Aspects on Long-term Outcome After Restorative Proctocolectomy

Jonas Bengtson

Department of Surgery
Institute of Clinical Sciences
The Sahlgrenska Academy at the University of Gothenburg

UNIVERSITY OF GOTHENBURG

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Abstract

Background Restorative proctocolectomy is the preferred surgical alternative for reconstruction after proctocolectomy for ulcerative colitis. The majority of patients are satisfied with the functional outcome. However, a proportion of the patients suffer from complications and impaired pouch function. Furthermore, about 10% of the patients will have a definitive failure of the pouch. The aim of this thesis was to explore some of the long-term aspects of this surgical procedure.

Methods *Paper I*: 42 patients were assessed with a pouch functional score and manovolumetry. The outcome after median 16 years were compared to two years after surgery in a paired analysis. *Paper II*: Grade of inflammation, possible dysplasia and pouch related problems were assessed in 13 patients with pouch failure and the pouch still in place but deviated with an ileostomy. *Paper III*: 36 patients with pouch failure were compared to 72, age and gender matched patients with functioning pouches, regarding sexual function, body image and health related quality of life. The instrument used for sexual function was the female sexual function index (FSFI) and the international index of erectile function (IIEF). Body image was assessed with the body image scale (BIS), and health related quality of life with SF-36. Swedish version. 2.0. *Paper IV*: is a randomized, placebo-controlled, double blind study on the effects of probiotics (*Lactobacillus plantarum* 299, *Bifidobacterium infantis* Cure21) on 31 patients with poor pouch function. Assessments were made with a pouch functional index, the pouchitis activity index (PDAI), endoscopy, histology and faecal biomarkers.

Results The pouch functional score showed impairment at 16 year as well as the manovolumetric characteristics, except for resting anal pressure. Increased age and pouch volume were correlated to a worse functional score (Paper I). The majority of patients had no problems with the defunctioned pouch and dysplasia was not found (Paper II). Patients with pouch failure demonstrated lower scores in all domains in the FSFI and IIEF, as well as lower summary score in both instruments. However, the differences were not statistically significant. BIS summary score was significantly lower for both sexes in the patients with pouch failure. All domain SF-36 scores were lower for both sexes with pouch failure, though not statistically significant (Paper III). There was no significant difference between the probiotics and placebo groups regarding pouch functional score, PDAI or faecal biomarkers after treatment. Initial values of PDAI correlated significantly to all faecal biomarkers (Paoer IV).

Conclusions A decline in pouch function at long-term, concurrent with alterations in pouch physiology as assessed with manovolumetry was demonstrated. The mucosa in the indefinitely deviated pouch showed no dysplasia. Furthermore, the majority of the deviated patients had no pouch related symptoms. This indicates that the pouch could be left in situ in case of pouch failure, but further follow-up is needed. Patients with pouch failure seem to have an impaired body image, but sexual function and health related quality of life were not significantly different compared to patients with functioning pouches. Probiotics did not improve poor pouch function compared to placebo.

Key words: restorative proctocolectomy; long-term function; pouch failure; sexual function; probiotics.

List of publications

This thesis is based on the following publications and manuscript, which are referred to in the text by their Roman numerals (I-IV):

I. Bengtsson J, Börjesson L, Lundstam U, Oresland T.
Long-term function and manovolumetric characteristics after ileal pouch-anal anastomosis for ulcerative colitis.
Br J Surg. 2007 Mar;94(3):327-32.

II. Bengtsson J, Börjesson L, Willén R, Oresland T, Hultén L.
Can a failed ileal pouch anal anastomosis be left in situ?
Colorectal Dis. 2007 Jul;9(6):503-8.

III. Bengtsson J, Lindholm E, Berndtsson I, Nordgren S, Oresland T, Börjesson L.
Sexual function after failed ileal pouch-anal anastomosis.
Accepted for publication in Journal of Crohns and Colitis

IV. Bengtsson J, Adlerberth I, Östblom A, Saksena P, Nordgren S, Oresland T, Börjesson L.
Effect of probiotics (*Lactobacillus plantarum* 299®, *Bifidobacterium infantis* Cure 21®) in patients with poor ileal pouch function: a randomised controlled trial.
Manuscript

Abbreviations

ECP	Eosinophilic cationic protein
FAP	Familial adenomatous polyposis
FSFI	The female sexual function index
HQoL	Health related quality of life
IBS	Irritable bowel syndrome
IIEF	The international index of erectile dysfunction
IPS	Irritable pouch syndrome
MPO	Myeloperoxidase
PDAI	Pouch disease activity index
RPC	Restorative proctocolectomy
SF-36	The Short Form (36) Health Survey
UC	Ulcerative colitis

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Paper I - IV

The pelvic ileal pouch in ulcerative colitis

Ulcerative colitis (UC) is a chronic mucosal inflammation of the rectum and colon. The first line of treatment is medical therapy in the form of corticosteroids, 5-ASA preparations, immunomodulatory drugs or "biologic" treatment (anti-TNF-α). Approximately 30% of the patients will at some point require surgery. There are two principal reasons for surgical treatment, which are medically refractory disease either in the acute or chronic setting, or development of dysplasia or even malignant transformations of the inflamed mucosa. Chronic disease constitutes about 50%, acute colitis 40% and neoplasia 7% of the indications for surgery[1]. Restorative proctocolectomy (RPC) is the surgical treatment of choice, with ileo-rectal anastomosis and conventional ileostomy as other alternatives.

Historical perspective

Irrigation and ileostomy
Surgical treatment for UC began to evolve more than a century ago with the efforts to irrigate the diseased colon and rectum, first via a sigmoidostomy[2] and later through an appendicostomy or ceacostomy. Debate eventually arose concerning the necessity of irrigation, putting the main focus on letting the diseased bowel rest. This was possible by creation of an ileostomy[3]. The next step taken was excision of the diseased bowel as a subtotal colectomy or a panproctocolectomy combined with an ileostomy. The ileostomy was initially hampered by problems, mainly due to the consequences of serositis and poorly functioning stomal appliances. The first problem was rectified by eversion of the mucosa, described by Brooke in 1952[4]. The continuous development of stomal appliances has considerably improved the quality of life for ostomists. In spite of such improvements, defecation through the normal route has of course been a desire for the majority of patients.

Ileorectal anastomosis
Restoration of bowel continuity in the form of an ileorectal (or ileosigmoidal) anastomosis after colectomy was performed with acceptable functional results, reported among others by Aylett[5]. The risk for cancer development and symptomatic relapse of the disease limited a widespread use. However, in present-day Sweden, ileo-rectal anastomosis is considered a main option for reconstitution of intestinal continuity[6]. The historical reported failure rate of about 50% has since decreased to 14% with a 10 year follow-up[7].

Continent ileostomy
Another alternative explored was the straight ileoanal anastomosis (without a pouch). Today, the method has been abandoned due to functional problems, such as incontinence and urgency[8][9]. Incorporation of a reservoir as an adjunct to the ileoanal anastomosis were first made in animal experiments during the 1950 and 60s[10][11]. The next and major step towards today's pouch surgery was the construction of the continent ileostomy by Nils Kock, presented 1969[12]. In spite of the presence of an abdominal stoma and the need for catheter evacuation, the continent ileostomy is a well functioning alternative to the conventional ileostomy. The main long-term problem is the relatively frequent need for revisional surgery (mainly due to problems with the nipple segment or fixation of the reservoir to the abdominal wall)[13][14].

Restorative proctocolectomy

Approximately ten years following the first publication on the continent ileostomy, Parks an Nicholls presented the restorative proctocolectomy including a pelvic ileal pouch-anal anastomosis, which was partly based on the experiences with the continent ileostomy[15]. The functional results where reported as good, except for problems with emptying of the pouch, as more than 50% had to use a catheter for evacuation, owing to the initial construction ("S-pouch") with a relatively long pouch outlet[16]. Alternative pouch designs that solved the evacuation problem were soon to be presented, with Utsunomiya's "J-pouch", until today, being the most frequently used[16-18].

Technical aspects

The J pouch consists of approximately 30 cm of the terminal ileum. Originally, the bowel was opened on the anti-mesenterical border, folded into a j-shape, and sutured to form a pouch. Presently, what is far more common is to do the construction with a stapling device. The ileoanal anastomosis was originally hand-sewn after mucosectomy from the dentate line, but was simplified relatively quickly through the use of a circular stapler (omitting the mucosectomy and leaving a short rectal cuff below the anastomosis). The two different techniques for making the pouch-anal anastomoses have been extensively studied. Most studies show only minor differences in terms of pouch function, e.g. a better night continence for the stapled anastomosis[19].
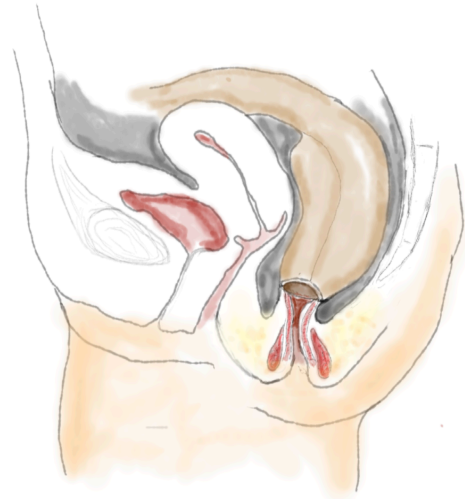
Fig I J-pouch with stapled ileoanal anastomosis
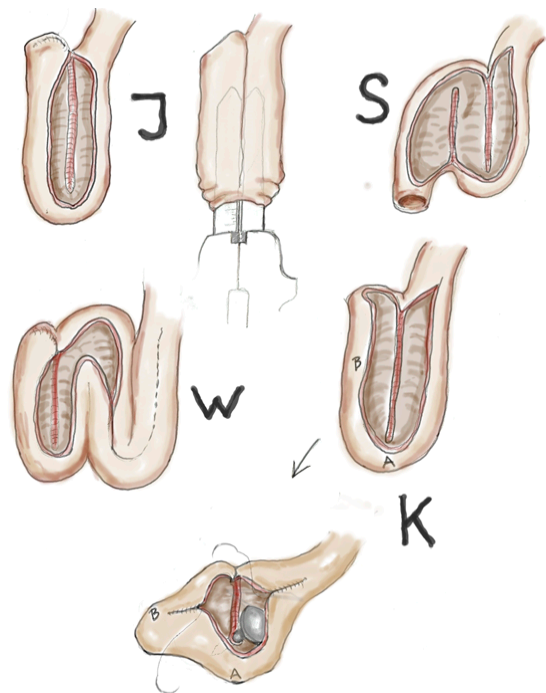
Fig II Alternative pouch designs

Another concern regarding the stapled anastomosis is the potential risk for development of dysplasia and malignancy in the remaining rectal mucosal cuff [20 21].

