposure to sperm and no contraception, culminating in a live birth[314-316].

The clinical definitions are oriented toward the early detection of infertility in individual patients with the aim of starting treatment as early as possible, while the demographic definition attempts to measure fertility and infertility on a population level. Accordingly, the clinical definition is important for understanding fertility issues on an individual level, while the population measures produced by the demographic definition are important inputs to understanding the magnitude, distribution, and underlying trends of fertility at a population level[307].

FERTILITY AND INFERTILITY

Historically, reproductive outcome was only dependent on the occurrence of intercourse at time of ovulation and underlying diseases, but after the introduction of contraceptives the average number of children born per woman in the world varies highly. Whereas the onset of fecundity is determined by first ovulation and menarche, the beginning of fertility is determined by social and cultural factors[317].

Fertility has been declining sharply in most industrialised and economically developed countries during the last decades[310, 318, 319]. Since the introduction of contraceptives in the 1960's fertility is affected by the desire for children, and women have increasingly postponed childbearing[320]. More recently, emergency post-coital contraception has further contributed to the available methods to control the reproduction. Higher fertility numbers are still seen in agricultural, less developed societies. Also, within countries, generally, more educated groups with higher incomes have lower fertility compared with

less educated groups with lower incomes[319, 321]. Currently, the mean maternal age at first birth is approaching 30 years in several European countries and many women deliver their first child at age 35 or older[318, 322-324]. Present levels of total fertility ranges from about six children per woman on average in Africa to under two children per woman in Europe. North America, Oceania, Latin America, and Asia have intermediate fertility rate[323].

Fertility defined as the capacity to conceive, starts to decline around 25–30 years of age[323]. The median age at last birth for females is 40–41 years in most natural fertility populations[324]. The age-related infertility slowly increases from 4.5% at age 25 years, 7% at age 30 years, 12% at age 35 years and 20% at age 38 years. Thereafter, it rises rapidly to about 50% at age 41, almost 90% at age 45 years and approaching 100% at age 50 years[324]. The age-dependent loss of fertility is determined by the continuous depletion of oocytes stored in both ovaries during foetal life, leading first to a decreased fertility and then to its subsequent expiration around a decade later at the onset of menopause[325]. Moreover, the oocyte quality deteriorates with advancing reproductive age. With increasing age premature recruitment of follicles can occur, as well as an increased prevalence ovulatory disorders, reduced ovulatory frequency and impaired luteal phase, all leading to a reduced conception rates[326]. The general postponement of children to later ages seen in many populations means that individuals are having children at ages when they have lower fecundity, leading to increasing infertility-related issues and exacerbating the rate involuntary childlessness.

The prevalence of infertility has been estimated to be one in every seven couples in the western world and one in every four couples in developing countries. In some regions of the world infertility rates may reach 30%, mainly due to tubal abnormalities after infection with a sexually transmitted disease[327]. Males are found to be solely responsible for 20–30% of infertility cases but contribute to 50% of cases overall. In summary, infertility is estimated to affect between 8 and 12% of reproductive-aged couples worldwide[323]. The number of childless individuals in Sweden is estimated to be around 19%, the median parity is two children (51%)[328].

VOLUNTARY CHILDLESSNESS

It has been assessed that around 5% of the 15–20% childless women in Europe have made an active choice to restrain from having children (voluntary childlessness). Becoming voluntary childless rarely seems to be planned at an early age, but rather related to postponement of childbearing and adaption to a childfree life. Economic, societal, and cultural freedom has been linked to voluntary childlessness. Differentiating

between voluntary and involuntary childlessness are challenging in the context of research[328].

FERTILITY IN CHRONIC DISEASES

Diseases may directly influence fertility through medical conditions that affect the fecundity, co-morbidities and mortality of the individual, as well as the risk of stillbirth[329]. Ill-health can also limit an individual's capacity to form relationships, an association that is partly affected by level of education[330], childless individuals are twice as likely to be single[328]. Concerns about the heritability of certain genetic conditions may explain voluntary childlessness in some diseases[331]. Some diseases are associated with lower socioeconomic status and unemployment which may amplify the psychosocial impact[332]. The strongest association with childlessness is observed for women with disease onset between 21 and 25 years old, and between 26 and 30 years old in men. Less effect on fertility was seen with early disease onset (before the reproductive years) and especially late disease onset (after the reproductive years)[328].

Disease-related infertility may affect both sexes, or it can be specific to only one sex. The factors affecting both sex's fecundity includes hypogonadotrophic hypogonadism, hyperprolactinemia, disorders of ciliary function, cystic fibrosis, genital infections and systemic diseases. Moreover, lifestyle-related factors like dietary restriction, over exercise, stress obesity, cigarette smoking, marijuana consumption and alcohol intake affect the fecundity. There are also disorders that only affect the female fecundity, such as premature ovarian insufficiency, polycystic ovary syndrome, endometriosis, uterine fibroids, and endometrial polyps[323].

Male infertility may be due to testicular and post-testicular deficiencies. Testicular dysfunction is the most frequent cause of disturbed spermatogenesis, and can be subdivided into congenital, acquired, or idiopathic testicular failure[333]. Post-testicular deficiency is due to either ejaculatory dysfunction or obstruction to sperm delivery. The obstruction may be located in the epididymis, vas deferens or ejaculatory duct and can be acquired or congenital. Moreover, sperm concentrations and semen volume in men have been decreasing during the last century. A possible explanation is exposure to endocrine disrupting chemicals in the environment. It is not known if this affects the male fecundity[323].

Some rare diseases are associated with almost complete lack of children, for example severe intellectual disability, childhood leuakemia and muscular dystrophy[328]. Other diseases linked to childlessness are different mental-behavioural disorders. Another disease category strongly associated with childlessness are endocrine-nutritional-

metabolic disorders. For example, poorly controlled diabetes[334] and coeliac disease are more prevalent in women experiencing unexplained infertility or recurrent miscarriage than in the general population[335]. Diabetes and coeliac disease are also more prevalent in men experiencing infertility. Several inflammatory diseases in different organ systems are associated with childlessness. Moreover, vitamin D insufficiency, active autoimmune conditions, and subclinical hypothyroidism also appear to be associated with a reduced chance of conception in both sexes[336]. The association is particularly clear in multiple sclerosis, systemic lupus erythematosus and juvenile idiopathic[328]. Hypertension can cause erectile dysfunction, either directly or as a side effect of medication[337].

FERTILITY IN IBD

Most patients with IBD are diagnosed between the ages of 15 and 40[338]. This coincides with the peak years of fertility and pregnancy and the onset might have effect on fertility[328]. Several different causes have been suggested to affect fertility in IBD. The most prominent are the inflammatory nature of disease, the medical treatment, the surgical treatmen,t and psychological causes[339].

FEMALE FERTILITY IN IBD

Several studies have reported fertility rates in non-surgically treated women with UC that are comparable with the general population[340-343]. However, in patients with pronounced disease activity fertility is reduced[344-347]. The systemic inflammation seen in active disease can lead to adverse conditions for successful conception[339]. The symptoms may also lead to less frequent sexual activity. Decreased fertility rates after flares have been described even after adjustment for contraceptive use, suggesting at least partly an impact on fecundity[345]. Achieving clinical remission may increase the probability of successful conception[339].

A more pronounced impact on fertility is seen in women with CD compared with UC[345, 348]. Prolonged time to pregnancy is seen in women with IBD, suggesting impact on fecundity[349]. Active CD may impair fertility by inflammation in the pelvis causing fallopian tube inflammation followed by tubal damage[350]. Diminished ovarian reserve is also seen in CD. The assessment of the ovarian reserve includes both biochemical analysis and ultrasound imaging of the ovary for antral follicular count. Of the different biochemical analysis available, anti-Müllerian hormone (AMH) is recognised as the best assessment of the ovarian reserve[351]. AMH levels of women with CD have been demonstrated to be significantly lower compared with healthy controls[352]. Furthermore, among CD patients, those with active disease had lower levels compared with patients in

remission. In some studies, this finding has only been apparent in women older than 30 years old and with chronic, active disease[353, 354].

Voluntary childlessness in IBD

Voluntary childlessness refers to the decision not to have children. Most previous studies examining fertility in IBD have had difficulty distinguishing voluntary from involuntary childlessness, but voluntary childlessness has been shown to be more frequent in patients with IBD (13–38%) compared with the general population (6%)[344, 355, 356]. Higher rates of voluntary childlessness are seen in CD compared with UC. Voluntary childlessness also increases with increasing age[348, 357]. It is correlated to poor pregnancy knowledge and fear of maternal and foetal complications[358]. The prevalence of volountary childlessness varies greatly between countries, and the figures are not easy to compare. It seems to be higher rates of voluntary childlessness in the Middle East and Asia, than in Western countries, inversely correlated to pregnancy-specific IBD knowledge[358]. Appropriate education on pregnancy and family planning for all patients with IBD of childbearing age is recommended to avoid decision on birth restriction on incorrect grounds[339]. It has lately been suggested that voluntary childlessness in IBD is affected by socioeconomic and demographic factors rather than the severity of IBD[359]. Association with lower educational level and financial uncertainty have been reported[358, 359].

Medical therapy and Female fertility

Medications used to treat IBD do not affect female fertility[343], with the exception of methotrexate which is associated with spontaneous abortion and embryotoxicity[360]. Initiating monotherapy with thiopurine is not recommended, and newer drugs (JAK inhibitors and S1P receptor modulators) should be avoided during pregnancy[361].

Surgical treatment and female fertility

A significant proportion of patients with UC will require colectomy despite medical therapy [344]. After the colectomy patients can choose to remain with ileostomy, or intestinal continuity can be recreated with either a IPAA or IRA. IPAA surgery may impair fertility[339, 344, 345, 362-373], with infertility rates rising from 15–20% pre-IPAA to 48–63% post-IPAA[366, 374]. The risk is even higher in the first year after surgery[344]. The cause of the reduced fertility seen post-operatively are damage of the reproductive organ due to deep pelvic dissection, formation of scar tissue and adhesions. Increased prevalence of dyspareunia post-operatively are also reported[364, 375]. There is a more pronounced reduction in fertility for patients with pouch failure[372]. The abdominal access when

performing an IPAA has traditionally been by laparotomy, but minimal invasive surgery is increasingly used and are recommended. One of the advantages with laparoscopic approach is implied lower infertility rates[367].

The impact of other surgical alternatives to IPAA on fertility is unknown[339]. Fecundity was significantly less affected in patients with familial adenomatous polyposis (FAP) who underwent reconstruction with IRA than those who were reconstructed with IPAA[376]. As this procedure avoids pelvic dissection and thus averting pelvic adhesions seen in open pouch surgery, the use of IRA to preserve female fertility during the reproductive years has been suggested also in UC[261].

MALE FERTILITY IN IBD

Fertility in men with IBD has been less studied than fertility in women[347]. Results from previous research suggest a reduced fertility in men with CD[377-379], but normal fertility in men with UC[378, 379]. Erectile dysfunction, decreased libido and abnormal ejaculation are commonly reported causes of male infertility[380]. Increased use of medications to treat erectile dysfunction in men with IBD have been reported[381]. No difference in sperm count, motility, vitality, or morphology has been demonstrated in men with IBD compared with the general population[382], apart from in an old study found where a marked reduction in sperm count and motility was seen in men with CD independent of medication[383]. Anti-sperm antibodies have been observed in men with IBD, but the clinical relevance of this is unclear[347]. The fecundity in men with IBD appears not to be significantly affected[348, 378].

Active inflammation in patients with IBD is associated with the release of pro-inflammatory cytokines which may affect male fecundity[384]. Men with active disease are also more likely to report sexual dysfunction[385], erectile dysfunction[386, 387] and difficulties in conceiving in contrast to those in remission[388]. Increased sperm motility in patients who achieved remission after a severe relapse is also seen[389].

Poor nutritional status, as commonly seen in severe IBD, can reduce fecundity due to zinc deficiency leading to reduced testicular function[390]. Hypogonadism and low testosterone levels, associated with both disease activity and treatment, have also been reported in men with IBD[391, 392].

Medical therapy and male fertility

Most of the commonly used IBD drugs have no demonstrated impact on male fertility[339]. Sulfasalazine is nevertheless known to cause reversible infertility. The

sulphapyridine moiety of sulfasalazine impairs sperm maturation, causing reduced sperm motility, sperm count and increased number of abnormal sperm forms[393, 394]. The adverse effects of sulfasalazine on sperm are fully reversible after discontinuation sperm recovery takes 3 months after cessation[395]. There has been one case report of reversible oligospermia associated with mesalazine, but no other 5-ASA formulations have been implicated[396]. Methotrexate has also been shown to cause reversible oligospermia and reduced sperm integrity[397, 398].

Surgical treatment and male fertility

Improved sexual function after surgical intestinal continuity restoration with IPAA has been reported[389, 399], but injury to the parasympathetic and sympathetic nerves intraoperatively, and fibrosis and anatomical alterations sometimes occur[400]. In men this may cause erectile dysfunction[401] and retrograde or even no ejaculation[399, 401-403]. After surgery, an increased prescription of a medication for erectile dysfunction has been described in men with UC[381]. Reduction of number of children born after an IPAA procedure has been reported, but the impact is not as pronounced as in women[361].

Data regarding postoperative sexual dysfunction and fertility associated with other surgical options after colectomy are limited[404], but creation of a stoma is associated with erectile dysfunction and diminished sexual satisfaction[405].

ASSISTED REPRODUCTIVE TECHNOLOGY

Up to 16% of couples in the general population have problems with infertility, leading some to seek assisted reproductive technologies (ART) such as in vitro fertilisation (IVF). In most cases a male, female or combined factors can be identified. IVF begins with hormonal ovarian hyperstimulation to promote the development of multiple follicles. If successful, multiple oocytes can be retrieved and subsequently fertilised, thereby increasing the probability of a live birth. After oocyte maturation, ultrasound-guided transvaginal oocyte retrieval is performed. The sperm and ovum are subsequently co-incubated in vitro. Embryos then are cultured and transferred into the uterus[406].