Another alternative pouch design, still employed in our own institution, is the "K-pouch", which can be described as the original continent ileostomy without the nipple segment. The K-pouch develops a spherical design, resulting in a proportionally larger volume for the length of ileum used[22]. The "W-pouch", a design promoted by Nicholls, also attains a similar

spherical appearance. There is some evidence that both the K- and W-shapes have slightly superior function than the J-pouch[23][24].

A defunctioning loop ileostomy is used by the majority of surgeons for reducing the potentially devastating consequences of a leak in the ileoanal anastomosis or from the suture lines in the pouch.

Pouch physiology

Rectum and the anal sphincters provide an integrated function for continence and evacuation[25]. Substantial parts of the physiological mechanisms involved are still unknown. The objective for reconstruction after proctocolectomy is to establish a good functional outcome, i.e. an acceptable defecation frequency, no urgency, easy evacuation of faecal content and continence. Some factors related to the functional outcome have been identified and studied in patients who have undergone RPC. These include anal sphincter function, pouch volume and pouch compliance. It is important to emphasise that pouch function is a complex composite variable that also includes other factors (small bowel function, pelvic volume, psychological factors etc.).

The anal sphincter complex is the major contributor to anal continence. The internal anal sphincter is a smooth muscle and the most important contributor to the resting anal pressure. The basal tone depends primarily on myogenic factors but is neurohumoraly regulated[26] and thus provides for passive continence. The external sphincter muscle, the puborectalis muscle and the other striated pelvic floor muscles can be considered a unit that is voluntarily controlled. The functional correlate of the external sphincter performance is the maximum squeeze pressure. Several studies have demonstrated that pelvic pouch surgery leads to reduced anal pressure. The pressure seems to recover over time, though not to pre-operative levels[27-29]. However, the impact of the reduced resting anal pressure on continence after RPC is conflicting. Some studies demonstrate a correlation between low pressures and poor continence[28][30-32] while other studies do not [33-35]. It seems plausible that other factors also contribute to incontinence, i.e. the deformation of the anal canal due to the surgical trauma and loss of/scaring of the anal transitional zone[36]. The relation between pouch pressure and resting anal pressure has also been studied as a potential parameter related to incontinence. In several studies, episodes of incontinence were associated with high-pressure waves in the reservoir; though diminished resting anal pressure was also recorded[29][37][38].

Pouch volume increases with time during the first year after construction, but seems after that to be relatively stable[39]. The pouch volume is related to the type of construction, with the lowest volumes, for equal length of ileum used, recorded for the J-pouch. Pouch volume and compliance are also determinants for pouch function and in some studies these parameters correlate to frequency of pouch emptying; a large pouch volume and compliance leads to a lower bowel frequency[30][32][39][40]. However, in the study by Öresland et al.[39], only about 20% of the total variance in functional outcome was explained by pouch volume and compliance.

Histopatology of the ileal pouch

Histological changes in the ileal mucosa of the continent ileostomy have been observed soon after construction, including a decrease in villous height and signs of an increased cellular turnover[41]. Those changes were stable for an observational period of 2 years, but a lower cell turnover and longer villi were seen after a follow-up period of 6-10 years[42]. No dysplasia was

described in those early studies. A 30-year follow-up study from this institution conducted on 40 patients showed that slightly more than 70% of the patients had a normal mucosa or mild to moderate villous atrophy with none to moderate inflammation. Remaining patients had marked atrophy with severe inflammation. No high grade dysplasia or cancer was found, but one and three patients, respectively (two independent groups of pathologists assessed the samples), demonstrated low grade dysplasia[43].

The same pattern of mucosal changes has been confirmed in the pelvic pouch[44-48], including a long-term follow-up from our institution[49]. For the majority of patients, there is a picture of a varying degree of chronic inflammation with or without change in villous architecture[50]. A change of the mucin production, from the sialomucins (predominant in small bowel) to colonic sulfomucins has also been reported[50 51]. These findings, together with a "flattening" of the mucosa, may represent a form of colonic metaplasia, though not complete[52-54].
Development of dysplasia in the pelvic pouch is a known reality, but appears to affect a very small number of patients. It seems that a prerequisite is a more severe degree of chronic inflammation in the pouch[49 50 55 56]. Even under these circumstances, high-grade dysplasia seems to be rare[49 50]. However, it is also of importance to be aware of the difficulties associated with establishing a secure/definitive dysplasia diagnosis in the presence of severe inflammation, especially when combined with mucosal regeneration[57]. The evident implication concerning dysplasia is the potential risk for malignant transition; though it is not known if small bowel (pouch) dysplasia has an equivalent potential to that in the colon for malignant transformation.

The first case of adenocarcinoma in a pelvic pouch was reported 1990, and up to date another 40 cases can be found in the literature[56 58 59]. The majority of cases seem to have their origin in rectal mucosal remnant below the anastomosis, or in the anal transitional zone. One proposed risk factor is a history of dysplasia or cancer in the excised colon/rectum. It seems obvious from the case reports that mucosectomy, due to deposits of mucosal remnants, does not offer secure protection[56 59].

Bacteriology of the pouch

Acting concurrently with the histological changes in the pouch, there is also a time dependent change in bacterial composition and counts. A more colon-like situation is established. Compared to the normal ileum and ileostomy, more bacteria per gram of content and a greater ratio of anaerobes to aerobes are recorded[45 60 61]. This field of research is now in a phase of rapid development due to the introduction of molecular techniques, as a complement to traditional culture-based methods[62 63]. A consequence of this is the discovery of a vast number of hitherto uncultured species. Former estimates from culture-based studies of around 300-400 species in the colon have now been revised; based on molecular techniques, about 100 times the number of species have been found[63 64].

The function of the pelvic ileal pouch

Functional results

Variables for the assessment of functional outcome after RPC vary between studies. However, the most used are bowel frequency (day and night time), incontinence/soiling and urgency (urge to defecate). The need to wear a pad, problems with evacuation of faecal content, need to take antidiarrhoeals, perianal soreness (i.e. because of soiling) and diet restrictions are sometimes also reported. Directly after surgery, bowel frequency tends to be high and a varying grade of incontinence is a common finding. However, function gradually stabilizes and improves, usually within the first six months.

There are a large number of reports concerning the functional outcome after RPC. Since a majority of patients are young (with a life-expectancy of more than 40 years), the long-term perspective is the most interesting. Considering data from larger studies with follow-up times of up to 20 years, a daytime bowel frequency of 5-7 occurrences, with a fairly large interpersonal and sometimes day-to-day variation, is commonly reported[65-72]. Corresponding figures for night time frequency are 0-2, also with a substantial variation; a considerable number of patients do not need to defecate during the night[65-72]. Reported frequencies of episodes of incontinence are more varying. This is an effect of several ways of reporting the data, but also due to variable definitions (soiling – seepage – incontinence). Daytime continence is perfect for 50% - >80%[65-68 70-72] and major incontinence is reported in 5-17%[66 68 73]. Perfect continence at night varies from 30-75%[65 67 68 70-73], with major disturbances in 13-47%[66 68 73]. Between 13-55% of the patients use a protective pad[65 68 74]. Urgency, in any form, is reported in 9-23% of the patients[65 69 70 72]. Perianal soreness, from occasional to permanent, is reported in two studies at a frequency of about 60%[65 69]. Around half of the patients use some form of medication for the regulation of stool consistence/bowel frequency[65 68 72 74].

These long-term data are hampered by the lack of common definitions for the measured variables, and when studied in detail, the relatively small numbers of patients studied at the longest follow-up times. It must also be acknowledged that patients with diagnoses other than UC i.e. Familial Adenomatous Polyposis (FAP) and Crohn's disease are included in some of the studies, though in an obvious minority[67 70 73].

Health related Quality of Life

RPC is an operation with the objective to improve the quality of life and as such it has to be evaluated not only by functional determinants as described above, but also from a quality of life perspective.