ASSISTED REPRODUCTIVE TECHNOLOGY IN IBD

ART, including IVF, is frequently required for women with IBD unable to conceive naturally[395]. The data regarding the outcome of IVF in IBD are somewhat contradictory. Small studies have found comparable live birth rates between IBD patients undergoing IVF treatment compared with infertility controls[407, 408]. In a population-based setting,

patients with IBD have a lower chance of live birth per cycle compared with infertile women without IBD, with worst prognosis for CD patients who had undergone previous surgery[409, 410]. Women with UC have rates of pregnancy and live birth after ART comparable to women without IBD[407, 408, 411, 412], but are 3.2-fold more likely to require IVF compared to women with medically managed UC[372, 413]. The efficacy of ART is not reduced in women with IPAA, apart from in those with IPAA failure[372, 411-415]. Prescribing corticosteroids in IBD patients before embryo transfer may improve the chances of a live born child[416]. Women with IBD have probably no greater risk of adverse outcomes from ART compared with women in the general population[407-409]. Higher risk of preterm birth in UC patients have been described, but no risk was observed when twin pregnancies were excluded[409].

AIMS

OVERALL AIMS

To determine the reproductive health and function of women and men with IBD in Sweden.

SPECIFIC AIMS

I. To measure fertility in a large cohort of unselected women with IBD.

II. To measure fertility in a large cohort of unselected men with IBD.

III. To compare the impact of colectomy on fertility between IBD patients with or without surgical reconstruction, in women and men with IBD.

IV. To investigate the underlying causes of the reduced fertility in women with UC post colectomy.

METHODS

CONCEPT OF FERTILITY

In this thesis the term fertility is used in its epidemiological meaning, indicating the outcome of reproduction (number of live births), whereas the physiological ability to have children is termed fecundity. Fertility rate is the number of live births in a year per 1000 individuals of reproductive age. Parity is the number of children born per individual, while parity progression is the proportion of individuals who progress from one parity to the next.

DATA SOURCES

Since 1947, all Swedish residents have been assigned a unique personal identification number. This identity number is used in all official registers, thereby enabling linkage between them[417]. Matching of Swedish medical registers allows for virtually complete coverage of the Swedish health care System.

The total population register (TPR) was established 1967 by Statistics Sweden (SCB) when local population registers were computerised. TPR includes data on name, place of residence, sex, age, civil status, place of birth (country, county, parish), citizenship, immigration (date, country, ground for settlement), and relations (married couples, child–parent)[417, 418].

The Swedish National Patient Register (NPR) contains information on discharge diagnoses and surgical interventions for all hospital admissions since 1964, reaching complete national coverage by 1987. Since 1997 information on day-surgery was included, and from 2001 details on all outpatient specialist care have been integrated[419]. It is mandatory for all physicians, private and publicly funded, to deliver data to the NPR and more than 99% of all somatic and psychiatric hospital discharges are registered in the NPR. Diagnoses in the NPR are coded according to the international classification of disease (ICD) system, first introduced in 1964. The ICD system is revised periodically, of which four times during the study period (ICD7-ICD10). At the time of forming the NPR, a new standard for classification of surgical procedure codes was introduced. In 1997, it was replaced by an adapted version of the Nordic Medico-Statistical Committee

(NOMESCO) Classification of Surgical Procedures. The NPR is a reliable data source for identifying patients with IBD, and patients that have undergone IBD-related surgery[420, 421].

The Swedish Multi-Generation Register (MGR) contains information on children born in Sweden since 1932. In the register the child's paternity automatically applies to the husband of the mother at the time of birth or "by acknowledgment" for unmarried mothers. Adoption or other nonbiological relations are marked in the register[422].

The nationwide population-based Swedish Medical Birth Register (MBR) was established in 1973. The MBR covers information on all livebirths (irrespective of gestational week) in Sweden as well as stillbirths from 22 completed gestational weeks. The MBR includes around 98% of all births in Sweden[423].

The Prescribed Drug Register (PDR) provides information on all Anatomical Therapeutic Chemical codes (ATC-codes) of prescriptions since 2005, but not on drugs given in hospital[424].

Education, income, and occupation are factors known to be associated with health and disease. Information about socioeconomic status (SES) was obtained from the Longitudinal Integrated database for Health Insurance and Labour market studies (LISA) established by Statistics Sweden (SCB) in 1990[425]. It contains data on individuals' education, income, occupation, employment, sick leave disability pension, civil status and migration based on calendar year.

The SWedish Inflammatory Bowel disease REGister (SWIBREG) was launched in 2005, and had national coverage reaching 59.0% in 2018, but constantly increasing[426]. SWIBREG contains, among other things personal identity number, address and information about completed surgical procedures and medical treatments.

Table 2. List of national registers used in paper I-IV.

Register	Abbreviation	Established year	Paper
Longitudinal integrated database for health insurance and labour market studies	LISA	1990	I-II
Medical birth register	MBR	1973	I
Multigeneration register	MGR	1932	I-III
National patient register	NPR	1964	I-III
Prescribed drug register	PDR	2005	I-II
Swedish inflammatory bowel disease register	SWIBREG	2005	IV
Total population register	TPR	1967	I-III

STUDY POPULATION

For papers I-III all women and men diagnosed with IBD in Sweden between 1964 and 2014 were identified through the NPR. Patients with ≥2 entries of an IBD diagnosis in the NPR during the study period were included. ICD codes for UC, CD, and IC were used; **UC** ICD7 572.20, 572.21, ICD8 578.03, 563.10, 569.02, ICD9 556* or ICD10 K51*; **CD** ICD7 572.00, 572.09, ICD8 563.00, ICD9 555* or ICD10 K50*; **IC** ICD7 572.30, ICD8 563.98, 563.99 or ICD10 K523. For the ICD9 period there was no specific code for IC, the broader ICD9 code 558* ('other and unspecified non-infectious gastroenteritides and colitides) was there for accepted as an indicator for the first date of IBD only if followed by any other IBD diagnosis as described above, since this diagnosis code also included non-IBD colitis. Patients having only an ICD9 code 558* and no other IBD code were treated as not having IBD at all, and therefore excluded.

Several schemes have been proposed to categorise IBD patients from register data; we used a mildly modified variant of the classification promoted by Everhov *et al*[128]. The final IBD diagnosis was defined as UC or CD in patients who had a consistent IBD discharge diagnosis. Patients with an initial diagnosis of IC, followed by a later diagnosis of UC or CD, were accepted as having UC or CD, respectively. Patients with a consistent IC diagnosis, as well as patients with combinations of UC, CD, or IC diagnoses, were defined as having IBD-U as the final diagnosis. Everhov *et al.* suggested that UC patients having an additional ICD code for mainly CD-related conditions, like perianal disease and small bowel involvement, should also be classified as having IBD-U in order to minimise misclassification and keep the UC and CD cohorts as consistent as possible[128], which also was done.

In paper I all women diagnosed with IBD in Sweden during the study period were included, while the men in the IBD cohort were included in paper II. In paper III both female and male patients from the original IBD-cohort who underwent colectomy during the study period were included. **Colectomy** was identified using intervention codes; 4651, JFH10, JFH11, or JFH96. Patients with multiple partial colonic resections cumulatively equivalent to a colectomy were also included. The final procedure in this chain of operations was regarded as the date of colectomy. Subgroup analyses in paper III were performed depending on the type of bowel reconstruction. The sub cohorts of patients in whom the colectomy was followed by restoration of intestinal continuity through an **IRA** was identified using intervention codes: 4650, JFH00, JFH01, JFC40, JFC41, JFG26, or JFG29 and **IPAA** intervention codes: 4654, 4823, JFH30, JFH33, JGB50, JGB60, or JGB61. **Proctectomy** was identified using intervention codes 4652, 4653, 4654, 4820, JFH20, JGB30, JGB31, JGB33 and JGB34.

To provide a comparison group in papers I-III, SCB identified a reference cohort of individuals [5:1] from the general population matched for sex and age. As the NPR initially did not have complete national coverage, matching for place of residence at the time patients were diagnosed with IBD was carried out in order to avoid ascertainment bias. 92% of the matching sets consisted of one IBD patient and five matched individuals. In the remaining 8% each IBD patient had at least one matched individual, but the number was reduced due to lack of eligible individuals.

In paper IV female patients with UC who underwent colectomy in fertile age (18-45) in Sweden 2000-2020 were identified through SWIBREG.

STUDY DESIGN

Papers I-III are population-based cohort studies, where fertility rates in the IBD cohorts were compared with fertility rates in matched individuals from the background population. Information about children born was obtained through linkage with the MBR and information about parentage was obtained from the MGR.

In papers I-II the impact of different parameters reflecting the severity of disease were analysed - hospital admissions, bowel resections, the intensity of medical treatment (only paper II) and perianal disease.

IBD patients with a severe flare are usually admitted to hospital in order to receive the most potent medical treatment, for example intravenous steroids or infliximab. Medicine given in hospital are not recorded in the PDR, therefore **the order of hospital admissions** with a diagnostic code for IBD since the first date of diagnosis was used as a time-varying covariate to describe the severity of disease.

Bowel resections were identified in the NPR using intervention codes 4630, 4631, 6640, 4641, 4642, 4643, 4644, 4648, 4649, 4650, 4651, 4651, 4653, 4654, 4713, 4736, 4793, 4795, 4820, 4821, 4822, 4823, 4828, JFB*, JFC*, JFF16, JFG53, JFG60, JFG70, JFG73, JFG76, JFG80, JFG83, JFG86, JFH* JGB*. The order of procedures performed was used as a time varying covariate to analyse the possible impact on fertility.

Perianal disease was identified using diagnostic codes for anal fistula, abscess or fissure; ICD7, 574*, 575*, ICD8 565*, 566*, 569.05, 616.98, 629,80, ICD 9 565*, 566 and ICD10 K60*, K61*, N36.0, N82.3, and the associated intervention codes; 4860, 4970, JHA00, JHA20, JHD20, JHD30, JHD33, JHW96.

Information on prescribed medical treatment was found in the PDR. Medical treatment (paper II) was grouped into low, medium and high intensity treatment. The following ATC-codes were used to identify the treatment groups; **low treatment intensity** A07EA, A07EC, H02AB (no treatment, rectal administered anti-inflammatory drugs or systemic corticosteroids); **medium intensity treatment** L01BB01, L01BB02, L01BA01, L04AX01, L04AX03 (immunosuppressing drugs); **high intensity treatment** L04AA17, L04AA33, L04AB02, L04AB04, L04AC05 (biologic therapies). The highest treatment intensity received during the study period was used to determine the severity of disease for each IBD patient.

In paper I **contraceptive use** was used as a surrogate marker of voluntary childlessness. Information on contraceptive use was obtained from PDR and NPR. The following ATC-codes was used; G03A* (oral contraceptives and subcutaneous hormonal implants and G02B* (vaginal or intrauterine hormonal contraceptives). From the NPR diagnostic code for insertion of intrauterine non-hormonal contraceptives was used; TLC00.

In papers I-II SES at diagnosis was modelled partly as disposable income (in 10 categories based on deciles) and partly as education to investigate impact of SES on fertility.

Paper IV is a cross-sectional cohort study. Fertility differences (outcome) in women with UC post colectomy with or without subsequent reconstruction (exposure) was examined using a questionnaire. Basic demographic information on disease phenotype, disease duration and medical and surgical treatment was collected from SWIBREG. The demographic information was linked to a study-specific questionnaire with 25 questions regarding disease history, family planning, difficulties in conceiving and concerns about the impact of a patient's diagnosis of IBD on their decision to have children. The survey was designed to assess opinions of patients with IBD regarding reproduction and to understand factors that affect their decision to have children.

STATISTICAL METHODS

In papers I-III the demography and characteristics of the cohorts were assessed, as well as the parity at diagnosis, the number of children born during follow-up, and the achieved parity at end of follow-up for each IBD sub-cohort and the corresponding matched cohorts. For the IBD patients and their matched referent individuals, follow-up started on the date when the IBD patient first received the diagnosis (paper I-II) or had colectomy (paper III). The follow-up ended when the IBD patients turned 45 years or on 31 December 2014, whichever occurred earliest.

The fertility of the women and men in the IBD sub-cohorts was compared with the corresponding matched referent sub-cohorts, expressed as the hazard ratio (HR) of childbirth over time using Cox regression, adjusting for covariates. The Andersen-Gill proportional hazards regression model was used in case of recurrent birth events, taking account of the reduced fertility during pregnancy and 1 year postpartum by using each pregnancy as a time-varying covariate. The stratification allowed for different baselines but assumed equal HRs across strata.

The impact of admissions to hospital and intestinal resections was analysed as time varying covariates, with truncation at ≥3 admissions and procedures, respectively (papers I and II). The analysis of the use of contraceptives (paper I) and the impact of the intensity of medical treatment (paper II) was limited to sets matched in 2005 and later as information on prescribed drugs was available first from 2005. The parity progression ratio, the proportion of patients with IBD who progress from one parity to the next compared with the matched cohort, was analysed using logistic regression (papers I and II).

To compare the impact of different surgical reconstructions and completion proctectomy on fertility further analyses were performed within the IBD cohort after colectomy, with patients who retained their ileostomy with the rectum intact as reference (paper III). The analyses were adjusted for age at disease onset, year of colectomy and parity at colectomy.

Sensitivity analyses were performed to investigate any impact of SES at diagnosis, deciles of disposable income and educational level were used (papers I and II). Information on SES was available from 1990, thus, only sets matched in 1990 and later were used in these analyses.

Trends were analysed with likelihood ratio test for models with and without interaction terms, and with the Mantel–Haenszel test for trend (paper II). Differences in proportions were analysed with the chi square test (papers I–III).

In paper IV descriptive statistics was used to compare surgical options post colectomy and reported as mean or proportions. Kruskal-Wallis H test was used to compare reproductive outcomes for the different subgroups. Chi square test and Fisher's exact test with Bonferroni correction was used to compare problems to conceive between the groups. Logistic regression was used to compare difficulties to conceive for the different reconstruction alternatives post colectomy.

The data in papers I-III were based on national official registries of high quality, there were no issues with missing values or loss of follow-up. Data in paper IV was also

virtually complete, as answering the questions in the digital survey was mandatory to proceed. All tests were 2-tailed and $p<0.05$ was considered statistically significant. All analyses (papers I–IV) were performed in Stata 15 [Stata Statistical Software: Release 15, StataCorp LLC, College Station, TX].

ETHICAL APPROVAL

Papers I-III were approved by the regional ethical review board in Linköping (registration number of ethical approvals including amendments: 2011/419–31, 2014/226–32, 2014/492–32 and 2015/123–32). Paper IV was approved by the national ethical review board (registration number of ethical approval: 2023-0143-01).

RESULTS

For papers I-III a study cohort of 56,435 patients of fertile age with ≥2 entries of an IBD diagnosis was identified in the NPR. The sex-, age- and geographically matched reference cohort (5:1) included 272,793 individuals. During the study period 6,760 patients with IBD underwent a colectomy. From SWIBREG, 294 female patients with colectomy for UC in 2000–2020 were identified for paper IV. The survey was completed by 214 women, giving a response rate of 72.8%. Since reproduction differs between the sexes, the results will be reported separately for women and men.

THE FEMALE STUDY POPULATION

The female IBD cohort consisted of 27,331 women (12,237 women with UC, 8,672 with CD and 6,422 with IBD-U) of which 2,989 underwent colectomy during the study period. The corresponding reference cohort consisted of 131,892 matched individuals.

DEMOGRAPHY OF THE FEMALE IBD-COHORT

In paper I, fertility was analysed in the entire female IBD cohort (Table 3). The average follow-up time was 10.8 (SD 7.6) years. The mean age at IBD diagnosis was 28.1 (SD 9.2) years. In subgroup analysis based on IBD-subtype, patients with CD and IBD-U were younger when diagnosed with IBD compared with UC ($p<0.001$). Patients with CD were also younger than other IBD patients at first surgery and more likely to undergo any bowel procedure (45.1%), compared with patients with IBD-U (37.1%) and UC (14.1%) ($p<0.001$).

Altogether 15,737 live births could be linked to women with IBD during the study period, equivalent to a mean parity at end of follow-up of 1.52 (SD 1.22) live births per 1,000 person-years. The corresponding number in in the matched cohort was somewhat higher (1.62, SD 1.28) ($p<0.001$). The parity was lower at diagnosis in CD (mean 0.81, SD 1.13) and IBD-U (mean 0.80, SD 1.12), compared with UC (mean 1.05, SD 1.18) ($p<0.001$). The difference remained at the end of the study period, with a final parity of 1.46 in CD (SD 1.23) and 1.48 in IBD-U (SD 1.23) compared with 1.59 in UC (SD 1.21) ($p<0.001$).

The occurrence of childlessness at the end of follow-up was higher among women with IBD compared with the matched cohort (28.1% vs 26.9%, $p<0.001$). Subgroup analyses revealed higher risk of childlessness in CD (30.8% vs 27.7%, $p<0.001$) and IBD-U (29.7% vs 27.2%, $p<0.001$), whereas UC patients were less likely to be childless than the matched individuals (25.3% vs 26.2%, $p=0.038$).

TABLE 3. Demography and characteristics of the female IBD patients and the population-based matched reference cohort (table from paper I).

			IBD-subcohorts		
Characteristics	**Matched cohort**	**IBD-cohort**	**UC**	**CD**	**IBD-U**
Patients, *n*	131,892	27,331	12,237	8,672	6,422
Age at diagnosis, years, mean (SD)	28.1 (9.2)	28.1 (9.2)	29.6 (9.1)	27.3 (8.9)	26.3 (9.4)
Follow-up time, years, mean (SD)	10.8 (7.6)	10.8 (7.6)	9.4 (7.0)	11.4 (7.9)	12.6 (7.9)
Bowel procedures, *n* (%)	N/A	8,016 (29.3%)	1,726 (14.1%)	3,910 (45.1%)	2380 (37.1%)
Age at first bowel surgery, years, mean (SD)	N/A	31.9 (10.8)	34.9 (11.4)	30.5 (9.9)	32.3 (11.4)
Age at first child, years, mean (SD)	26.6 (5.1)	26.6 (5.2)	27.0 (5.1)	26.0 (5.2)	26.6 (5.3)
Parity at baseline, mean (SD)	0.95 (1.19)	0.92 (1.16)	1.05 (1.18)	0.81 (1.13)	0.80 (1.12)
Achieved parity at end of follow-up, mean (SD)	1.62 (1.28)	1.52 (1.22)	1.59 (1.21)	1.46 (1.23)	1.48 (1.23)
Childless at baseline, *n* (%)	69,502 (52.7%)	14,614 (53.5%)	5,746 (47.0%)	5,088 (58.7%)	3,780 (58.9%)
No child during follow up, *n* (%)	81,615 (61.9%)	17,391 (63.6%)	8,100 (66.2%)	5,441 (62.7%)	3,850 (60.0%)
Childless at end of follow up, *n* (%)	35,493 (26.9%)	7,679 (28.1%)	3,102 (25.3%)	2,669 (30.8%)	1,908 (29.7%)
Year at inclusion, *n* (%) 1964–1973	6,846 (5.2%)	1,481 (5.4%)	444 (3.6%)	690 (5.7%)	427 (7.2%)
1974–1983	18,305 (13.9%)	3,759 (13.8%)	1,286 (10.5%)	1,763 (14.6%)	974 (16.4%)
1984–1993	22,607 (17.1%)	4,688 (17.2%)	1,863 (15.2%)	2,223 (18.4%)	1,083 (18.2%)
1994–2003	35,409 (26.8%)	7,337 (26.8%)	3,548 (29.0%)	2,750 (22.8%)	1,724 (28.9%)
2004–2014	48,725 (36.9%)	10,066 (36.8%)	5,096 (41.6%)	3,090 (35.6%)	1,880 (29.3%)

CHARACTERISTICS OF WOMEN UNDERGOING COLECTOMY

In paper III fertility was studied in the subgroup of patients who underwent colectomy during the study period. The female part of the study cohort consisted of 2,989 women (UC 1,191; CD 415; IBD-U 1,383), with a matched cohort of 15,590 women. The average follow-up time was 12.2 (SD 7.6) (Table 4).

Less than half of the women underwent reconstruction after the colectomy (1,229 patients, 41.1%) (Figure 10). Most female patients

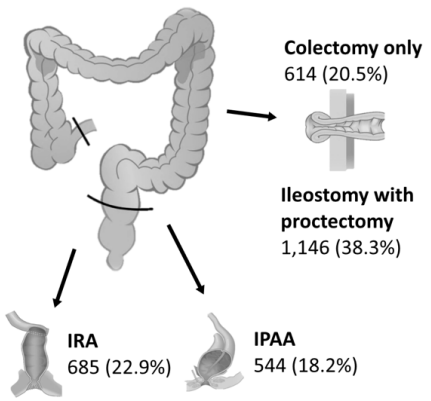

Figure 10. Distribution of reconstruction options after colectomy in women in paper III. Illustrations modified and reprinted with permission of © Typoform.

accordingly retained their ileostomy without restoration of intestinal continuity after colectomy, either with the rectal stump left in place (614, 20.5%) or removed by completion proctectomy (1,146, 38.3%). Among the women who underwent reconstructive surgery (1,229, 41.1%) the use of IPAA and IRA were almost equally common in UC and IBD-U, whereas almost no female CD patients had an IPAA.

No significant difference in parity was seen at diagnosis in women with IBD or in the sub-cohorts, compared with the matched cohorts (Table 4). Altogether 1,215 live births occurred post colectomy in women with IBD during the study period. In the female cohort, the parity was slightly higher in the matched cohort already at time of colectomy. The difference increased after both colectomy and reconstruction. The mean achieved parity at end of follow-up was 1.5 (SD 1.2) in the female IBD cohort, compared with the observed 1.8 (SD 1.3) in the matched cohort (p<0.001). The impact was most pronounced in women with CD (mean 1.4, SD 1.2) and IBD-U (mean 1.4, SD 1.2), and less affected in UC (mean 1.6, SD 1.2) (p<0.001). The parity was lower at the time of reconstruction in patients having IRA than in those reconstructed with IPAA (p<0.001).

TABLE 4. Demography and characteristics of women with IBD undergoing colectomy during the study period compared with population-based matched reference cohort (table from paper III).

				IBD subcohorts		
Characteristics		**Matched cohort**	**IBD cohort**	**UC**	**CD**	**IBD-U**
Patients, *n*		15,590	2,989	1,191	415	1,383
Age at diagnosis, years, mean (SD)		26.09 (8.73)	26.12 (8.75)	28.00 (8.71)	25.93 (8.42)	24.56 (8.58)
Age at colectomy, years, mean (SD)		N/A	30.01 (8.33)	31.38 (8.22)	29.52 (7.95)	28.99 (8.38)
Age at reconstruction, years, mean (SD)		N/A	35.29 (12.58)	36.22 (12.17)	35.77 (14.17)	34.33 (12.37)
Follow-up time, years, mean (SD)		12.43 (7.61)	12.24 (7.62)	10.64 (7.12)	13.60 (7.82)	13.22 (7.73)
Time to colectomy, years, mean (SD)		3.90 (5.10)	3.89 (5.09)	3.38 (4.80)	3.59 (5.34)	4.42 (5.20)
Time to reconstruction, years, mean (SD)		5.22 (10.13)	5.27 (10.17)	4.85 (9.66)	6.25 (11.95)	5.35 (10.00)
Age at first child, years, mean (SD)		26.24 (5.19)	26.19 (5.39)	26.22 (5.13)	24.99 (5.53)	26.52 (5.52)
Parity at diagnosis, mean (SD)		0.85 (1.14)	0.84 (1.11)	1.01 (1.17)	0.77 (1.03)	0.71 (1.07)
Parity at colectomy, mean (SD)		1.12 (1.22)	1.06 (1.18)	1.21 (1.21)	0.95 (1.07)	0.97 (1.17)
Achieved parity at end of follow up, mean (SD)		1.76 (1.26)	1.48 (1.19)	1.57 (1.20)	1.38 (1.14)	1.43 (1.19)
Childless at diagnosis, *n* (%)		8,855 (56.8%)	1,673 (56.0%)	581 (48.8%)	237 (57.1%)	855 (61.8%)
No child at colectomy, *n* (%)		7,075 (45.4%)	1,364 (45.6%)	482 (40.5%)	191 (46.0%)	691 (50.0%)
Childless at end of follow up, *n* (%)		3,408 (21.9%)	801 (26.8%)	305 (25.6%)	121 (29.2%)	375 (27.1%)
Year of colectomy, *n* (%)	1950–1979	2,819 (18.1%)	537 (18.0%)	188 (15.8%)	116 (28.0%)	233 (16.8%)
	1980–1989	4,254 (27.3%)	824 (27.6%)	289 (24.3%)	138 (33.3%)	397 (28.7%)
	1990–1999	4,183 (26.8%)	804 (26.9%)	339 (28.5%)	92 (22.2%)	373 (27.0%)
	2000–2009	3,027 (19.4%)	578 (19.3%)	247 (20.7%)	49 (11.8%)	282 (20.4%)
	2010–2014	1,307 (8.4%)	246 (8.2%)	128 (10.7%)	20 (4.8%)	98 (7.1%)

CHARACTERISTICS OF WOMEN IN PAPER IV

Out of 294 eligible women undergoing colectomy for UC in 2000–2020, 214 completed the questionnaire that constituted the inclusion criterion for participating in paper IV (Table 5). The respondents were on average 22.9 (SD 0.5) years of age at disease onset, 29.8 years of age at colectomy (SD 0.5) and 30.2 (SD 0.6) years at reconstruction. The mean age of the respondents at the time the study was conducted was 42.6 (SD 0.5) years. After colectomy 67 (31.3%) women retained their ileostomy, of those 24 (35.8%) underwent completion proctectomy. Of the 24 women with ileostomy and proctectomy, 6 (25.0%) had a continent ileostomy (Kock pouch) instead of a conventional Brooke ileostomy. Surgical restoration of bowel continuity was performed in 147 (68.7%) women, with an IRA in 66 (30.8%) women and with IPAA in 78 (37.9%). Of the 61 women who underwent primary reconstruction with IRA, 9 (13.6%) women underwent subsequent reconstruction with IPAA.

TABLE 5. Demography and characteristics of women with UC undergoing colectomy and responding to the survey (table from paper IV).