Several studies have explored this issue; however, due to a variety of instruments used and variation in follow-up time, comparisons between them are not easy. With awareness of those limitations, the health related quality of life (HQoL) seem overall to be positive[65 67 68 75-78] and comparable to that of the normal population[65 76]. Even if the majority experiences a good HQoL, it has been shown that a poor functional outcome correlates to an inferior result[65 67 76 77]. Furthermore, some studies indicate that pouch patients in the older age groups have a somewhat reduced HQoL (probably linked to a worse pouch function)[67 68 76]. It should be

emphasized that recorded HQoL after RPC has to be viewed in light of the fact that most of the patients with RPC have a poor preoperative HQoL (for a recent review regarding HQoL and UC, see Irvine [79]).

Sexual function

Pelvic surgery yields the risk of incurring damage to nerves for sexual function. In this context, it could be emphasised that this problem is valid for both sexes. Furthermore, there is a risk for deterioration of female fertility; the most common explanation for this is adherences to the ovaries and fallopian tubes induced by surgery. Conversely, there is a potentially favourable effect on sexual function by excision of inflamed bowel with an overall improved health status.

From a methodological point of view, the situation is similar to that of HQoL; thus, multiple instruments have been used and solid validation is absent for many of them. Furthermore, presumably due to the sensitivity of the issue, low response rates are common. An additional problem is recall bias; most of the studies rely on a remembrance of the situation/circumstances before surgery.

Results from studies of sexual function in patients with RPC differ in their conclusions regarding both sexes. Some studies indicate an unaltered or better function after reconstruction, while other report results in the opposite direction, see table I.

	N	Method	Validation Of method	Sex activity	Dyspareunia	Erection	Orgasm	Conclusion	Response rate
1. Metcalf [80] 1986	50 RPC/50 CI ♀	Interview	No	Increased	Decreased	-	=	Enhanced function	NS
2. Öresland [81] 1994	21 ♀	Questionnaire (20/21) Interview	No	20/20	5/20	-	14/20	19/20 satisfied	21/60 invited, participated
3. Damgard [82] 1995	23 ♀ 26 ♂	Interview	No	♀increased ♂ =	0/23	25/26	♀= ♂ 25/26	Improved	No decline
4. Tiainen [83] 1999	51 ♀ 44 ♂	Questionnaire	No	NS	Increased	38/44	♀=	Improved	95/110
5. Berndtsson [84] 2004	18 ♀ 25 ♂	Questionnaire	No	Increased	Increased	25/25	=	Improved	43/48
6. Gorgun [85] 2005	122♂	Questionnaire (IIEF)	Yes	Increased?	-	?	=	Improved	122/500
7. Davies [86] 2008	20 ♀ 22 ♂	Questionnaire (FSFI, IIEF)	Yes	NS	NS	NS	NS	♀improved ♂ =	42/110, at 12 months
8. Michelassi [87] 1993	26 ♀ 24 ♂	Diary	No	NS	22%	0/26?	NS	?	NS
9. Counhian [88] 1994	110♀	Questionnaire	No	=	Increased	-		Impaired	110/206
10. Bambrick [89] 1996	92 ♀	Questionnaire	No	=	Increased	-	=	Impaired?	92/262
11. Hueting [90] 2004	76 ♀ 35 ♂	Questionnaire	No	NS	30%	26% (see below)	NS	Impaired	11/137
12. Ogilvie [91] 2008	83 ♀	Questionnaire (FSFI)	(Yes)	NS	NS	-	NS	Impaired?	83/166
13. Larson [92] 2009	74 ♀ 51 ♂	Questionnaire (FSFI, IIEF)	Yes	NS	NS	NS	NS	Se below	125/289

Table I RPC and sexual function. CI: continent ileostomy. NS: not stated. IIEF: International Index of Erectile Function. FSFI: Female Sexual Function Index.

Fertility and pregnancy

Compared to patients with medically treated UC, or to a reference female population, fertility seems to be reduced following RPC[81 88 93-98]. As for sexual function, the studies on fertility are subject to criticism. The definition of fertility differs between the studies, although in most studies it is defined as "failure to become pregnant during 12 months of unprotected intercourse". The response rates vary (if reported[93 94]) from just above 30% to over 80%. Furthermore, nearly all studies are retrospective, with the risk of potential recall bias.

Reported infertility rates vary from 16-97%, compared to 0-38% in the medically treated patients[81 88 93-98]. It is important to emphasise that in patients with infertility, a high success rate is reported for *in vitro* fertilization; interestingly, probably better than in the background population[96].

When pregnancy occurs in a patient with RPC, there seems to be no increased risk for the foetus or for major pouch related complications[99 100]. Bowel frequency, incontinence episodes and pad-usage all increase during pregnancy, especially in the third trimester, but seem to return to pre-pregnancy levels during the first year after delivery[100 101]. However, there is a controversy regarding the optimal method for delivery. Sphincter status has been evaluated with endo-anal ultrasound. Defects were found in about 50% of women who had vaginal delivery compared to 13% of those who underwent caesarean section[102]. However, there is reason to believe that some of those occult injuries could affect continence function in a long-term perspective.

Reasons for impaired functional outcome

RPC is a major procedure, marred with the risks of anastomotic leaks, bleeding, prolonged postoperative paralytic ileus, wound-infection, as well as more general adverse events, such as urinary tract infections, airway problems etc. However, the frequency of these more unspecific complications to major surgery does not seem to be more prevalent in RPC than in other procedures of the same magnitude.

Septic complications

A septic complication after RPC may or may not be associated with the pouch. Considering complications directly related to the pouch, a septic complication can be defined as leakage from the ileo-anal anastomosis or from the suture lines in the pouch. The patients presents with a pelvic abscess, a fistula, or both[103-106]. The reported frequency of septic complications varies from well under 10% to nearly 40%[103 104 106-113]. The substantial variation could be explained partly by the different definitions, length of follow-up and surgeons experience. Septic complications can emerge early or surprisingly late (years after primary surgery) after RPC, though the definition of those time frames varies between studies[104 106 109]. Several authors have attempted to identify risk factors for septic development of complications. In some studies, steroids was a risk factor[104 109 114]; however, other studies did not confirm those results[115]. Surprisingly, in one study, steroids was associated with increased pouch salvage after septic complications[106]. The mechanism behind a potential detrimental effect of preoperative steroid-use currently remains unknown. Impaired wound healing or down-regulation of the immune system are frequently suggested theories. However, use of steroids could also be a marker of a subset of more clinically deranged patients. Beside steroids, preoperative misdiagnosis of Crohn's disease[112 116], preoperative anal sepsis/pathology and female sex are all suggested risk factors[109 112 116].

Timing and method of choice for treatment of a septic complication after RPC are dependent on the type of complication and on the patient's clinical condition. Septic collections should be drained rapidly. Several studies have demonstrated that septic complications are one reason for pouch failure. The frequency of pouch failure seems to be associated with the intervention required to solve the problem. In one study, 87% of the patients retained the pouch when percutaneous drainage was sufficient; on the contrary, approximately 50% was recorded for patients who needed a more extensive procedure[106]. Furthermore, salvage surgery due to septic complications seems to be associated to worse pouch function (and thus HQoL)[117 118].

Among the types of septic complications, pouch-vaginal fistula has been extensively studied. Frequencies from 3 to over 10% have been reported [104 119 120]. Interestingly, the association to other pelvic septic complications, or to technical problems, is not always obvious[116 119-121]. The fistula originates most commonly at, or below the ileoanal anastomosis[105 116 119 121], but the type of anastomosis (hand-sewn or stapled) does not appear to be of consequence[107 112]. Misdiagnosed Crohn's disease seems to be a relatively common causative factor in terms of pouch-vaginal fistula[116 120 121].

The treatment options vary from local repair with different approaches, to major surgical procedures (re-do surgery). Reported success rates vary considerably[119 120].

Pouchitis

Acute inflammation in the continent ileostomy was described in 1976[122]. The clinical picture was characterized by a need for frequent emptying of a more liquid, sometimes bloody intestinal content. Abdominal pain, general malaise and fever were also commonly noted. Incidence figures varied, however frequencies well over 40% were reported. Endoscopy showed a reddened and oedematous pouch mucosa; contact bleeding and ulcerations were occasionally present. Histological examination showed an acute unspecific inflammation in addition to the more or less obligate chronic inflammatory changes[123]. Incidence figures varied, but frequencies well over 40% were reported. Treatment was, for the majority, conservative, with initial salicylazosulfapyridine and in some cases continuous drainage of the pouch[122]. However, it soon became evident that most patients responded favourably to a short course of metronidazole[124].

Not long after the introduction of RPC, studies emerged with reports of similar clinical and histopathological representations in this setting[125-127].

Incidence
Around 50% of patients with UC and RPC experience at least one episode of pouchitis[110 128][129]. Recurrences will likely affect more than 50% of these, but the majority will only experience a few episodes[110 130]. A course of frequent relapses or chronic pouchitis is reported in 5-19%[110 130].

Diagnosis
The diagnosis of pouchitis should ideally be based on clinical, endoscopical and histological findings, as it is demonstrated that these three features do not necessarily coexist[44 131 132]. The first scoring system that gained a more widespread use was the Pouchitis Disease Activity Index (PDAI)[133]. PDAI is based on a previously developed histological scoring index[44 134], and consists of three component scores: symptom, endoscopy, and histology (see Methods , table III).

Etiology
An initial hypothesis was that *fecal stasis,* with subsequent bacterial overgrowth in the pouch, could be responsible for pouchitis[123 124]. However, the theory was essentially abandoned, as it was demonstrated that pouches with evacuation problems did not show accentuated inflammation[135 136]. Furthermore, there was no correlation between the grade of inflammation and pouch residual volume[44].