	All (*n*=214)	**Ileostomy** (*n*=43)	**Proctectomy** (*n*=24)	**IRA** (*n*=66)	**IPAA** (*n*=81)	***p*-value**
Age, years, mean (SD)	42.6 (0.5)	41.7 (1.0)	41.3 (1.2)	42.4 (0.9))	43.7 (0.8)	0.304
Age at diagnosis, years, mean (SD)	22.9 (0.5)	24.6 (1.2)	21.7 (1.4)	22.2 (0.8)	23.0 (0.8)	0.283
Age at colectomy, years, mean (SD)	29.8 (0.5)	32.3 (1.0)	29.7 (1.4)	28.3 (0.8)	29.6 (0.7)	0.125
Age at reconstruction, years, mean (SD)	30.2 (0.6)	N/A	N/A	28.8 (0.8)	29.6 (0.7)	0.181
Relationship						0.714*
Married/living w. partner, *n* (%)	173 (80.8%)	33 (76.8%)	22 (91.7%)	51 (77.3%)	67 (82.7%)	
In a relationship, *n* (%)	8 (3.7%)	2 (4.7%)	0	3 (4.6%)	3 (3.7%)	
Same-sex relationship, *n* (%)	1 (0.5%)	0	0	1 (1.5%)	0	
Divorced, *n* (%)	14 (6.6%)	4 (9.3%)	0	4 (7.6%)	5 (6.2%)	
Single, *n* (%)	18 (8.4%)	4 (9.3%)	2 (8.3%)	6 (9.4%)	6 (7.4%)	
Employment						0.999*
Employed, *n* (%)	183 (85.5%)	36 (85.7%)	21 (87.5%)	51 (83.6%)	66 (84.6%)	
Student, *n* (%)	4 (1.9%)	1 (2.4%)	0	2 (3.3%)	1 (1.3%)	
Parental leave, *n* (%)	9 (4.2%)	2 (4.8%)	1 (4.2%)	3 (4.9%)	2 (3.9%)	
Permanent disability, *n*(%)	13 (6.1%)	2 (4.8%)	2 (8.3%)	4 (6.6%)	5 (6.4%)	
Unemployed, *n* (%)	5 (2.3%)	1 (2.4%)	0	1 (1.6%)	3 (3.9%)	
Self-reported health status						0.388*
Excellent, *n* (%)	77 (36.0%)	19 (44.2%)	6 (25.0%)	28 (42.4%)	24 (29.6%)	
Very good, *n* (%)	92 (43.0%)	13 (32.6%)	14 (58.3%)	23 (34.9%)	41 (50.6%)	
Good, *n* (%)	26 (12.2%)	7 (16.3%)	2 (8.3%)	7 (10.6%)	10 (12.4%)	
Fair, *n* (%)	16 (7.5%)	3 (7.0%)	1 (4.2%)	7 (10.6%)	5 (6.2%)	
Poor, *n* (%)	3 (1.4%)	0	1 (4.2%)	1 (1.5%)	1 (1.2%)	
Disease severity						
Immunomod. treatment, *n* (%)	121 (56.5%)	23 (53.5%)	11 (45.8%)	37 (56.1%)	50 (61.7%)	0.541
Biologic treatment, *n* (%)	117 (54.7%)	27 (62.8%)	14 (58.3%)	35 (53.0%)	41 (50.6%)	0.602
PSC, *n* (%)	16 (7.5%)	2 (4.7%)	1 (4.2%)	6 (9.1%)	7 (8.6%)	0.737
CRC, *n* (%)	4 (1.9%)	1 (2.3%)	1 (4.2 %)	2 (3.0%)	0	0.433

P-value with Bonferroni and *Fishers exact test.

Most of the respondents (84.5%) were married or had a partner. The majority were employed (85.5%) and rated their health status as excellent or very good (79.0%) at the time of the study. Around half (54.7%) of the women had used biologic treatment at some point during the disease course; the corresponding number for immunomodulatory treatment was 56.5%. Co-morbidity with PSC was reported by 16 (7.5%) women, and four women were treated for colorectal cancer at some point.

Demographic information of the non-responding 80 women (27.2%) could be obtained from SWIBREG. The non-respondents were somewhat older than the respondents both at disease onset (35.6 years, SD 0.9, p=0.003), colectomy (32.0 years, SD 0.8, p=0.009) and reconstruction (32.3, SD 1.2, p=0.049). There was also a difference in choice of reconstruction after colectomy between the respondents and the non-respondents (p=0.008). A greater proportion of the non-respondents retained their ileostomy post colectomy (48.8%). Out of the reconstructed non-responding women 22 (53.7%) had IRA and 21 (46.3%) had IPAA, that is reverse ratios compared with those included in the study. Unfortunately, no information of the parity of the non-respondents were available.

FERTILITY IN WOMEN WITH IBD

In paper I, fertility was lower in the CD cohort (HR 0.88, 95% CI 0.85–0.91) and in the IBD-U cohort (HR 0.86, 95% CI 0.83–0.89) compared with the matched reference cohorts (Table 6). On the contrary, the fertility was only marginally reduced among women with UC (HR 0.96, 95% CI 0.93–0.98) compared with the matched cohort.

Fertility was impaired at all ages in women with CD, when fertility was analysed in different age ranges. Additional analyses of trend carried out after publication of paper I are shown in Table 6. In UC and IBD-U, fertility was reduced in young women, but improved with age (test for trend p<0.001). Normal levels were seen at older ages in UC. When analysing fertility in different time periods, fertility improved with each decade for all subtypes of IBD. In UC and IBD-U, fertility rates were reaching normal levels in the last decade, while the improvement in fertility plateaued at HR 0.90 from the 1980s onwards in CD.

TABLE 6. Fertility for women according to subtypes of IBD, compared with matched reference individuals. Fertility is expressed as hazard ratio (HR) in strata of age and time periods (table modified from paper I).

	UC			CD			IBD-U		
	HR	**95 % CI**	***p*-value***	**HR**	**95 % CI**	***p*-value***	**HR**	**95 % CI**	***p*-value***
Overall	0.96	0.93–0.98		0.88	0.85–0.91		0.86	0.83–0.89	
Age-specific fertility			<0.001			0.025			<0.001
15–19 years	0.74	0.57–0.97		0.90	0.70–1.14		0.65	0.49-0.86	
20–24 years	0.89	0.82–0.97		0.85	0.79–0.92		0.84	0.77–0.92	
25–29 years	0.97	0.92–1.02		0.92	0.87–0.96		0.85	0.81–0.91	
30–34 years	0.96	0.92–1.00		0.89	0.84–0.94		0.83	0.78–0.88	
35–39 years	0.97	0.91–1.04		0.80	0.73–0.86		0.99	0.91–1.08	
40–44 years	1.08	0.92–1.26		0.85	0.70–1.04		0.89	0.71–1.12	
Fertility in time periods			<0.001			0.355			0.008
1964–1973	0.93	0.82–1.05		0.77	0.69–0.86		0.70	0.55–1.03	
1974–1983	0.87	0.80–0.93		0.83	0.78–0.89		0.74	0.69–0.80	
1984–1993	0.92	0.86–0.97		0.90	0.85–0.95		0.84	0.79–0.90	
1994–2003	0.96	0.92–1.01		0.92	0.87–0.98		0.90	0.85–0.96	
2004–2014	1.05	1.00–1.11		0.90	0.84–0.96		1.10	1.01–1.19	

All analyses are adjusted for the protective effect of ongoing pregnancy and first year postpartum. * The test for trend is a Likelihood Ratio test comparing models with and without interactions.

IMPACT OF THE SEVERITY OF DISEASE

The impact on fertility of three factors associated with severity of the disease were analysed in women with IBD. Additional analyses of trend carried out after publication of paper I are shown in Table 7. Factors associated with a lower chance of giving birth were an increasing order of hospital admissions (test for trend $p<0.001$) and an increasing number of bowel resections (test for trend $p<0.001$) in all subtypes of IBD.

TABLE 7. Impact of disease severity on fertility in women with IBD according to IBD subtypes. The fertility is expressed as hazard ratio (HR) for giving birth relation to the order of hospital admissions during follow up and number of bowel procedures compared with matched reference cohorts (table modified from paper I).

	UC-cohort			CD-cohort			IBD-U-cohort		
	HR	**95 % CI**	***p*-value**	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Order of admissions			<0.001*			<0.001*			<0.001*
0	1.04	1.00–1.09	0.052	0.91	0.86–0.98	0.007	1.03	0.96–1.11	0.360
1	0.82	0.77–0.88	<0.001	0.96	0.89–1.05	0.382	0.87	0.79–0.96	0.006
2	0.89	0.80–0.99	0.030	0.88	0.80–0.97	0.006	0.79	0.71–0.88	<0.001
3	0.96	0.84–1.09	0.494	0.96	0.86–1.07	0.466	0.77	0.68–0.88	0.001
<3	0.74	0.67–0.82	<0.001	0.74	0.68–0.79	<0.001	0.69	0.65–0.74	<0.001
***N*. of bowel procedures**			<0.001*			<0.001*			<0.001*
0	1.00	0.97–1.02	0.767	0.92	0.89–0.96	<0.001	0.94	0.91–0.98	0.006
1	0.69	0.63–0.77	<0.001	0.87	0.83–0.91	<0.001	0.74	0.69–0.79	<0.001
2	0.59	0.40–0.86	0.003	0.61	0.50–0.74	<0.001	0.45	0.35–0.58	<0.001
3	0.58	0.39–0.75	0.001	0.52	0.30–0.80	<0.001	0.43	0.34-0.62	<0.001
<3	0.55	0.20–1.61	0.254	0.14	0.02–1.01	0.006			

Adjustment for pregnancy and first year postpartum, age and year at diagnosis in multivariable analysis. The order of admission and of bowel resections were analysed as time-varying covariates. *The test for trend is a Likelihood Ratio test comparing models with and without interaction.

In CD perianal disease was linked with a further reduction of fertility; HR 0.75 (95% CI 0.69–0.82) with perianal disease and 0.90 (95% CI 0.87–0.93) without (p<0.001).

USE OF CONTRACEPTIVES

Women with IBD used contraceptives more often than matched individuals before diagnosis, this was seen in all subtypes of IBD and for all categories of contraceptives (Table 8). Following diagnosis, all types of contraceptives remained more common for all IBD subtypes except for oral contraceptives in UC and IBD-U.

TABLE 8. Use of contraceptives before and after diagnosis of IBD, compared with matched individuals, expressed as odds ratio (OR).

Type of contraceptive	Use in relation to date of diagnosis	UC		CD		IBD-U	
		OR	95% CI	OR	95% CI	OR	95% CI
Oral	before	1.04	1.01–1.08	1.07	1.04–1.11	1.06	1.01–1.11
	after	1.00	0.99–1.02	1.09	1.07–1.12	1.01	0.98–1.04
Vaginal or intra-uterine hormonal	before	1.11	0.94–1.30	0.97	0.83–1.13	1.17	0.88–1.58
	after	1.67	1.59–1.75	1.99	1.89–2.11	1.90	1.77–2.04
Subcutaneous hormonal implant	before	1.02	0.75–1.39	1.17	0.80–1.71	1.07	0.64–1.77
	after	1.45	0.53–3.94	2.33	1.01–5.40	2.38	1.09–5.17
Intra-uterine non-hormonal	before	1.20	0.99–1.46	1.61	1.26–2.05	1.16	0.82–1.65
	after	1.22	0.93–1.61	1.46	1.04–2.07	1.46	0.98–2.18

The difference in contraceptive use before diagnosis is analysed by logistic regression.

PARITY PROGRESSION IN WOMEN

The parity progression ratio was decreased in women with CD and IBD-U (Figure 11). The most obvious impact was noted in CD patients with one child before diagnosis, who were much less likely to give birth once (OR 0.71, 95% CI 0.64–0.79) or twice more (OR 0.64, 95% CI 0.53–0.76). The parity progression ratio was consistently not affected in UC, with the exception of women that already had two children at diagnosis, which showed a reduced parity progression.

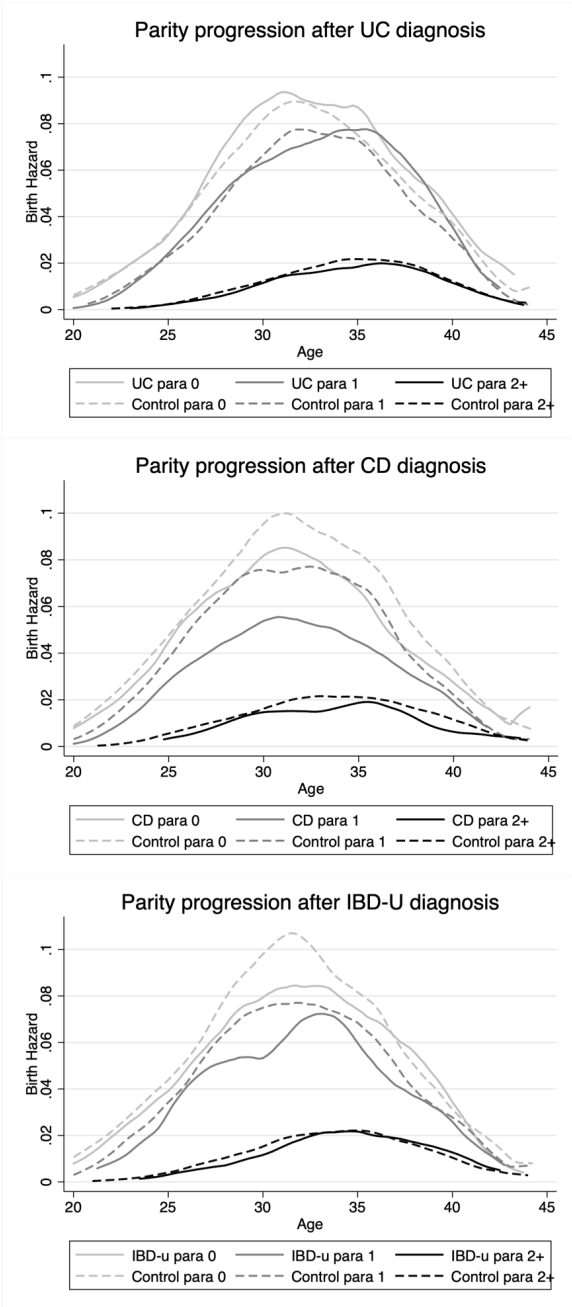

Figure 11. Parity progression (the probability of having another child) in women after IBD diagnosis compared with matched individuals. No child at baseline (para 0), one child at baseline (para 1) and two or more children at baseline (para 2+) (figure from paper I).

FERTILITY IN WOMEN AFTER COLECTOMY

In paper III the fertility post colectomy was analysed. Women with IBD had a markedly lower fertility after colectomy compared with the matched cohort from the general population (HR 0.65, CI 0.61–0.69). The fertility was least affected for those who retained the rectum and ileostomy (HR 0.79, CI 0.70–0.90) (Table 9). Additional surgery appeared to further affect the female fertility regardless of type of procedure. The impact was least after reconstructive surgery with IRA (HR 0.67, CI 0.60–0.76), more pronounced after IPAA (HR 0.61, 0.53–0.71) and most severely reduced after completion proctectomy for any IBD subtype (HR 0.52, CI 0.47–0.58).

TABLE 9. Impact of colectomy with or without subsequent reconstructive surgery or proctectomy on female fertility for IBD subtypes, expressed as hazard ratio (HR) for giving birth compared with the matched reference cohorts (table from paper III).

	IBD cohort			IBD subcohorts								
				UC			CD			IBD-U		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Colectomy only	0.79	0.70–0.90	<0.001	0.81	0.66–0.98	0.032	0.69	0.47–1.00	0.052	0.80	0.68–0.96	0.015
IRA	0.67	0.60–0.76	<0.001	0.75	0.58–0.97	0.026	0.67	0.53–0.83	<0.001	0.65	0.55–0.77	<0.001
IPAA	0.61	0.53–0.71	<0.001	0.57	0.46–0.72	<0.001	N/A			0.65	0.54–0.79	<0.001
Proctectomy	0.52	0.47–0.58	<0.001	0.60	0.51–0.72	<0.001	0.39	0.30–0.52	<0.001	0.52	0.45–0.60	<0.001

With adjustment for pregnancy and first year postpartum.

To further analyse the impact of reconstruction and proctectomy after colectomy, fertility within the IBD cohort was compared with those who had ileostomy and the rectum intact as reference. Adjustment for age at disease onset, year of colectomy and parity at colectomy was done (Table 10).

TABLE 10. Impact on fertility from reconstructive surgery or proctectomy after colectomy in women with IBD expressed as hazard ratio (HR) (table from paper III).

	UC			CD			IBD-U		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Unadjusted									
Colectomy only	1.00			1.00			1.00		
IRA	0.89	0.66–1.21	0.472	1.21	0.81–1.83	0.355	0.83	0.66–1.04	<0.001
IPAA	0.64	0.49–0.84	0.002	N/A			0.79	0.62–1.01	<0.001
Proctectomy	0.61	0.48–0.78	<0.001	0.70	0.45–1.10	1.121	0.63	0.51–0.78	<0.001
Adjusted for age at disease onset, year of colectomy and parity at colectomy									
Colectomy only	1.00			1.00			1.00		
IRA	0.86	0.63–1.17	0.329	1.07	0.70–1.63	0.772	0.86	0.68–1.08	0.196
IPAA	0.67	0.50–0.88	0.005	N/A			0.85	0.66–1.08	0.081
Proctectomy	0.65	0.49–0.85	0.002	0.61	0.38–0.96	0.032	0.68	0.55–0.85	0.001

The results were most evident in UC, where fertility was more severely reduced after completion proctectomy (HR 0.65, CI 0.49–0.85) and IPAA (0.67, 0.50–0.88) than after IRA (HR 0.86, 0.63–1.17) compared with no further surgery. The difference between IRA and IPAA was not as clear in IBD-U patients, but the fertility was clearly impaired after completion proctectomy (HR 0.68, 0.55–0.85). In CD, analysis of fertility after IPAA was not possible due to few eligible patients but fertility was markedly reduced after procedures involving proctectomy (HR 0.61, CI 0.38–0.96).

CAUSES OF REDUCED FERTILITY IN WOMEN

In paper IV, women had on average 1.67 children (95% CI 1.53–1.81) at the time of the study. Women with IPAA had on average 1.54 (95% CI 1.34–1.79) (p=0.674) children, women with ileostomy and proctectomy 1.71 (95% CI 1.34–2.07), IRA 1.76 (95% CI 1.51–2.00) while women with colectomy only had 1.77 (95% CI 1.44–2.08). Higher parity (1.07, 95% CI 0.83–1.32) was observed at the time of reconstruction in women undergoing reconstruction with IPAA compared with women reconstructed with IRA (0.68, 95% 0.43–0.93) (p=0.034). No other statistically significant differences in parity were seen.

IMPACT OF THE DISEASE ON FERTILITY

The desire to have children was affected by disease onset in more than half (59.4%) of the women responding the questionnaire (Table 11). Corresponding numbers for the effect of colectomy was 44.9%, and for the effect of reconstruction the proportion was 36.7%. Of those expressing that the disease had influenced their wish to have children, 39.4% stated that they had fewer children because of the disease and 30.7% that they had children despite the disease. Almost a fifth (18.9%) expressed that they could not conceive after diagnosis, beyond that 9.5% expressed that they restrained completely from having children due to the disease (voluntary childlessness). No women stated that the disease onset increased their desire of children.

TABLE 11. Impact of disease onset, colectomy, reconstruction and co-morbidity on the desire to have children for 214 women with UC and previous colectomy (table from paper IV).

	All (*n*=214)	Colectomy only (*n*=43)	Proctectomy (*n*=24)	IRA (*n*=66)	IPAA (*n*=81)	*p*-value
Impact of disease onset	127 (59.4%)	20 (46.5%)	14 (58.3%)	40 (60.6%)	53 (65.4%)	0.237
Not able to conceive	24 (18.9%)	2 (10.0%)	5 (35.7%)	3 (7.5%)	14 (26.4%)	
Voluntary childlessness	12 (9.5%)	3 (15.0%)	0	5 (12.5%)	4 (7.6%)	
Fewer children	50 (39.4%)	7 (35.0%)	4 (23.1%)	19 (47.5%)	20 (37.7%)	
Children despite disease	39 (30.7%)	6 (35.0%)	5 (35.7%)	12 (30.0%)	15 (28.3%)	
Adopted children	2 (1.6%)	1 (5%)	0	1 (2.5%)	0	
Impact of colectomy	96 (44.9%)	15 (34.9.0%)	14 (58.53%)	31 (47.0%)	36 (44.4%)	0.306
Not able to conceive after colectomy	18 (18.8%)	0	5 (35.7%)	4 (12.9%)	9 (25.0%)	
Voluntary childlessness due to colectomy	13 (13.5%)	4 (26.7%)	2 (14.3%)	2 (6.5%)	5 (13.9%)	
Waited to conceive until after colectomy	8 (8.3%)	2 (13.3%)	0	4 (12.9%)	2 (5.6%)	
Fewer children due to colectomy	25 (26.0%)	5 (33.3%)	4 (28.6%)	9 (29.0%)	7 (19.4%)	
Children despite colectomy	30 (31.3%)	4 (26.7%)	3 (21.4%)	11 (35.5%)	12 (33.3%)	
Adopted children due to colectomy	2 (2.1%)	0	0	1 (3.2%)	1 (2.8%)	
Impact of reconstruction	54 (36.7%)	N/A	N/A	22 (33.3%)	32 (39.5%)	0.440
Not able to conceive after reconstruction	12 (22.2%)			2 (9.1%)	10 (31.3%)	
Voluntary childlessness due reconstruction	5 (9.3%)			3 (13.6%)	2 (6.3%)	
Waited to conceive until after reconstruction	7 (13.0%)			5 (22.7%)	2 (6.3%)	
Choosed to conceive before reconstruction	8 (18.2%)			2 (9.1%)	6 (18.8%)	
Fewer children due to reconstruction	2 (3.6%)			1 (4.6%)	3 (9.4%)	
Children despite reconstruction	16 (29.6%)			8 (36.4%)	8 (25.0%)	
Adopted children due to reconstruction	2 (3.6%)			1 (4.6%)	1 (3.2%)	
Impact of co-morbidity						
Any co-morbidity	98 (45.8%)	18 (41.9%)	10 (41.7%)	36 (54.6%)	34 (42.0%)	0.400
Impact of co-morbidity	24 (11.2%)	1 (2.3%)	1 (4.2%)	11 (16.7%)	11 (13.6%)	0.071

P-value with chi square test.

DIFFICULTY CONCEIVING

Of the 214 responders, 78 (36.5%) expressed that they had experienced difficulty to conceiving (Table 12). More women undergoing reconstruction with IPAA (OR 5.54) than women reconstructed with IRA (2.57) reported problems conceiving, compared with women retaining their ileostomy. The mean time to pregnancy for the sub-cohort of women reporting fertility problems was 48 (SD 3.9) months, longer for women reconstructed with IPAA (58, SD 5.5) compared with women reconstructed with IRA (33, SD 6.0) (p=0.002). Of the 78 women expressing difficulty to conceiving, 72.4% (55 women) had undergone a fertility investigation at some point, most commonly after reconstruction. Fertility investigation was more common among women reconstructed with IPAA (p<0.001). Around half of the women (57.3%) used IVF treatment, most commonly after reconstruction. IVF was successful in 68.4% of the women after a median of three attempts.

TABLE 12. Difficulty conceiving and use of IVF in 78 female patients with UC after colectomy. The remaining 136 of the original 214 female patients did not report difficulty conceiving (table from paper IV).

	All	Colectomy only	Proctectomy	IRA	IPAA	*p*-value
Difficulty conceiving, *n* (proportion)	78 (36.5%)	7 (16.3%)	8 (33.3%)	21 (31.8%)	42 (51.9%)	<0.001
Time to pregnancy in months, mean (SD)	48 (3.9)	21 (5.3)	63 (12.1)	33 (6.0)	58 (5.5)	0.002
Fertility investigation	55 (72.4%)	1 (1.4%)	2 (28.6%)	14 (66.7%)	27 (73.0%)	<0.001
Before IBD-diagnosis	1 (1.3%)	1 (16.7%)	0	0	1 (2.4%)	
After diagnosis, before colectomy	5 (6.6%)	2 (33.3%)	2 (25.0%)	0	1 (2.4%)	
After colectomy, before reconstruction	9 (11.8%)	3 (50.0%)	3 (37.5%)	2 (9.5%)	2 (4.9%)	
After reconstruction	40 (52.6%)	N/A	N/A	12 (57.1%)	23 (54.8%)	
IVF-treatment	43 (57.3%)	2(28.6%)	4 (50.0%)	10 (47.6%)	27 (64.3%)	0.105*
Before IBD-diagnosis	0	0	0	0	0	
After diagnosis, before colectomy	1 (1.3%)	0	0	0	2 (4.8%)	
After colectomy, before reconstruction	9 (12.0%)	3 (33.3%)	4 (50.0%)	1 (4.8%)	4 (9.35%)	
After reconstruction	33 (44.0%)	N/A	N/A	9 (42.9%)	21 (50.0%)	
Number of IVF attempts, median (range)	3 (1–14)	3 (1–5)	4 (100%)	2 (1–14)	3 (1–9)	0.097*
Successful IVF	30 (71.4%)	2 (100%)	4 (100%)	7 (70.0%)	17 (65.4%)	0.607

More than one answer possible. P-value with Fisher's exact test and *Bonferroni.

REASONS FOR VOLUNTARY CHILDLESSNESS

Reasons for limiting the number of children born was listed by 118 women with UC in paper IV who chose not to have children (voluntary childlessness), or limited their childbearing due to the disease (voluntary birth restriction) or expressed that the disease onset affected the decision to have children (Table 13). The most common reasons were concerns about perineal tear in relation to their underlying diagnosis of UC (59.3%), concerns of a worsening of UC during pregnancy or a relapse (41.5%), and concerns about the heredity of the disease (36.4%). A substantial proportion of women also stated that they limited their sexual activity because of the bowel disease (17.0%), but an even larger proportion expressed concerns about being able to conceive (46.6%).

TABLE 13. Reasons for voluntary childlessness in 118 female patients with UC choosing not to have children or who have restricted the number of children due to their UC (table from paper IV).

	All (*n*=118)	Colectomy only (*n*=16)	Proctectomy (*n*=13)	IRA (*n*=39)	IPAA (*n*=50)
Doctors' advice	8 (6.8%)	2 (12.5%)	0	3 (7.7%)	3 (6.0%)
Concerns about heredity	43 (36.4%)	6 (37.5%)	5 (38.5%)	15 (38.5%)	17 (34.0%)
Limited ability to care for a child	26 (22.0%)	2 (12.5%)	2 (15.4%)	9 (23.1%)	13 (26.0%)
Concerns about added stress from raising a child	15 (12.7%)	2 (12.5%)	1 (7.7%)	7 (18.0%)	5 (10.0%)
Concerns of birth defects	10 (8.5%)	1 (6.3%)	0	4 (10.3%)	5 (10.0%)
Concerns about miscarriage	26 (22.0%)	4 (25.0%)	5 (38.5%)	8 (20.5%)	9 (18.0%)
Concerns of UC getting worse/relapse	49 (41.5%)	6 (37.5%)	4 (30.7%)	19 (48.7%)	20 (40.0%)
Concerns of difficulties conceiving	55 (46.6%)	8 (50.0%)	6 (46.2%)	15 (38.5%)	26 (52.0%)
Concerns about perineal tear	70 (59.3%)	7 (43.8%)	3 (23.1%)	25 (64.1%)	35 (70.0%)
Restricted sexual activity	20 (17.0%)	5 (31.3%)	2 (15.4%)	6 (15.4%)	7 (14.0%)
Other	18 (15.3%)	3 (18.8%)	4 (30.8%)	5 (12.8%)	6 (12.0%)

More than one answer possible.

FERTILITY COUNSELLING

A third (36.9%) of the women responded that they had never discussed fertility or fertility related issues with their doctor (Table 14). Among those who had addressed fertility the most common occasion was before the colectomy, at which time 39.5% of the women talked to their gastroenterologist or surgeon. Out of the 147 women undergoing reconstruction post colectomy, 37.4% reported that the choice of reconstruction method was influenced by their desire to have children (Table 15). IRA was chosen by 10.3% to preserve fertility and was recommended by the surgeon to preserve fertility about as often (12.3%).

TABLE 14. Fertility related discussion/discussions with gastroenterologist and/or surgeon in 214 women with UC undergoing colectomy (table from paper IV).

	All (*n*=214)	Colectomy only (*n*=42)	Proctectomy (*n*=24)	IRA (*n*=66)	IPAA (*n*=81)	*p*-value
Never	79 (36.9%)	21 (48.8%)	9 (37.5%)	18 (27.3%)	31 (38.3%)	0.151
At diagnosis	38 (18.5%)	8 (18.6%)	3 (12.5%)	15 (22.7%)	16 (19.8%)	0.787
Before colectomy	81 (39.5%)	18 (41.9%)	7 (29.2%)	31 (47.0%)	27 (33.3%)	0.273
Before reconstruction	41 (29.4%)	N/A	N/A	26 (39.4%)	21 (25.9%)	0.652
Other occasion	25 (12.2%)	3 (7.0%)	7 (29.2%)	8 (12.1%)	8 (9.9%)	0.072

More than one answer possible. P-value with Fischer's exact test.