The fact that a majority of patients with pouchitis respond to antibiotics has motivated several qualitative as well as quantitative studies on *pouch microbiota*. These studies are based on bacterial cultures. In summary, no consistent pattern has been shown. There are reports of an increase in total bacterial count in patients with pouchitis[137 138], although others have reported no differences[139 140]. Some studies have recorded an increase in the number of aerobes[138 141], while others show a decrease in the count of lactobacilli and bifidobacteria[142], or an increase in sulphate reducing bacteria[143 144]. Shortcomings of the studies are the varying definitions of pouchitis and the generally small numbers of patients. Furthermore, the fact that a majority of the related bacteria is impossible to culture makes the relevance of the results uncertain. Studies using molecular techniques are emerging, but with diverging results[62 145].

Short chain fatty acids are produced by anaerobic bacterial fermentation of undigested dietary carbohydrates. A reduction has been found in patients with pouchitis. However, the application of topical short chain fatty acids served to deteriorate symptoms[146-148].

Bile salts are deconjugated by bacteria in the distal small bowel (pouch) into secondary bile acids. These can be cytotoxic and one hypothesis stated that secondary bile acids could induce

pouchitis due to the higher count of bacteria and consequently larger amount of deconjugated bile acids in the pouch compared to the normal distal ileum[149] [150]. As a single explanation, the theory is contradicted by the much lower incidence of pouchitis observed in patients with FAP.

Another theory has been that when the *pouch mucosa* develops into a more colon like one, similar pathogenic mechanisms that induced UC could be activated[151]. An argument against pouchitis being considered a *"recurrence" of UC,* is based on the excellent effect of antibiotics in patients with pouchitis[152].

There is some evidence for a *genetic susceptibility* for the development of pouchitis[153-155].

It has been proposed that mucosal (intermittent or chronic) *ischemia* plays a role in the pathogenesis of poucitis[156]. The strongest evidence against this is again the far lower incidence in patients with FAP with the same pouch construction. Allopurinol, a free-radical scavenger, has also been studied in a randomized trial, but has been found to have no prophylactic effect against pouchitis[157]

One flourishing theory is that an imbalance exists in the bacterial content within the pouch *(dysbiosis),* which results in immune activation and inflammation in susceptible individuals[158]. Part of the evidence for this is the beneficial effect of antibiotics and perhaps probiotics. However, an explanation on how/why dysbiosis develops is still lacking.

Coffey et al. have recently proposed a *unifying theory,* which is that colonic metaplasia develops in the pouch with the increased synthesis of sulphomucin, which is a substrate for sulphate reducing bacteria found in elevated counts in pouchitis[159]. Sulphate reducing bacteria produces H_2S, which is observed in active pouchitis and has been correlated with disease severity; H_2S (could) induce inflammation. Among the arguments for the theory are statements stating the reduction of sulphate reducing bacteria and H_2S with antibiotics and exclusive colonisation with these bacteria in UC pouches.

Risk factors

Several conditions have been proposed as being associated with a higher risk for the development of pouchitis. Among these are extensive colitis[160], backwash ileitis[161] [162], primary sclerosing cholangitis[162] and the use of NSAIDs (non-steroidal anti-inflammatory drugs)[163].

Specific causes for pouchitis

For a proportion of patients with pouchitis, the disease could have a specific etiology. Secondary pouchitis seems to take a more chronic, antibiotic-refractory course. Colonisation of a pouch with *Clostridium difficile* could be a relatively common situation and this agent has been reported in patients with chronic pouchitis[164].

Cytomegalovirus has also been observed in patients with chronic pouchitis[165-167].

NSAID drugs could provide a clinical picture resembling pouchitis[168].

Crohn's disease could also be considered as a secondary pouchitis with a clinical and endoscopically similar picture to that of idiopathic pouchitis (See below for further discussion on Crohn's disease).

Treatment

Antibiotics are the first line treatment for idiopathic pouchitis. In routine clinical praxis, metronidazol and ciprofloxacin are by far the drugs most used, either as a single treatment or in combination. The evidence for the use of antibiotics is primarily the observed favourable effect in clinical practice. A randomized controlled study compared metronidazol and placebo in 13 patients with chronic recurrent pouchitis[152]. Patients who received metronidazol reported a reduction in bowel frequency, but there were no differences in either the

endoscopic or histological grades of inflammation and furthermore, no reduction in symptoms. Metronidazol and ciprofloxacin were compared in a randomized controlled study on 16 patients, with a significant reduction in PDAI for both treatments. Significantly more patients had remission in the ciprofloxacin group[169]. In the case of treatment failure on either metronidazol or ciprofloxacin, a change to the other drug or a combination of both could be attempted[170]. A clinical observation is that some patients with a chronic, recurrent course of pouchitis could retain remission with antibiotics on a low dose every other day or even less frequently[171].

There is some evidence, based on two randomized controlled studies, for the use of probiotics (VSL#3 a mixture of eight strains of probiotics: *Lactobacillus (L. casei, L. plantarum, L. acidophilus, L. delbrueckii subsp. Bulgaricus), Bifidobacterium (B. longum, B. breve, and B. infantis), and Streptococcus salivarius subsp. Thermophilus*) for the maintenance of remission of chronic or recurrent pouchitis after induction of remission with antibiotics[172][173]. Another randomized controlled study assessed VSL#3 as a primary prophylaxis after RPC, and reported a significantly lower incidence of pouchitis in the patients receiving probiotics[174]. Lactobacillus GG has, in another randomized controlled study, showed no effect compared to placebo[175].

The mechanisms behind a possible beneficial effect of probiotics are manifold, including the competitive blocking of pathogens, production of bactericidal substances, modulation of the immune system and the barrier function (for recent reviews, see: [176][177]). Besides the aforementioned studies on pouchitis, probiotics have been studied in several other areas of gastrointestinal disease. The best evidence for a beneficial effect is in childhood diarrhoea, especially rotavirus infection[178]. There is also some evidence for probiotics as prophylaxis of traveller's diarrhoea[179], in maintenance of remission in UC (as good as mezalamine)[180] and in irritable bowel syndrome[181].

Pre-pouch ileitis

Inflammatory changes in the pre-pouch ileum, not associated to CD or to the use of NSAIDs have been demonstrated in the continent ileostomy and have recently been described also in the pelvic pouch[182][183]. The condition is denoted pre-pouch ileitis and seems to almost exclusively affect patients with pouchitis[182]. Pre-pouch ileitis can be found in asymptomatic patients but could, similarly to pouchitis, be associated with acute symptoms or take a more chronic course. The incidence is reported to be 6-14% for the general pouch population (UC), and 13-24% in patients with pouchitis[138][182]. Pre-pouch ileitis has been proposed as an equivalent to backwash ileitis in patients with UC. However, a history of backwash ileitis does not seem to be correlated to development of pre-pouch ileitis[182]. Interestingly, antibiotics seem to be an effective treatment for the majority of patients with pre-pouch ileitis[184].

Cuffitis

Inflammation of the retained rectal mucosa is denoted cuffitis. The condition is seen in 10-40% of the pouch patients (UC). This condition can be considered as remaining UC and the rectal remnant displays varying grades of macro- and microscopic inflammation. The majority of patients with cuffitis are asymptomatic, but the condition could mimic that of pouchitis and thus be associated with urgency, perineal/anal pain and bleeding[185][186]. The treatment is predominantly local, with steroids or 5-ASA preparations[185].

Poor pouch function and irritable pouch syndrome

It has been shown that 25-50% of the patients with typical symptoms for pouchitis, de facto either possess no signs of inflammation in the pouch or other inflammatory entities, i.e. cuffitis or Crohn's disease[187] [188]. Shen et al. (2002) proposed the term irritable pouch syndrome (IPS). The condition consists of a clinical picture with increased bowel frequency, urgency, bloating and abdominal cramps/pain/pelvic discomfort. The other criterion is absence of endoscopic or histological signs of acute inflammation in the pouch, or in the rectal cuff[188]. The name IPS deliberately alludes to irritable bowel syndrome (IBS); the two conditions have symptomatic similarities and also share the absence of specific macro- and microscopical findings. Depression and anxiety, prevalent in patients with IBS[189], seems to be co-morbid entities[190] [191]. Other findings that could further strengthen the connection to IBS are reports of an increased level of enterochromaffine cells and intestinal hypersensitivity in IPS, observations that are also reported in IBS[192-195].
The IPS concept has been challenged; others claim that the IPS concept is merely a blanket diagnosis, which actually covers a mixture of non-inflammatory disorders with symptoms similar to pouchitis. Furthermore, some of these patients could be amenable for a specific treatment, i.e. patients with bacterial overgrowth or bile acid malabsorption[196].
Reports on treatment for IPS/functional pouch disorders are anecdotal. In the original article, about 50% of the patients with IPS improved on a combination of "reassurance", dietary modification, dietary fibre supplementation, antidiarrheal, antispasmodics, and antidepressant therapy"[188].

Anatomical causes of poor pouch function

Long outlet segment
In the first published series with RPC, the pouch used was of the "S-type", with a several centimetre long outlet, and it soon became evident that a majority had problems with evacuation of the pouch. The S-type pouch was subsequently modified with a shortened outlet; the problems diminished, although not entirely. The evacuation problems associated with a long outlet segment are well recognized and the problem can be avoided by employing other pouch types and leaving a rectal stump of no more than 1-2 cm.