TABLE 15. Influence of the desire for children on the choice of and type of restorative procedure. Question only answered by the 147 women who underwent bowel reconstruction (table from paper IV).

	All (*n*=147)	IRA (*n*=66)	IPAA (*n*=81)
Reconstruction method was influenced by fertility desire	55 (37.4%)	30 (45.5%)	25 (30.9%)
Waited with children until reconstruction	10 (6.9%)	3 (4.6%)	7 (8.6%)
Waited with reconstruction until after children	8 (5.5%)	2 (3.1%)	6 (7.4%)
Choose IRA to preserve fertility	15 (10.3%)	15 (23.1%)	0
Surgeon recommended IRA to preserve fertility	18 (12.3%)	17 (26.2%)	1 (1.2%)
Other reason	17 (11.6%)	5 (7.7%)	12 (14.8%)

More than one answer possible.

THE MALE STUDY POPULATION

The IBD cohort consisted of 29,104 men (13,966 with UC, 8,283 with CD and 6,855 with IBD-U) of which 3,771 underwent colectomy during the study period (Table 16).

DEMOGRAPHY IN THE MALE IBD-COHORT

The average follow-up time was 10.4 (SD 7.5) years. The mean age at IBD diagnosis was 27.8 (SD 9.5) years, men with UC were somewhat older (29.0 years, SD 9.2) compared with patients with CD (26.8 years, SD 9.5) and IBD-U (26.5 years, SD 9.7) (p <0.001). Patients with CD were younger (30.3 years, SD 10.0) compared with other IBD patients

(UC 34.4 years, SD 10.9 and IBD-U 32.7 years, SD 11.2) (p <0.001) at first surgery. Men with CD were also more likely to be exposed to bowel surgery (45.1%) compared with patients with IBD-U (36.6%) and UC (17.8%) (p < 0.001).

A total of 17,627 births were linked to men with IBD during the study period. From this the achieved parity at end of follow-up could be estimated, which was found to be 1.28 (SD 1.27) among men with IBD, somewhat lower than in the matched reference cohort at 1.35 (SD 1.35) (p<0.001). Men with UC had a higher parity at diagnosis (0.74, SD 1.09), compared with men with CD (0.63, SD 1.03) and IBD-U (0.60, SD 1.02). The parity at end of follow-up was impaired in CD (mean 1.25 SD, 1.29) (p < 0.001) and IBD-U (mean 1.28, SD 1.28) (p<0.001), and to a lesser extent also by UC (mean 1.30, SD 1.26) (p<0.001).

The proportion of childless men at the end of follow-up was lower among men with IBD than among matched individuals (37.9 vs. 39.6%, p<0.001). The increased incidence of childlessness was only seen in UC (38.4 vs. 36.5%, p<0.001) and IBD-U (39.9 vs. 37.6%, p <0.001), whereas no statistically significant difference was seen between men with CD and their matched cohort (41.5 vs. 40.4%, p = 0.055).

TABLE 16. Demography and characteristics of the male IBD patient and population-based matched reference cohort (table from paper II).

			IBD sub-cohorts		
Characteristics	**Matched cohort**	**IBD cohort**	**UC**	**CD**	**IBD-U**
Patients, *n*	140,901	29,104	13,966	8,283	6,855
Age at inclusion, years, mean (SD)	27.8 (9.5)	27.8 (9.5)	29.0 (9.2)	26.8 (9.5)	26.5 (9.7)
Follow-up time, years, mean (SD)	10.4 (7.5)	10.5 (7.5)	9.6 (7.0)	11.0 (8.0)	11.9 (7.7)
Bowel surgery, *n* (proportion)		8,731 (5.1)	2,489 (17.8)	3,733 (45.1)	2,509 (36.6)
Age at first bowel surgery, mean (SD)		32.1 (10.8)	34.4 (10.9)	30.3 (10.0)	32.7 (11.2)
Age at first child, years, mean (SD)	29.1 (5.4)	29.3 (5.4)	29.6 (5.4)	29.0 (5.5)	29.3 (5.4)
Parity at baseline, mean (SD)	0.70 (1.08)	0.68 (1.06)	0.74 (1.09)	0.63 (1.03)	0.60 (1.02)
Achieved parity at end of follow-up, mean (SD)	1.35 (1.31)	1.28 (1.27)	1.30 (1.26)	1.25 (1.29)	1.28 (1.28)
Childless at baseline, *n* (%)	90,148 (64.0%)	18,851 (64.8%)	8,613 (61.7%)	5,553 (67.0%)	4,685 (68.3%)
No child during follow-up, *n* (%)	89,314 (63.4%)	18,908 (65.0%)	9,289 (66.5%)	5,362 (64.7%)	4,257 (62.1%)
Childless at end of follow-up, *n* (%)	53,367 (37.9%)	11,536 (39.6%)	5,359 (38.4%)	3,439 (41.5%)	2,738 (39.9%)
Year of inclusion, *n* (%) 1964–1973	6,844 (4.9%)	1,479 (5.1%)	485 (3.5%)	588 (7.1%)	406 (5.9%)
1974–1983	17,578 (12.5%)	3,603 (12.4%)	1,433 (10.3%)	1,230 (14.8%)	940 (13.7%)
1984–1993	23,764 (16.9%)	4,883 (16.8%)	2,179 (15.6%)	1,401 (16.9%)	1,303 (19.0%)
1994–2003	39,122 (27.8%)	8,063 (27.7%)	4,067 (29.1%)	1,878 (22.7%)	2,118 (30.9%)
2004–2014	53,595 (38.0%)	11,076 (38.1%)	5,802 (41.5%)	3,186 (38.5%)	2,088 (30.5%)

CHARACTERISTICS OF MEN UNDERGOING COLECTOMY

In paper III fertility was studied in men who underwent colectomy during the study period. The study cohort consisted of 3,771 men (UC 1,850; CD 321; IBD-U 1,600). Corresponding matched cohorts consisted of 19,502 men. The average follow-up time 11.2 (SD 7.2) for men (Table 17).

Somewhat more men than women underwent bowel reconstruction after colectomy, but still less than half (1,635 patients, 4.4%) Reconstructive surgery was performed in 1,635 men (43.4%) after colectomy at a mean age of 35.6 (SD 12.3) years. In total 2,136 (56.6%) men retained their ileostomy, of which 885 had the rectal stump left in situ whereas 1,251 underwent completion proctectomy (Figure 12). In contrast to female patients, the most frequent reconstruction in men with UC was IPAA. The use of IPAA and IRA were almost as common in IBD-U patients, whereas only very few CD patients were reconstructed with IPAA consistent with the findings in women.

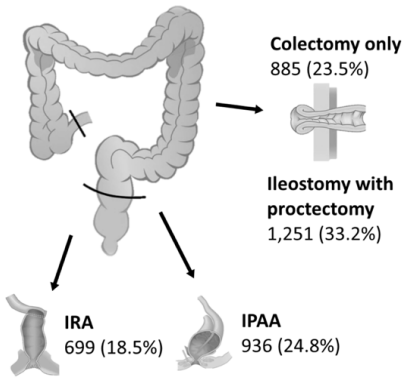

Figure 12. Distribution of reconstruction options after colectomy in men in paper III. Illustrations modified and reprinted with permission of © Typoform.

TABLE 17. Demography and characteristics of men with IBD undergoing colectomy during the study period compared with population-based matched reference cohort (table from paper III).

				IBD subcohorts		
Characteristics		**Matched cohort**	**IBD-cohort**	**UC**	**CD**	**IBD-U**
Patients, *n*		19,502	3,771	1,850	321	1,600
Age at diagnosis, years, mean (SD)		26.34 (8.55)	26.36 (8.58)	27.64 (8.42)	25.16 (8.32)	25.11 (8.60)
Age at colectomy, years, mean (SD)		30.40 (8.12)	30.41 (8.13)	31.20 (7.99)	29.18 (8.49)	29.73 (8.14)
Age at reconstruction, years, mean (SD)		35.62 (12.27)	35.62 (12.28)	35.77 (11.86)	36.91 (14.73)	35.19 (12.20)
Follow-up time, years, mean (SD)		11.63 (7.12)	11.34 (7.21)	10.37 (6.76)	13.90 (8.09)	11.95 (7.33)
Time to colectomy, years, mean (SD)		4.06 (5.37)	4.05 (5.38)	3.57 (5.13)	4.02 (5.74)	4.61 (5.53)
Time to reconstruction, years, mean (SD)		5.22 (9.90)	5.21 (9.90)	4.56 (9.15)	7.73 (13.60)	5.46 (9.77)
Age at first child, years, mean (SD)		28.96 (5.44)	29.29 (5.41)	29.41 (5.32)	28.11 (5.28)	29.39 (5.52)
Parity at diagnosis, mean (SD)		0.63 (1.03)	0.57 (0.97)	0.64 (1.01)	0.50 (0.91)	0.51 (0.93)
Parity at colectomy, mean (SD)		0.88 (1.15)	0.78 (1.07)	0.83 (1.10)	0.73 (1.04)	0.74 (1.04)
Achieved parity at end of follow up, mean (SD)		1.57 (1.31)	1.38 (1.25)	1.37 (1.26)	1.38 (1.28)	1.39 (1.23)
Childless at diagnosis, *n* (%)		12,993(66.6%)	2,594 (68.8%)	1,211 (65.5%)	229 (71.3%)	1,154 (72.1%)
No child at colectomy, *n* (%)		10,770 (55.2%)	2,210 (58.6%)	1,049 (56.7%)	191 (59.5%)	970 (60.6%)
Chiildless at end of follow up, *n* (%)		5,799 (29.7%)	1,325 (35.1%)	660 (35.7%)	114 (35.5%)	551 (34.4%)
Year of colectomy, *n* (%)	1950–1979	2,563 (13.1%)	493 (13.1%)	211 (11.4%)	87 (27.1%)	195 (12.2%)
	1980–1989	4,330 (22.2%)	835 (22.1%)	382 (20.6%)	115 (35.8%)	338 (21.1%)
	1990–1999	5,387 (27.6%)	1,047 (27.8%)	529 (28.6%)	67 (20.9%)	451 (28.2%)
	2000–2009	4,853 (24.9%)	940 (24.9%)	488 (26.4%)	30 (9.3%)	422 (26.4%)
	2010–2014	2,369 (12.1%)	456 (12.1%)	240 (13.0%)	22 (6.9%)	194 (12.1%)

No significant difference in parity was seen at diagnosis in men with IBD or in the sub-cohorts, compared with the matched reference cohorts. A total of 1,914. live births occurred post colectomy in men with IBD. The mean achieved parity at end of follow-up (1.38, SD 1.25) was lower than in the matched reference cohort (1.57, SD 1.31) (p<0.001).

The impairment was about the same in all subtypes of IBD. Patients undergoing a later reconstruction with IRA were throughout slightly younger at diagnosis, colectomy and reconstruction, than patients reconstructed with IPAA.

FERTILITY IN MEN WITH IBD

In paper II fertility in men was somewhat impaired in all subtypes of IBD compared with the matched individuals (IBD-U HR 0.92, 95% CI 0.89–0.95, UC, HR 0.93, 95% CI 0.91–0.96 and CD HR 0.95, 95% CI 0.92–0.98) (Table 18). When analysing fertility at different ages, markedly depressed fertility at the lowest ages was seen in UC and IBD-U compared with the matched reference individuals. The impact was less pronounced with increasing age (test for trend, UC $p<0.001$ and IBD-U $p<0.008$). In an analysis of fertility for each decade of the long study period, no apparent temporal trend was observed. Inclusion of SES in a multivariable analysis did not change the fertility numbers.

TABLE 18. Fertility for men according to subtypes of IBD compared with matched reference cohorts, expressed as hazard ratio (HR) in strata of age and time periods (table from paper II).

	UC			CD			IBD-U		
	HR	**95% CI**	***p*-value***	**HR**	**95% CI**	***p*-value***	**HR**	**95% CI**	***p*-value***
Overall	0.93	0.91–0.96		0.95	0.92–0.98		0.92	0.89–0.95	
Age			0.001			0.063			0.008
15–19 years	0.46	0.26–0.79		0.79	0.48–1.30		0.43	0.23–0.82	
20–24 years	0.71	0.64–0.79		0.83	0.74–0.92		0.69	0.61–0.78	
25–29 years	0.89	0.85–0.94		0.92	0.87–0.98		0.87	0.82–0.93	
30–34 years	0.94	0.90–0.98		0.94	0.90–1.00		0.96	0.90–1.01	
35–39 years	0.99	0.94–1.04		1.01	0.95–1.08		1.00	0.93–1.07	
40–44 years	1.00	0.92–1.09		1.02	0.92–1.14		0.93	0.83–1.04	
Time-periods			0.091			0.127			0.178
1964–1973	0.95	0.85–1.05		1.01	0.92–1.11		0.94	0.83–1.04	
1974–1983	0.91	0.85–0.97		0.99	0.92–1.05		0.88	0.81–0.95	
1984–1993	0.89	0.84–0.94		0.94	0.88–1.00		0.87	0.81–0.92	
1994–2003	0.96	0.92–1.00		0.92	0.87–0.98		0.96	0.90-1.01	
2004–2014	0.96	0.91–1.01		0.95	0.88–1.02		0.96	0.88-1.05	

The test for trend is a Likelihood Ratio test comparing models with and without interaction.

IMPACT OF THE SEVERITY OF DISEASE IN MEN

The impact of four parameters reflecting the severity of disease was analysed (Table 19). Any admission to hospital due to IBD was associated with a lower chance of becoming father compared with the matched individuals. There was a trend towards decreasing fertility in UC and IBD-U with increasing number of hospital admissions (test for trend, $p<0.012$ and $p<0.001$, respectively). An increasing number of bowel resections was associated with a reduced fertility for men with IBD-U only compared with the matched

population (test for trend, $p<0.034$). Data regarding drug treatment was available from 2005 onwards). A tendency for higher medical treatment intensity to affect fertility more was seen., this trend was only statistically significant in CD (test for trend, $p<0.033$) possibly due to the small sample. No effect on male fertility was seen from perianal disease in CD, HR was 0.93 (95% CI 0.86–1.00) with perianal disease and 0.95 (95% CI 0.92–0.98) without.