Stricture
Stenosis/stricture at the level of the ileoanal anastomosis is reported in 4-40% of RPC patients[69] [197-200]. This wide incidence range could be due to varying definitions of a stricture[200]. There could be an increased risk for fibrosis and a subsequent stenosis after an anastomotic leak/septic complication, or tension/ischemia in the anastomosis. However, reports supporting a relationship are conflicting[198 200]. The impact of stapler size has also been studied and has been found to have no impact on the stricture incidence[200]. Patients with stricture could be asymptomatic, but could present with straining, increased bowel frequency and anal/perineal pain[201]. The vast majority of strictures are short and web like and can be easily treated with dilatation. However, there is some evidence that pouch function is suboptimal, even after simple dilatation[201]. Long, fibrotic strictures can be a major problem and in some patients, a pouch advancement procedure is necessary[69 197 199 201 202]. Pouch failure caused by stricture has also been reported[69 199 201].

Stricture/obstruction of the afferent limb to the pouch is another, albeit infrequently reported problem. The condition is sometimes referred to as "afferent limb syndrome". Crohn's disease, post-surgical adhesions with acute angulation of the pouch inlet or intussusceptions

of the distal ileum, could cause the obstruction[203] [204]. Treatment options are endoscopic dilatation, resection, or bypass of the affected segment[203] [205].

Crohn's disease

Unrecognized or new diagnosis of Crohn's disease was identified as a considerable problem in patients with continent ileostomies and was regarded as a major source of complications and failure[206]. Interestingly, fairly good outcomes have been reported with continent ileostomy in selected patients[207]. Frequencies of missed Crohn's disease diagnoses in RPC patients is reported in about 2-13%, depending on the diagnostic criteria, duration of follow-up, study sample size etc. [208-211].

The clinical manifestations of Crohn's disease in RPC patients include pouchitis-like symptoms, abscesses, fistulas or bowel strictures (in, near or remote from the pouch). Patients occasionally present with fever, weight loss and other general symptoms. The endoscopic picture of the pouch is often difficult to distinguish from the one seen in idiopathic pouchitis. Ulcerations in the afferent limb have been suggested as markedly associated with Crohn's disease. Biopsies of the pouch should be taken, but they are most commonly inconclusive. Granulomas seem to be uncommon; one study reported a frequency of 10%[212]. In many of the studies, there is a mixture of patients with Crohn's disease diagnosis based on histology and a diagnosis purely on clinical grounds, which renders interpretation of results difficult[212-214]. There is also a potential bias introduced by comparing patients with a Crohn's disease diagnosis established on the colectomy/rectum specimen and patients with Crohn's disease diagnosis made after an actual complication or manifested pouch failure. The former group could very well have a Crohn's disease phenotype with a more favourable clinical course, indicated by a more unfavourable course for the patients with a diagnosis established based on complications[214] [215]. Overall however, the frequency of complications is increased in the Crohn's disease pouch patient compared to the patient with UC[213-215].

The pouch failure rate for patients with Crohn's disease in the pouch is reported to be between 10-50%[214-217]. The large variance likely depends on the same issues with patient selection, as for (Crohn's disease) complications.

Reports on specific medical treatment for patients with Crohn's disease established in a pouch are scarce. Azathioprine, 5-ASA preparations and cortisone, either topical or systemic, are used, basically in the same regiments as for patients without RPC. However, success rates are poorly reported. Some results, besides pure case reports, have emerged on biologics (infliximab and adalimumab). A remission rate of 60-70% is reported in the short-term perspective[218] [219].

Indeterminate colitis

In about 10% of patients with colitis, the definite UC or Crohn's disease diagnosis could not be made[220]. Initially, the indeterminate colitis diagnosis was made on the colectomy specimen, but a shift to classify patients as indeterminate colitis pre-colectomy could be seen[221]. Indeterminate colitis could be further sub-classified into indeterminate colitis with UC predominance, with Crohn's disease predominance and "pure indeterminate colitis". A proportion of patients with RPC and indeterminate colitis convert to Crohn's disease over time, with reported figures between 6-16 %[208] [217] [222]. For those patients with RPC and an indeterminate colitis diagnosis who do not convert to Crohn's disease, the functional outcome for the majority seems to follow that of the ordinary UC patient, though a slightly increased frequency of complications and failure is seen in some studies[208] [217] [222].

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The failing ileal pouch

Salvage surgery

As mentioned above, RPC is a major procedure and the optimal (surgical) management of different complications remain continuous points of contention. Local perineal procedures have been used predominantly to deal with low perianal/pouch vaginal fistulas and short strictures. Success, defined as salvage of the pouch with more or less acceptable function are reported in 40-75% (higher figures when only drainage in some form solved the problem)[223-225]. For more complex problems, an abdominal or a combined abdominal/perineal procedure is necessary. Extent of the surgical procedure depends on the specific problem(s) encountered. The options include construction of a completely new pouch, augmentation procedures, pouch revisions and, after resection of a stricture or retained rectal mucosa, pouch advancement. In most reports, septic complications with fistula and stenosis/fibrosis are the most common reasons for salvage surgery[224-229]. In most studies, the success rate seems to be worse after salvage surgery due to septic complications and in patients with Crohn's disease[224 227 229]. However, the largest study up to date reported similar positive outcomes for septical complications[228]. Pouch salvage is reported from 70 to over 90% in studies that cover more than complications related to sepsis[224 225 227-229]. It is important to take the issue of patient selection into account when interpreting these results; many of the reports come from large referral centres, and the external validity is unclear. Finally, it must be emphasised that the salvage of the pouch does not necessarily mean a preserved good function.

Pouch failure

Pouch failure is defined as the excision or indefinite diversion (variably specified in studies as more than 1/2 to 2 years) of the pouch with a loop or end ileostomy. Conversion of the pouch to a continent ileostomy could be seen as a special case of failure. Hueting et al. used a meta-analytical approach in a survey of complications and pouch failure published until the year 2000[230]. The pooled pouch failure rate at a median of 3 years follow-up was 6.8% (5.4–8.4, 95% confidence interval) based on 39 studies (with a variation of 2.3 – 24% between the studies). The failure rate increased to 8.5% (5.4–13.2, 11/39 studies) after a follow-up time of at least 5 years. There was no obvious association between failure rate and study sample size or publication year. However, the variation in failure frequency was larger between the smaller studies. The failure rates in studies published after the year 2000 are in the same range[65 68 70 72 103 231-233].

The most frequent reason (in some studies over 50%) for failure is a septic complication[103 233]. Poor function due to anatomical reasons (i.e. stricture, retained rectal mucosa) or no obvious cause, follows next in order as reasons for failure[233 234]. Chronic pouchitis seems to be a relatively uncommon cause for failure[233].

Crohn's disease as a reason for pouch failure is a complex factor to assess. Crohn's disease can be recorded as a separate reason. However, the clinical picture in a patient with Crohn's disease can be often be split into a variety of symptoms or signs (poor function, pouchitis, fistula etc.) and the most evident one recorded as reason for failure. Furthermore, as mentioned above, criteria for Crohn's disease vary between studies[103 235].

Conversion to continent ileostomy

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An alternative to excision or diversion in the case of pouch failure is conversion to a continent ileostomy. The Cleveland Clinic in Ohio reported outcomes for 64 patients; 95% had a functioning continent ileostomy 4.2 (1-19) years after conversion and 45% had required revisonal surgery (mostly due to malfunctioning nipple segment). The majority of patients reported a better HQoL than prior to their conversion[236]. Behrens et al. reported outcome from five clinics on 42 patients, all presenting with failure due to incontinence. In total, 95% had satisfactory function, about 30% had required at least one revision and the overall HQoL (SF-36) increased after conversion. The authors concluded that the converted pouches fared as well as the first pouches[237]. Börjesson et al. showed good function in 10/13 patients with converted pouches after (median) 6 years. Two pouches were excised and eight had at one point required pouch revision[238]. Wasmuth et al. demonstrated good function in 8-11 conversions at a median follow-up of 7 (0-19) years[239]. The experience reported from St. Marks is in contrast to the studies mentioned above; in a group of seven patients, at least six failed and the pouches were later excised[240].

To summarize, conversion is an alternative to a permanent ileostomy for suitable, well-informed patients that are willing to take the risk of additional surgery. The worst-case scenario for these patients is failure of the pouch a second time, with the risk of short bowel syndrome.

Morbidity and HQoL after failure

Considering RPC in a broad perspective, pouch failure must be regarded as a major problem. Outcome after pouch failure, in terms of morbidity and HQoL, has not been extensively studied. Karoui et al. reported a total morbidity of 62% in the failure patients (including ileus, septic complications and wound healing problems). The most common long-term problem was delayed healing of the perineal wound (40%) after pouch excision, requiring a median of two (1-6) additional surgical procedures[240]. In another study by Prudhomme et al., 7/24 patients had problems with persistent perineal sinuses (6/7 with a final Crohn's disease diagnosis)[235]. Lepistö et al. reported inferior HQoL (SF-36) for 19 patients after pouch excision, compared to both patients with functioning pouches and to a reference population[241]. Das et al. compared HQoL (SF-36 and Cleveland global quality of life score) in patients with excision of the pouch to failure patients with indefinitely diverted pouches and concluded that there was no difference. However, compared to a UK reference population, both groups showed reduced levels in all SF-36 domains[242]. These results were confirmed in a study from our own institution; patients with failure had an inferior HQoL (SF-36) compared to patients with functioning pouches, as well as an age and gender-matched Swedish reference sample[65].

Aims of this thesis

The aims of the present investigation were to describe and analyze:

° Long-term function after RPC; special focus was placed on manovolumetric characteristics

° Reasons for pouch failure

° Consequences of pouch failure; special focus was placed on sexual function and HQoL

° Histological changes in the mucosa of the permanently deviated pouch

° Potential beneficial effect of probiotics in patients with poor pouch function.

Patients

Study I

The study group was comprised of 42 of the first 97 consecutive patients with UC who underwent RPC at Sahlgrenska University Hospital from 1982 to 1987. Another three patients were examined, but had incomplete data for the 24 months follow-up. They were excluded from the final analysis, except for the impact of possible pouchitis on the functional score at 16 years. All patients had an S- or J- type pouch, mucosectomy and hand-sewn anastomosis. The patients' median age at the time of the study was 53.5 years (range 35-76). A total of 35 patients had J-pouches.

Study II

A total of 620 patients underwent RPC at Sahlgrenska University Hospital between 1982-2004. Fifty-six patients with pouch-failure were identified. Twenty-two patients had the pouch indefinitely deviated with a loop (8) or an end ileostomy. Twenty-three patients had pouch excision and the remaining 11 patients had their pouches converted to a continent ileostomy. Thirteen patients with an indefinitely deviated pouch were included in the study. Nine patients lived far from Gothenburg, or refused to participate.

Study III

The patients were recruited from the same cohort as in study II, with the exception that patients with other pre-RPC diagnoses than UC and Crohn's disease were excluded and extended to include patients operated in 2005. Fifty-four patients with pouch failure out of 594 operated patients were identified. Fifty-one patients with failure were available for the study and 36 patients participated. Four women in the study group had a possible Crohn's disease diagnosis (not histologically confirmed), with no obvious disease activity at the time of study. Fifteen patients refused participation (offering no specified reason). Those patents did not differ regarding age at RPC or at the time of the study. Eighty-three patients with functioning pouches that were matched for age and gender were contacted and 72 accepted to participate as a control group. All patients in the control group had UC.

Study IV

Inclusion criteria for this study were chronic or temporary poor pouch function, UC and >12 months after loop ileostomy takedown.
Thirty-three patients (eight women) were randomized. Twenty-three patients were recruited from the pouch clinic and ten patients from the pouch registry (pouch functional score >7). Another 83 were assessed for eligibility; 64 did not meet the inclusion criteria, or had one or more exclusion criteria. Two patients, allocated to probiotics, were excluded from the final analysis; one due to early withdrawal and one due to protocol violation (use of antibiotics until the day before study start.

Methodological considerations

RPC registry

Since 1982, consecutive data for patients operated on with RPC at Sahlgrenska University Hospital have been registered. The register includes diagnoses, data associated to the surgical procedure (with complications) and follow up data (function, complications). The registry has been regularly validated.

Pouch functional score (I, III, IV)

Pouch function was assessed with a pouch functional score that was developed by our institution[243]. The variables that constitute the score have been commonly used in varying combinations in the literature since the beginning of the RPC era. The instrument is intended to be used as a summary score (0-15, 15 being the worst).

Score items		Score points		
		0	**1**	**2**
No of bowel movements	Day	≤ 4	5	≥ 6
	Night	0	> 1/week	≥ 2/night
Urgency [inability to defer evacuation > 30 min]		no	yes	
Evacuation difficulties [> 15 min spent for evacuation]		no	yes	
Soling, seepage	Day	no	> 1/week	
	Night	no	> 1/week	
Perianal soreness		no	occasional	permanent
Protective pad	Day	no	> 1/week	
	Night	no	> 1/week	
Dietary restrictions		no	yes	
Medication		no	yes	
Social handicap due to pouch/pouch problems		no	yes	

Table II Pouch functional score.

An effort to validate the score has been performed as the score was developed[244]; 60 patients completed the pouch functional score and subsequently plotted their self-experienced function on a visual analogue scale (graded 0-15, 0 being the best possible function). A good correlation between the two recordings was achieved ($r = 0.55$, $p < 0.001$). However, with a tendency for the patients to grade their function better than the summary score point. The relative weight of the score points and the choice of the individual items included, could be challenged. In a recent paper Lovegrove et al. have tried to develop a new score for evaluation of pouch function[245]. The aim was to only include items related to HQoL (Cleveland Global Quality of Life); furthermore, each item in the score was given a weight that correlated to the impact on HQoL. Several of the items in the score proposed by Lovegrove et al. are similar

the ones in the score used in throughout the present studies (bowel frequency, urgency, grade of incontinence and use of medication). However, some of the items were not included (evacuation difficulties, perianal soreness, diet and social restrictions). Interestingly the item "pad usage" was evaluated but was not significantly correlated to HQoL and thus not included in the final score.

A strength with the used score is that it has been used in several studies from our institution, as well as by others[161 246 247], for more than 20 years. It is also used for functional assessment in clinical practice.

Pouchitis Disease Activity Index (IV)

PDAI is based on the triad of symptoms, endoscopic picture and histology[133]. Each component scores from 0-6 (6 worst); the total score ranges from 0-18. A score of ≥ 7 is defined as pouchitis.

Some aspects of the PDAI have been criticised. The histology component focuses only on acute changes. The Heidelberg Pouchitis Activity Score[132] was developed, based on the same histological index as the PDAI. However, this instrument also considers chronic inflammatory changes.

Another problem with the PDAI is the lack of (*solid*) validation. The score was introduced after a study of only 10 patients with chronic/recurrent pouchitis and 15 controls. The authors concluded that the instrument required validation on a larger group of patients with more varying pouch function[140]. To our knowledge, the only serious attempt to validate the PDAI was done in parallel to a validation of the Heidelberg score[132]. In total, 41 patients (103 examinations) were assessed with the two scoring systems and were compared to assessments by two experienced clinicians (in turn based on symptoms, endoscopic and histologic findings). Endoscopic and histological components of both the PDAI and the Heidelberg score seemed to be valid and correlated. However, the symptom component could not be validated and there were no correlations to the endoscopic or histological component score. It was also concluded that the PDAI sensitivity for pouchitis (PDAI ≥ 7) was only 60% with a concurrent

The Pouchitis Disease Activity Index

Criteria	
Clinical	
Stool frequency	
Usual postoperative stool frequency	0
1–2 stools/day > postoperative usual	1
3 or more stools/day > postoperative usual	2
Rectal bleeding	
None or rare	0
Present daily	
Faecal urgency or abdominal cramps	
None	0
Occasional	1
Usual	2
Fever (temperature ≥ 37.8° C)	
Absent	0
Present	1
Endoscopic inflammation	
Oedema	1
Granularity	1
Friability	1
Loss of vascular pattern	
Mucous exudates	
Ulceration	1
Acute histological inflammation	
Polymorphic nuclear leukocyte infiltration	
None	0
Mild	1
Moderate + crypt abscess	
Severe + crypt abscess	
Ulceration per low-power field (mean)	
None	0
25%	1
25–50%	2
50%	3

Table III PDAI

specificity 96%. A cut-off for pouchitis at ≥5 points was proposed as a more useful level since the sensitivity increased to about 80% (specificity 67%) with this adjustment.

As a consequence of the low correlation for the symptom component to endoscopy and histology components, a score that omits the symptom component has been proposed[248]. This construction excludes the possibility of a pouchitis diagnosis with practically no signs of inflammation. Contrary to this, Shen et al.[249] have argued for omitting the histology

component. They consider that component inefficient due to time delay and costs and claim that the modification can be done with preserved sensitivity and specificity. None of the proposed modifications has hitherto created impact in the literature.

Manovolumetry (I)

Anorectal manovolumetry was performed using a device with two units that permitted simultaneous recording of anal pressure and pouch volume during isobaric distension of the pouch[250]. The anal pressure was obtained using a water filled balloon of an endotracheal tube with an outer diameter of 10 mm. The pouch volume was recorded with a flaccid polyethylene balloon with a fixed length of 12 cm and a maximal volume of 600 ml. In contrast to the commonly used latex balloons, this balloon could not expand longitudinally and it was therefore possible to record more accurate pouch volume[250]. The equipment used in the current study was the same as the one used for the recordings obtained in the -80s.
Recordings were obtained for resting anal pressure (mm Hg), anal squeeze pressure (mm Hg), pouch volume at different distension pressures (cm H_2O), pouch volume (ml) and pressure at the first sensation of pouch filling and pouch volume and pressure at urge to defecate.

Endoscopy (II, IV)

Olympus video-gastroscopes were used for macroscopic evaluation and mucosal biopsies. The macroscopic evaluation included assessment of mucosal edema, granularity, friability, loss of vascular pattern, presence of mucous exudate and ulcerations[133]. All endoscopies and mucosal assessments (except for two in study II) were conducted by the same investigator.

Histopathology (II, IV)

The biopsies were fixed in 4% buffered formaldehyde. Sections were embedded in paraffin, cut to a thickness of 3-4 micrometer and stained with haematoxylin-eosin (II, IV), PAS for neutral mucins, and Alcian blue/high iron diamine (HID/AB) for sialomucins and sulphomucin content (IV).
Morphological changes in the defunctioned pouch (II) were grouped into three modified types according to Veress et al.[50 251] and Setti Carraro et al.[48] as follows: type A: normal mucosa and few inflammatory cells. Type B: transient atrophy with reduced height and broadened villi with moderate to severe inflammation and increased Peyer's patches. Type C: persistent villous atrophy, sometimes demonstrating erosions, intense inflammatory reaction and large amounts of hypertrophic Peyer's patches. Grading of dysplasia was made according to established international criteria[57 252].
It is important to be aware of that Veress original grading (A-C) assumed assessment at more than one point of time and does not include any assessment of grade of inflammation. Consequently, a direct comparison between the modified grading and Veress becomes difficult.