TABLE 19. Impact of disease severity on fertility in men with IBD according to IBD subtypes. The fertility is expressed as hazard ratio (HR) for giving birth in relation to the order of hospital admissions during follow-up, bowel procedures, and intensity of medical treatment, compared with matched reference cohorts (table from paper II).

	UC			CD			IBD-U		
	HR	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Order of admissions			0.012*			0.266*			<0.001*
0	0.99	0.95–1.03	0.615	0.98	0.91–1.05	0.602	0.99	0.92–1.06	0.744
1	0.90	0.85–0.94	<0.001	0.95	0.90–1.01	0.107	0.97	0.91–1.04	0.428
2	0.94	0.88–1.00	0.057	0.98	0.91–1.05	0.552	0.88	0.81–0.96	0.004
3	0.88	0.81–0.96	0.003	0.97	0.89–1.07	0.561	0.93	0.84–1.03	1.172
>3	0.90	0.85–0.96	0.002	0.91	0.86–0.97	0.005	0.86	0.81–0.91	<0.001
No. of bowel procedures			0.958*			0.689*			0.034*
0	0.93	0.91–0.96	<0.001	0.93	0.89–0.97	0.001	0.93	0.90–0.97	0.001
1	0.95	0.87–1.03	0.203	1.01	0.97–1.06	0.580	0.91	0.84–0.98	0.015
2	0.90	0.81–1.00	0.058	0.86	0.77–0.97	0.013	0.84	0.75–0.93	0.002
3	1.10	0.80–1.50	0.552	0.94	0.74–1.19	0.621	0.84	0.66–1.06	0.140
>3	0.87	0.51–1.48	0.600	0.89	0.65–1.21	0.462	0.87	0.61–1.22	0.413
Intensity of treatment†			0.336*			0.033*			0.588*
Low	0.96	0.90–1.02	0.144	1.01	0.90–1.13	0.877	0.90	0.81–1.01	0.064
Medium	0.90	0.69–1.18	0.449	0.89	0.77–1.05	0.156	1.09	0.82–1.47	0.547
High	0.68	0.32–1.43	0.287	0.79	0.62–1.01	0.054	0.89	0.54–1.47	0.642

With adjustment for the spouse pregnancy and first year postpartum, age and year at diagnosis in multivariable analysis. The order of admission and number of bowel resections were analysed as time-varying covariates. *The test for trend is a Likelihood Ratio test comparing models with and without interaction. †Medications only available from the Prescribed Drug Register from 2005 and onwards.

PARITY PROGRESSION RATIO

The parity progression ratio was decreased in all subtypes of IBD (Table 20). The most pronounced impact was observed for patients with low parity at disease onset (no or one child). Especially childless patients diagnosed with UC or IBD-U were much less likely to become father twice.

TABLE 20. Male parity progression ratio (the probability of having one or two additional children) according to parity at diagnosis and subtypes of inflammatory bowel disease, compared with matched reference cohorts expressed as odds ratio (OR) (table from paper II).

Parity at	Parity	UC			CD			IBD-U		
diagnosis	progression	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Childless	+1	0.92	0.88–0.96	0.001	0.93	0.88–0.99	0.020	0.91	0.85–0.97	0.003
	+2	0.88	0.83–0.93	<0.001	0.92	0.86–0.98	0.011	0.87	0.81–0.94	<0.001
Para 1	+1	0.94	0.85–1.04	0.218	0.97	0.84–1.11	0.627	0.91	0.78–1.07	0.258
	+2	0.88	0.76–1.02	0.086	0.99	0.81–1.20	0.903	0.93	0.75–1.14	0.475
Para 2 +	+1	1.03	0.98–1.09	0.290	1.01	0.93–1.09	0.839	1.02	0.93–1.11	0.689
	+2	0.80	0.66–0.98	0.028	1.04	0.82–1.32	0.755	0.84	0.64–1.11	0.214

No child at baseline (childless), one child at baseline (para 1) and two or more children at baseline (para 2 +).

FERTILITY IN MEN AFTER COLECTOMY

In men, a consistent slight impairment of fertility was seen (HR 0.89, CI 0.85–0.94) after colectomy compared with matched individuals (Table 21). The finding was regardless of IBD-subtype and possible subsequent reconstruction. Nor when the comparison was made within the IBD cohort, with ileostomy only as reference, could any effect on fertility be noted after reconstruction or proctectomy (Table 22).

TABLE 21. Impact of colectomy with or without subsequent reconstructive surgery or proctectomy on male fertility for IBD subtypes, expressed as hazard ratio (HR) for partner giving birth compared with matched reference cohorts (table from paper III).

	IBD-cohort			IBD-subcohorts								
				UC			CD			IBD-U		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Colectomy only	0.85	0.77–0.94	0.002	0.94	0.81–1.10	0.435	0.75	0.56–1.00	0.054	0.81	0.69–0.94	0.005
IRA	0.88	0.78–0.98	0.026	0.95	0.79–1.15	0.625	0.85	0.65–1.11	0.227	0.83	0.70–0.99	0.038
IPAA	0.88	0.80–0.96	0.006	0.85	0.75–0.96	0.011	1.43	0.29–7.11	0.664	0.91	0.79–1.05	0.186
Proctectomy	0.91	0.84–0.98	0.012	0.93	0.83–1.04	0.217	0.77	0.62–0.97	0.024	0.93	0.83–1.03	0.178

Table 22. Impact on fertility from reconstructive surgery or proctectomy after colectomy in men with IBD expressed as hazard ratio (HR) (table from paper III).

	UC			CD			IBD-U		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Unadjusted									
Colectomy only	1.00			1.00			1.00		
IRA	0.97	0.77–1.21	0.795	1.12	0.77–1.62	0.555	1.00	0.81–1.23	0.973
IPAA	1.00	0.83–1.20	0.968	1..61	0.39–6.65	0.504	1.12	0.93–1.34	0.249
Proctectomy	1.08	0.91–1.29	0.368	1.01	0.72–1.43	0.934	1.15	0.97–1.36	0.114
Adjusted for age at disease onset, year of colectomy and parity at colectomy									
Colectomy only	1.00			1.00			1.00		
IRA	0.98	0.78–1.22	0.875	1.05	0.72–1.53	0.792	1.00	0.81–1.24	0.972
IPAA	0.92	0.76–1.11	0.378	1.46	0.24–8.71	0.680	1.14	0.94–1.38	0.192
Proctectomy	1.17	0.97–1.41	0.095	0.91	0.64–1.28	0.582	1.07	0.89–1.27	0.482

DISCUSSION

This thesis contains the largest population-based cohort studies of fertility in women and men with IBD. The long average follow-up time and data covering the entire reproductive history of the included for both women and men allows for reliable calculations regarding reproductive outcome. The terms used to describe reproductive capacity are somewhat ambiguous and general consensus does not exist. The number of children born may be extracted from population registers (fertility), but changes in fertility do not always accurately reflect fecundity (biological reproductive capacity), as fertility is affected by many social and environmental factors.

FERTILITY IN WOMEN WITH UC

Fertility was nearly normal in women with UC in paper I, in accordance with most previous studies of various designs[343, 345, 348, 427]. It was particularly evident that fertility was normal in women with UC when women undergoing bowel procedures were excluded from the calculations, while the fertility deteriorates already after first bowel procedure. This is in accordance with previous studies, where only limited impact on fertility has been demonstrated in non-surgically treated women with UC[212, 345, 348, 427-429]. Treatments for IBD have changed profoundly during the long study period. The improvement of fertility for women with UC seen over time in paper I may be a consequence of improved medical and surgical treatment.

The risk of colectomy continues throughout the patients' lifetime; in our material around 10% of the female patients with UC underwent colectomy during their fertile years. An evident impact on fertility was seen in the sub-cohort of patients who underwent colectomy in paper III. For many it is stigmatising to live with a stoma, not least during the years when many meet their partner and start a family[253, 430] Despite young age, only around 40% of the women with UC was reconstructed during the study period. The reason for the low proportion is not known. It has previously been reported that women who have undergone primary surgery at a hospital performing reconstructive surgery are reconstructed to a greater extent[254, 255]. The desire to undergo reconstruction is likely greater than the number of patients who actually complete reconstruction, leaving some patients with an unwanted stoma[305].

Internationally IPAA is the standard procedure for bowel restoration post colectomy. Unlike in most other countries, IRA and IPAA are used to about the same extent in Sweden[254]. Population-based comparison of the effects of the surgical methods are therefor particularly well suited in Sweden. In paper III IPAA was used in 58% of the female patients with UC undergoing bowel reconstruction, with IRA used in 42%. Women with UC had a lower fertility post colectomy compared with the matched individuals from the general population. Colectomy with end ileostomy had the least impact on fertility, followed by IRA, while fertility after IPAA and completion proctectomy was affected to a greater extent. Thus, women with UC undergoing pelvic surgery experienced the most pronounced impact on their fertility. The extensive dissection needed to remove the chronically inflamed rectum for IPAA or completion proctectomy may be contributing factors to the impaired fertility. Higher rates of hydrosalpinx, fimbrial damage and tubal obstruction following pelvic surgery are considered the most likely contributing mechanisms[375]. The reduced fertility after reconstruction with IPAA are well recognised. The finding was first seen in patients with FAP[366, 376, 431] and later also IBD[362, 366, 374]. Whether IRA affects fertility has previously been largely unknown. In a recent French report no difference in fertility was seen after IRA compared with IPAA[304]. However, the study has several methodological weaknesses which makes the conclusion questionable, including an uneven distribution of open and laparoscopic surgery between the groups, short follow-up time and absence of subgroup analysis depending on IBD subtype. In recent years, laparoscopic surgery has been shown to have many advantages[432, 433]. Indications of improved fertility after laparoscopic IPAA surgery exist, but population-based studies are lacking[428]. Unfortunately, the number of laparoscopic surgeries in paper III were too few to allow subgroup analysis.

IRA is used to a limited extent in many countries due to the risk of developing cancer or recurrent inflammation in the rectal remnant left in situ. However, the absolute risk of cancer in the first few years is small, although it increases with time[217]. As previously suggested, IRA is therefore likely a good alternative preserve fertility during the childbearing years[261]. Regular endoscopic monitoring of the rectum is necessary if it is left in place to detect possible dysplasia and cancer development.

In population-based register studies it is not feasible to measure fertility desire of the included study participants. It is therefore not possible to determine whether the reduced fertility after colectomy reflects an effect on fecundity or if has psychological reasons. It is also not possible to determine the cause of the fertility difference after IPAA and IRA. It is notable that the cohorts in paper III reconstructed with IPAA and IRA respectively are not comparable at baseline. The patients reconstructed with IPAA were on average

slightly older and had a higher parity at the time of colectomy. The desire to have children may therefore differ between the groups choosing the different reconstruction options. In some cases, the operating surgeon may also have suggested IRA in order to maintain fertility during the childbearing years causing selection bias. In paper IV these questions were approached through a questionnaire survey.

Less than half of the study participants in paper IV stated that their fertility desire did affect the type of reconstruction performed. Only one in ten chose reconstruction with an IRA to preserve fertility. About the same number were recommended IRA by their surgeon for the corresponding reason. Beyond that, it is of course possible that the surgeon additionally advocated IRA for women in childbearing age without clearly communicating the reason.

More than half of the included patients in paper IV stated that the onset of UC, the colectomy or any subsequent reconstruction affected their desire to have fertility. However, it was more common to limit the number of children born (voluntary birth restriction) than to completely refrain from having children (voluntary childlessness). As in previous studies, concerns that the disease will worsen as a result of pregnancy and concerns about the heredity of the disease appear to be important causes for voluntary childlessness and reduction of number of children born[356, 359]. In this material the most common cause was concerns about sustaining a perineal tear, given the underlying UC, which is possibly explained by the fact that women post colectomy may have great fear for incontinence problems.

Paper IV moreover revealed high incidence of difficulty conceiving after colectomy among women with UC. Almost 40% reported difficulty conceiving and 19% that they could not conceive at all. A quarter of the women who answered the questionnaire in paper IV had sought fertility counseling and around 20% had chosen to try to have a child with the help of IVF. Notably, it was much more common to report difficulty conceiving and inability to conceive, among women reconstructed with IPAA than those reconstructed with IRA. In addition, fertility counselling and the use of IVF was more commonly reported after IPAA surgery.

The increased use of fertility treatment in women with IBD, particularly those reconstructed with IPAA, is in accordance with previous findings[412]. IVF is the most effective fertility treatment method available. Every third child born after IPAA was a product of IVF in Denmark[413]. Knowledge about the outcome of IVF in IBD is partly contradictory[415], but most reports shown that IVF is successful in women with IBD[407, 412, 413]. In paper IV IVF was successful to the same extent expected.

IRA is associated with a better fertility than IPAA after reconstruction in women with UC, and possibly a way to preserve fertility following colectomy. IPAA performed secondary to an IRA has the same long-term survival as a primarily constructed IPAA[268] and constructing an IRA after colectomy could be an alternative to postpone proctectomy with or without IPAA. To fairly compare the impact on fertility of IPAA and IRA it would be necessary to conduct a randomised controlled trial. Such a study has previously not been possible to carry out[305].

FERTILITY IN WOMEN WITH CD

Fertility was clearly impaired in women with CD in paper I, in accordance with findings in previous studies[340, 341, 345, 348, 434, 435]. This was seen throughout the long study period, although some improvement was noted over time. Increased number of bowel resections, order of admissions and presence of perianal disease was used as surrogate markers to identify patients with severe disease. All markers had a clear association with reduced fertility.