Sexual function (III)

International index for erectile function (IIEF) is an instrument developed in conjunction with the trials for sildenafil[253]. It is extensively validated and found to fulfil good psychometric

standards. It is also validated in several languages, including Swedish. The instrument consists of 15 items, divided into five domains of sexual function: erectile function (6 items), orgasmic function (2), sexual desire (2), intercourse satisfaction (3), and overall satisfaction (2). Each item scores from 0 or 1 to 5 (5 best), giving a maximal sum of 75 (min. 5). Besides the use in treatment studies, IIEF has been employed in the assessment of erectile dysfunction in patients with hypertension[254], diabetes[255], trauma (pelvic[256] and spinal cord injuries[257]), and after surgery (aortic aneurysm procedures[258] and radical prostatectomy[259]). In all settings, it has proved to provide sensitive and reliable information regarding the presence and severity of erectile dysfunction .

We used a cut-off score for sexual dysfunction adopted from a study on sexual dysfunction after rectal cancer surgery[260]. This cut-off score has been employed in at least one other study on RPC patients[86].

However, some potential problems with the IIEF instrument have been recognized. It has a strong focus on the current sexual function (4 weeks prior to completing the instrument). The evaluation of components other than erectile dysfunction is superficial. Furthermore, IIEF also has no ability to provide information on the etiology of the dysfunction.

Female sexual function index (FSFI) is an instrument developed by the same group that developed the IIEF instrument[261]. FSFI is also validated and has been found to be psychometrically sound. It consists of 19 items, which are then divided into 6 domains: desire (2 items), arousal (4), lubrication (4), orgasm (3), satisfaction (3) and pain (3). As for IIEF, it focuses on the preceding 4 weeks. Each item scores from 0 or 1 to 5 (5 best), and the summary score in each domain is multiplied with a domain factor. The full-scale score is obtained by adding the six domain scores, giving a maximal sum of 36 (min. 2).

A cut-off score for sexual dysfunction has been developed based on a sample of more than 500 women with known sexual dysfunction and healthy controls[262].

There are limitations to the FSFI, as there are with IIEF, regarding the focus on current sexual function. Furthermore, to provide an interpretable result, sexual activity with a partner is required to an even higher extent than for the IIEF instrument.

In this context it can be mentioned that there is a general concern regarding the use of personal professional assessment. Instruments like the FSFI and especially the IIEF could miss the more subtle nuances of sexual function. However, an advantage with a self-administered instrument is the utilization of fewer resources, giving opportunities for more assessments. A self-administered instrument could also be preferred when the questions evaluate a sensitive matter (such as sexuality).

Body image (III)

Body image could be defined as "a person's perception of her or his own physical appearance and self-esteem as an overall evaluation of one's worth or value"[263].

The body image scale is a ten-item scale designed to assess body image in cancer patients. It was originally validated in patients with breast cancer and the instrument has been used in several studies in this setting[264]. However, BIS has also been considered reliable and valid in the assessment of benign disease. It has been employed in evaluation of benign gynaecological surgery[265] as well as in benign colorectal surgery; the last setting includes patients who underwent RPC[263].

The instrument consists of affective items (e.g. feeling feminine/masculine, feeling attractive), behavioural items (e.g. finding it hard to look at oneself naked, avoiding people because of appearance), and cognitive items (e.g. satisfied with appearance, or with scar/stoma).

Responses are graded in 4 levels; "not at all" (score 0), "a little" (score 1), "quite a bit" (score 2) and "very much" (score 3). A summary score is used (0-30; 0 best).

One problem with the body image scale is that it has not been validated for RPC patients. However, there is a lack of validated body image instruments for the surgical patient and we considered the evaluation of body image as important in the context of the study.

Health related quality of life (III)

HQoL was evaluated using the Swedish version of the SF-36 Health Survey version 2.0[266][267]. SF-36 is an instrument designed for assessment of generic health concepts, not specific for age, disease or type of treatment. Of all generic health-status measures, SF-36 is the most widely used.

The 36-item questionnaire measures eight different health domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. Each subscale contains two to ten items, giving a total of 35 questions. Subscale scores are computed according to standardised procedures and normalised to range from 0 to 100; higher scores indicate better health status.

SF-36 is a thoroughly validated general HQoL instrument, though not for evaluation of pelvic pouch surgery. However, it has been used in several studies in this setting. Berndtsson et al.[65] showed results comparable to a reference norm population in a long-term (median 15 years) follow-up. Furthermore, correlation between worse HQoL and an inferior functional outcome was demonstrated. Similar results, though with shorter follow-up time (a median of 4.3 years), were demonstrated by Carmon et al.[76]

Probiotics (IV)

Lactobacillus plantarum 299 (5x109) and *Bifidobacterium infantis* Cure 21 (5x109), taken twice daily, were used as study drugs.

These two probiotics strains have not been previously used in the context of pouchitis or IBD/IBS.

L.plantarum 299 has been shown *in vitro* to have antibacterial effects against potentially pathogenic species (e.g. Escherichia coli, Shigella flexneri, Yersinia enterocolitica and Enterococcus faecalis)[268] and to reduce cytokine production after exposure to enteric pathogens[269]. *L.plantarum* 299 has been shown to reduce bacterial translocation in several animal models[270]. Trials in humans have demonstrated potential beneficial effects in patients with pancreatitis and ventilator-associated pneumonia; a reduced consumption of antibiotics after major surgery has also been shown[271][272].

B. infantis Cure 21 has, in animal studies, demonstrated beneficial effects in DSS induced colitis[273].

Beneficial effects were demonstrated for *B. infantis* Cure 21 in animal studies (DSS induced colitis[273]). However, there is also a possible beneficial effect, for both the *L. plantarum* and *B. infantis* species, in patients with pouchitis[172][174] or IBS[274][275].

It is important to be aware of the fact that benefits of one probiotic strain "cannot be extrapolated to other probiotic strains without experimentation"[276]. However, it is also likely that group specific properties exist between strains.

Faecal biomarkers (IV)

Calprotectin is a calcium-binding protein that constitutes around 60 percent of cytosolic protein in neutrophile leucocytes[277]. Calprotectin is considered to have antibacterial and antifungal effects. It can be found in all body fluids, including faeces and correlates to the level of inflammation[278]. Calprotectin levels were determined using the PhiCal Calprotectin ELISA kit (Immunodiagnostik AG, Bensheim, Germany). The reference value using this assay is set to < 50 mg/kg.

Lactoferrin is a protein with anti-bacterial effects found in neutrophile leucocytes (in secondary granulas). Levels are considered proportional to neutrophil translocation to the intestines[279]. Lactoferrin levels were determined using the HK 329 Lactoferrin ELISA kit (Hycult biotech, Uden, The Netherlands). The reference value for lactoferrin in human faeces is approximately 1 μg/g.

Myeloperoxidase (MPO) is a glycoprotein predominantly found in primary granules of neutrophile lecocytes and released during acute inflammation. MPO is considered to play a role in the oxygen-dependent killing of microorganisms and tumour cells. The concentration of MPO is proportional to the number of neutrophile leucocytes[280][281]. MPO levels were determined using an MPO ELISA kit for stool and urine samples (Immunodiagnostik AG). The reference value for stool samples is < 2000 ng/g.

Eosinophilic cation protein (ECP) is a protein in eosinophile granulocytes. ECP is part of the defence against luminal parasites. Furthermore, ECP is cytotoxic and has immunomodulatory properties[280]. ECP levels were determined using a fluorescent enzyme immuno assay (FEIA) on an immunoCAP 250 instrument (Phadia, Uppsala, Sweden). The reference value for ECP in faeces is < 19 μg/L.

Calprotectin and Lactoferrin are used in gastroenterological daily clinical practice and have been proposed as tools to differentiate pouchitis from non-inflammatory pouch disorders[248][282]. The sensitivity and specificity for Calprotectin in differentiating IBD from IBS/functional disorders are reported to be 63-100% and 74-88%, respectively. Corresponding figures for Lactoferrin are 78-92% and 68-99%[283][284]. Calprotectin and Lactoferrin are less studied in the context of pouchitis; a sensitivity of 80-90% and specificity of 53-76% are reported for Calprotectin[248], with corresponding figures for Lactoferrin of 100% and 85%, respectively[282][285].

Levels of MPO and ECP are elevated in UC and Crohn's disease compared to healthy individuals[280]; however, they are not in clinical use in these settings.

Randomization and evaluation of data (IV)

Study drugs/placebos were administered and randomized by Probi AB, SE – 223 70 Lund, Sweden (identically packed; each one containing 42 doses). At the beginning of the study, the patients were given a consecutive package. All study personnel and patients remained blinded until the end of the trial.

The treatment effect (i.e., difference between pre- and post-treatment scores (pouch functional score, PDAI) or levels of inflammatory markers in faeces) was calculated for each patient. These differences were used for comparisons between the probiotic and placebo groups.

Statistics

The software used for calculations in Study I was StatView (Abacus Concepts Berkely, Ca, USA) and in study III – IV SPSS 16.0, 18.0 and 19.0 (SPSS Inc., Chicago, Il, USA).