According to reports in the literature up to 80% of all patients with CD will require an intestinal resection[209, 225]. In paper I, where only surgery carried out before the age of 45 was analysed, a corresponding figure of 45% was reported. Patients with CD may require surgery for medically refractory disease, or because of complications. The impact of surgical interventions on fertility in CD is previously largely unknown[340, 428, 434] but the number of bowel procedures was clearly associated with reduced fertility in IBD in paper I. The most common bowel procedure in CD is a small bowel resection, classically an ileocaecal resection. Patients with CD may also undergo colectomy, but subsequent IPAA formation is uncommon due to risk of disease recurrence and resulting pouch failure[434]. In paper III a pronounced effect on fertility after colectomy was seen; the fertility did not deteriorate further after IRA, but did deteriorate further after proctectomy. From this material it is not clear whether the reduced fertility is an effect of surgery itself or a consequence of more severe disease.

The order of hospital admissions was likewise strongly associated with decreased fertility in women with CD. This was selected as an indicator of the intensity of disease activity rather than prescribed medication, as many patients start to medicate with corticosteroids at flares without new prescriptions. Moreover, many commonly used drugs used to treat flares and even maintenance therapy are given in hospital and are thus not included in the PDR. Active disease and flares could theoretically impair fertility through systemic effects and local inflammation involving reproductive organs. A

decreased ovarian reserve as measured by AMH has been reported in women with active CD, with a risk of accelerated loss of fertility with age as concequence[352, 436, 437]. Active inflammation in CD has also been associated with depression, malnutrition, and anemia, which may all confound the ability to conceive[343, 347, 438, 439]. Apart from biological reasons, the reduced fertility with more severe disease may be due to physicians' recommendations and reduced sexual desire. As active disease at the time of conception and during pregnancy may increase the risk of preterm birth and lower birthweight[440], women with IBD are recommended to be in remission before trying to conceive[339, 343, 438]. Reduced fertility after flares has previously been reported in population-based setting, in accordance with our findings[345]. Several systematic reviews have likewise reported reduced female fertility during active disease[347, 441] however, the quality of the original studies has however lately been questioned[339].

A majority of female IBD patients reports decreased sexual activity[442] Decreased libido is associated with active disease and dyspareunia from active perianal disease is also reported, in keeping with our finding that perianal disease in CD had a profound negative effect on fertility.

Voluntary childlessness has been shown to be an important cause of the reduced fertility seen in women with IBD[355, 356, 359, 443, 444], it is more commonly reported by women with CD, than UC[339, 348, 444]. In paper I, an increased use of contraceptives was seen both before and after diagnosis, which was interpreted as an expression of voluntary childlessness[345]. These findings are somewhat ambiguous, as contraceptive use also has been suggested to contribute to the development of IBD and is also used as symptom relief, sometimes even before the diagnosis[445, 446].

FERTILITY IN WOMEN WITH IBD-U

Fertility in women with IBD-U has not been studied before. The term IBD-U is increasingly being used for IBD cases when characteristic features of UC and CD are absent[118, 122, 447]. Some cases of IBD-U are clearly due to a misdiagnosis in early disease stages, especially among young children, or due to incomplete investigations[117]. The use of the term is particularly beneficial in registry-based studies, where the uncertainty surrounding the correctness of the diagnoses is sometimes great as the clinical presentation and the subsequent coding can vary over time, and misclassification errors also occurs[128]. With this approach the UC and CD cohorts are as well defined as can reasonably be achieved, on the contrary the IBD-U cohort includes a mixture of IBD subtypes making results more difficult to interpret. In paper I the fertility in IBD-U was

markedly reduced, especially during the most reproductive years. The IBD-U cohort was moreover characterised by the lowest age of onset, by the lowest fertility and also by the most pronounced impact on fertility by disease severity. This poorly understood intermediate phenotype has been suggested to be an own entity[448] associated with a more severe disease course when compared with classical UC[123], consistent with our findings.

FERTILITY IN MEN WITH IBD

The impact of IBD on male fertility has previously been largely unknown. Only a few population-based studies of fertility in men with IBD have been reported, based on a few hundred patients in total and with data collected from clinical records and without a population-based reference group[377-379]. The main finding from paper II is slightly reduced fertility in men with all subtypes of IBD. The impaired fertility remained throughout the study period, as no temporal trend was identified when fertility was analysed in different decades. The impaired fertility in CD is consistent with previous studies[377-379], but according to the present results the impact is not as profound as previously reported. A previous systematic review revealed 18-50% reduced fertility, but with preserved fecundity[348]. Earlier studies on fertility in UC show partially contradictory results,[378, 379, 449] while our results demonstrate a clear impairment. The fertility in IBD-U has not been studied before but was reduced to about the same extent as in UC and CD in paper II.

Consistent with previous studies, increasing severity of disease was associated with decreasing fertility in men with IBD in paper II[339, 388]. The impact of four different parameters reflecting the severity of disease were analysed. The order of hospital admissions was associated with reduced fertility in UC and IBD-U. Disease activity, with pro-inflammatory cytokines (such as TNF-α and IL-1) and reactive oxygen species as mediators[450, 451], seems to affect both reproductive ability and sexual function[347, 388, 452, 453]. Male patients with active disease more often report difficulties to conceive in contrast to those in remission[388]. A higher incidence of erectile dysfunction in active disease is also reported, while men in in clinical remission or with mild symptoms have a similar rates as healthy controls[452]. Erectile dysfunction is more common in IBD compared to other chronic diseases, and common already at diagnosis[454]. Impaired semen quality in severely active IBD, compared with patients who achieved remission has been reported[455].

Previous data on the effect of surgery on fertility rates in men with IBD are limited[404]. The number of bowel procedures in UC and CD had no negative effect on fertility in

paper II, consistent with previous sparse findings[373, 456]. The number of intestinal resections in IBD-U was associated with impairment of fertility. In paper III colectomy was associated with somewhat reduced fertility in all subtypes of IBD. Surgical reconstruction was not associated with a further reduction in fertility regardless of diagnosis. Pelvic surgery for any reason may lead to erectile or ejaculatory problems[343]. Retrograde ejaculation and erectile dysfunction have been reported in men with UC after IPAA[402, 403, 457]. This was more common in men aged >50 at time of IPAA[458], and uncommon in young patients[459]. Sildenafil improves erectile dysfunction in most patients with pelvic parasympathetic nerve damage after proctectomy[460]. However, overall no change or even an improvement in sexual function and erectile dysfunction occurs after bowel reconstruction[399, 429, 460], whereas creation of a stoma is associated with erectile dysfunction[404, 405, 461]. In a Danish study, an increase in birth rates was observed after IPAA[373]

In paper II more intensive medical treatment was associated with impaired fertility in CD in the latter part study, when information on prescribed medications were available. Sulfasalazine may adversely affect sperm and cause oligospermia, poor sperm motility, and increased risk of morphologically abnormal effect. The effect is reversal after discontinuation[450, 462]. Methotrexate is associated with oligospermia in some reports and mesalazine have been associated oligospermia in one study[393, 404]. No other medications used in IBD is known to affect fertility in males[450, 456].

The last of the four factors associated with the severity of the disease was perianal disease. Perianal disease was not associated with any impairment in fertility in men.

Despite the limited impairment of fertility seen in men with IBD in papers II and III there are several findings that support a biological impact on reproductive ability in men. Increased use of medication for erectile dysfunction[381, 404] and elevated rates of sexual dysfunction[404] among men with IBD have been reported. Female partners to men with an IBD diagnosis are additionally more likely to use assisted reproductive techniques[388] and infertility counselling is more common among men with CD[462, 463]. Underlying mechanisms explaining the reduced fecundity may include malnutrition, which is highly prevalent in patients with IBD. Poor nutritional status can reduce fertility due to zinc deficiency leading to reduced testicular function[390]. Oligospermia is seen in men with a zinc restricted dieat[464]. Low testosterone levels, associated with disease activity and treatment, have been reported in men with IBD. Furthermore, anti-sperm antibodies have been observed in men with IBD, but the clinical relevance of this is unclear[347]. Apart from physiological factors voluntary birth control could contribute to the reduced fertility in male IBD patients for similar reasons to those observed in women, including

fear of congenital abnormalities caused by the disease, concerns of transmitting IBD and concerns of teratogenicity of medications[443]. Additionally, factors such as body image perception and sexual desire may affect sexual function[392].

There are several factors that may be differently distributed between patients with IBD and matched individuals, which may also affect fertility and thus the study results. Alcohol use in patients with IBD can aggravate the intestinal symptoms, the use of alcohol may therefore be limited in IBD compared with the reference population. Alcohol may also impair fertility by testicular atrophy and decreased sperm count[404]. Smoking impairs fertility but may also affect the course of IBD, including need for surgery and surgical outcome[49, 54, 465], and may be differently distributed between the cohorts. Body mass index (BMI) may also be differently distributed between the cohorts, as nutritional problem is more commonly reported among patients with CD[102]. BMI is likewise known to affect fertility[466]. NPR contains no information on alcohol consumption, tobacco use, or BMI, neither in the patients nor in their partners. Both alcohol use, smoking, and BMI are also associated with SES. Somewhat surprisingly, no difference in fertility was seen in either women or men after adjustment for SES in papers I-II. It cannot be ruled out that the stable fertility rates, regardless of adjustment for SES, are the result of several factors that affect fertility in the opposite direction.

CONCLUSIONS

Fertility, measured as the number of children born, was impaired in unselected Swedish women of fertile age with IBD compared with matched individuals from the general population. The impact on fertility was more pronounced in women with CD and IBD-U, and to a lesser extent in UC. The severity of the disease measured as the order of hospital admissions and bowel resections were associated with reduced fertility in women with all IBD subtypes, in CD also perianal disease.

Fertility was more dramatically reduced in women undergoing colectomy due to IBD compared with matched individuals. Retaining the ileostomy with the rectum left in situ after colectomy affected fertility the least, while proctectomy affected fertility the most. If the patient chose to undergo a subsequent reconstruction, fertility was more affected after IPAA compared with IRA in women with UC.

Increased use of contraceptives and reduced parity progression at higher parities suggest that an element of voluntary reduced fertility is implicated in women with IBD. The main reasons for reduced reproductive outcome after colectomy in women was yet a limitation of the number of children born per woman, difficulty conceiving and only to a lesser extent a decision to completely refrain from having children. Although women reconstructed with IPAA reported higher rates of difficulty conceiving and greater use of IVF some selection bias was seen, as some patients reconstructed with IRA likely chose that method to preserve fertility.

The fertility in men with IBD was only marginally reduced compared with matched individuals. The severity of the disease was clearly associated with decreased fertility in men. The order of hospital admissions, independent of IBD subtype, the intensity of treatment in CD and bowel resections in IBD-U were factors used to describe the severity of disease that were associated with decreased fertility. The impact of colectomy and reconstructive surgery in men with IBD was only minor.

SVENSK SAMMANFATTNING

(Summary in Swedish)

Inflammatoriska tarmsjukdomar är kroniska tillstånd som förlöper skovvist, de debuterar ofta i ung ålder. Huvudtyperna är ulcerös kolit och Crohns sjukdom. Termen oklassificerbar kolit brukar användas när det inte säkert går att säga vilken typ av inflammatorisk tarmsjukdom som är aktuell. Huvudsyftet med den här avhandlingen var att kartlägga hur inflammatorisk tarmsjukdom påverkar fertiliteten.

Fertiliteten studerades hos 56,435 personer mellan 15–44 år som insjuknat i inflammatorisk tarmsjukdom mellan 1964–2014 och jämfördes med fertiliteten hos ungefär fem gånger så många personer med samma ålder och kön utan inflammatorisk tarmsjukdom. Kvinnor med inflammatorisk tarmsjukdom födde färre barn, än de personer som inte hade inflammatorisk tarmsjukdom under studieperioden. Påverkan var mest påtaglig vid Crohns sjukdom och oklassificerbar kolit, men inte lika uttalad vid ulcerös kolit. Sjukdomsaktivitet, genomgångna operationer och vid Crohns sjukdom även förekomst av sjukdom kring ändtarmen påverkade fertiliteten på ett ogynnsamt sätt hos kvinnor. En betydande andel, nästan 3000 kvinnor, behövde operera bort hela tjocktarmen under studieperioden. Kvinnorna som opererades med borttagande av tjocktarmen hade en påtagligt nedsatt fertilitet jämfört med personer utan tarmsjukdom. Fertilitetspåverkan var minst uttalad hos de patienter som efter operationen hade en tunntarmsstomi och där ändtarmen lämnades orörd. I de fall då tarmkontinuitet återskapades vid ulcerös kolit var fertiliteten betydligt mindre påverkad då ändtarmen kopplades ihop med tunntarmen (ileorektal anastomos) än hos de patienter där ändtarmen opererades bort och en tunntarmsreservoar kopplades till ändtarmsöppningen (bäckenreservoar). Mest uttalad fertilitetspåverkan, oberoende av typ av inflammatorisk tarmsjukdom, sågs hos de patienter där både tjock- och ändtarm opererades bort.

Då 214 (av 294 tillfrågade) kvinnor i åldern 18–44 år som opererat bort tjocktarmen på grund av ulcerös kolit mellan 2000–2020 fick fylla i en enkätstudie framkom att drygt hälften upplevde att insjuknandet hade påverkat deras önskan att få barn. Den vanligaste konsekvensen var att begränsa antalet födda barn. Det var dock vanligare att inte kunna få barn alls, än att helt avstå från att skaffa barn på grund av sjukdom.

Även hos män påverkades fertiliteten av inflammatorisk tarmsjukdom, men effekten var inte lika uttalad som hos kvinnor. Fertilitetspåverkan var större hos de patienter som hade en mer uttalad sjukdomsaktivitet. Vid Crohns sjukdom och oklassificerbar kolit påverkade även intensiv medicinsk behandling och tarmkirurgi fertiliteten. Fertiliteten hos den de knappt 3800 män som fick sin tjocktarm bortopererad var endast marginellt påverkad och oberoende av typ av rekonstruktionsalternativ.

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Papers

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