Values are presented as median (range) when not otherwise stated. Mainly non-parametric methods are employed due to the nature of the data (no assumptions of normally distributed data could be done). Wilcoxon Signed Rank Test was used for comparisons of paired data (I, IV) and a Mann-Whitney u-test for unpaired data (I, III, IV). Parametric techniques are traditionally used for data obtained from SF-36 and comparisons were therefore made using the student's t-test (III). Frequencies were compared with Fisher's exact test (III). For correlations, Spearman Rank Correlation Test was used (III, IV). Linear simple and stepwise regression was used for further evaluation and determination of correlations (I). The significance level was set to 95%.

Results and comments

Long-term function (I)

The median functional score at 2 years had increased at 16 years follow-up; the functional score was a median of 3.5 score points (range 0–10) at 2 years and 5 (1-11) at 16 years (P = 0.013). The median number of bowel movements during the day was 5 (3-12) at 2 years and 5 (3–13) at 16 years (P = 0.005). Respective values at night were 0 (0-2) and 1 (0-2), (P < 0.001). All the other individual items in the score, except for the use of medication to alter bowel transit, showed a possible an increase (worsening). However, statistical evaluation was not conducted.
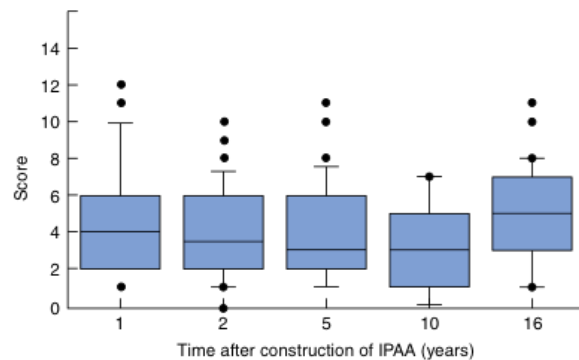

Fig III The development of the pouch functional score

Age was positively correlated with the functional score at 2 (r = 0.37, P = 0.016) and 16 years' (r=0.40, P=0.011).
A total of 24/42 patients had experienced a possible pouchitis (see below). There was no difference in the functional score at 16 years compared to the "non-pouchitis" patients (p = 0.712)

Manovolumetric findings (I)

The main comparisons were made for 2 and 16 years follow-up. Physiological parameters showed a decrease at 16 years, except for resting anal pressure. For details see table IV.

Parameters	Median (range) 2 years	Median (range) 16 years	p
Pouch functional score	3.5 (0 – 10)	5 (1 – 11)	0.013
Resting anal pressure (mm Hg)	50 (25 – 95)	70 (20 – 100)	<0.001
Maximal squeeze pressure	215 (110 – 475)	200 (105 – 325)	0.008
Pouch volume at 10 cm H_2O (ml)	62.5 (0 – 205)	20 (0 – 135)	<0.001
20 cm H_2O	153 (47 – 320)	120 (5 – 310)	0.005
40 cm H_2O	222.5 (65 – 425)	210 (30 – 380)	0.058
First sensation (volume, ml)	157 (52 – 412)	105 (5 – 270)	<0.001
(pressure, mm Hg)	30 (15 – 60)	20 (10 – 60)	0.008
Urge to defecate (volume, ml)	260 (80 -300)	175 (45 – 300)	<0.001
(pressure, mm Hg)	60 (30 – 80)	40 (10 – 80)	<0.001

Table IV Manuvolumetry at 2 and 16 years.

Pouch functional score did not correlate to any of the manovolumetric parameters, except weakly to pouch volume at 10 cm H_2O distension pressures at 16 years (r = 0.33, P = 0.034).

Comments

This study describes functional and manovolumetric alterations with time after RPC. A strength associated with the study is the paired analysis; each patient serves as her/his own control throughout the study. The results indicate that pouch function seems to deteriorate with time. Relatively few studies have been done on functional outcome in the long-term perspective. Conclusions from these are positive, as function remains stable over time[68 71 286]. However, when figures regarding individual determinants (bowel frequency, incontinence) are considered in detail in some of the studies, the reported results point towards a deterioration[70 287].
The functional score increased by 1.5 points between the 2 and 16 years follow-up. It could be questioned whether this is clinically relevant and this study gives no answer to the question. We believe that an alteration in functional score for the individual patient, with at least two points could be considered a significant clinical change; two points were considered relevant in the planning of study IV. When each patient were studied, 13 had increased their score points with ≥ 2 points and five had lowered ≥ 2 points at 16 years compared to 2 years. In other words, about 30% had deterioration in functional score of at least two points.

Increasing age correlated with an inferior functional score at both 2 and 16 years in this study. This finding is in line with other studies[68 74]. However, there are also reports of a functional result that did not differ significantly between age groups[288 289]. The development of manovolumetric pouch characteristics in a long-term perspective was not previously described.

The long term recorded increase in resting anal pressure was a surprising discovery in the current study. It is well established that resting anal pressure and maximal squeeze pressure (to a lesser degree) decreases as a consequence of RPC, with gradual recovery over time[29]. Resting anal pressure is considered to be related to night continence[290 291]. The recorded increase in resting anal pressure might explain the minor increase in reported night time incontinence. There is no obvious explanation for the recorded increase in resting anal pressure to near preoperative values. Another question is whether the anastomotic technique has an impact on anal pressure. In this study, all patients had a hand-sewn anastomosis. Several retrospective studies have indicated more leakage/soling and lower resting anal pressure after hand-sewn, compared to stapled anastomosis, at least in the short perspective[292 293]. However, a meta-analysis of four randomized studies on this issue could not demonstrate any significant differences between the two techniques[294].

The study demonstrates a minor decrease in pouch volume in the long-term. There was a weak correlation for pouch volume at 10 cm H_2O distension pressure to the functional score. An increase in pouch volume during the first year after surgery is previously demonstrated[39 295]. The volume seems to be stable thereafter. Furthermore, pouch volume has also been correlated to function[39]. Goldberg et al. compared pouches with good or bad function and found no difference in anal pressures or pouch sensitivity; however, a significant difference in maximal tolerated volume was noted[40].

The study did not focus on the impact of RPC on HQoL; the only parameter that gives such an indication is the item in the functional score regarding pouch function as a social handicap. Only five patients have answered yes at 16 years compared to four at 2 years. However, several assessments in the long-term perspective, , indicates that the overall HQoL is good[65][67][68]. In a study from our institution, HQoL was demonstrated to be in parity with a reference population sample. Furthermore, the pouch function correlated significantly to HQoL[65]

A previous diagnosis of pouchitis had no significant impact on the study variables. A weakness in the analysis was that the diagnosis of pouchitis was based on symptoms, not always confirmed with endoscopy.

A point to be made is the fact that the patients in this study are among the first 100 that had RPC surgery in Gothenburg and it is possible that the surgeon's learning curve has an impact on the long-term results.

Mucosal assessment of the diverted pouch (II)

13/22 patients with diverted pouches underwent pouch endoscopy with biopsies from different parts of the pouch. Eleven patients had at least discrete macroscopical signs of mucosal inflammation. The histopathological evaluation showed varying degrees of inflammation in 12/13 patients (the one without inflammation had never had the pouch in function). Five patients were graded as "possible" Veress type C. No dysplasia was found.

Comments

The concern regarding histological changes in the pouch mucosa emanates from the observed increased risk of development of dysplasia and cancer in UC and Crohn's disease. There appears to be no increased risk for such changes in a functioning pouch, at least not for patients without suggested risk factors. At the time of this study, there was no available data regarding histological changes in the indefinitely diverted pouch. The results in the present study are in accordance with what Das et al. demonstrated in a similar study on 20 patients with diverted pouches; thus, without indications of mucosal dysplasia[296]. The authors identified two patients with type C changes but without dysplasia. The grading in Study II was modified from Veress[50] (the atrophy component) and Moskowitz[44] (grade of inflammation) and it seems that the same method was employed by Das et al. The importance of finding type C changes lies in the suggested increased risk for dysplasia with this mucosal pattern and the implicit argument for future endoscopic follow-up[50].

Pouch failure (II)

A total of 620 patients underwent RPC at the Sahlgrenska University Hospital from the start in 1982 until 2004. At the time of analysis, 56 patients in this cohort had pouch failure (9.2%). The diagnoses at pouch surgery for these patients were 52 UC, one Crohn's disease, two collagenous colitis and one FAP. The diagnosis was later (at, or before the time for definitive failure) revised to Crohn's disease for two patients (histologically confirmed) and in an additional six patients there was a clinical suspicion of Crohn's disease.

Reasons for failure	n	Fate of the pouch	n
Poor function	25	Excision	8
		Diversion	11
		Conversion	6
Septic complication	22	Excision	9
		Diversion	9
		Conversion	4
Pouchitis	7	Excision	5
		Diversion	1
		Conversion	1
Anal fissure	2	Excision	1
		Diversion	1
Summary: fate of the pouch			
Excision			23
Diversion			22
Conversion			11

Table V Reasons for pouch failure and fate of the pouch.

The morbidity among the 22 patients with pouch diversion can be considered acceptable. The majority experienced occasional minor mucus discharge from the pouch. Two patients had troublesome perianal pain (both have had their pouch excised since the study was done, with as far as we know, decreased pain, but without an obvious explanation to the discomfort). Only three patients had stoma related problems. At the time of study, no one was interested in further surgery.

Comments

The frequency of pouch failure in this cohort is in parity with previously reported figures (around 10%[230]). The failure rate in a cohort of patients with RPC increases with follow-up time. However, there are indications that the relative failure frequency decreases by team experience (both technically and with regard to management of complications)[103 233]. The frequency of RPC at Sahlgenska University Hospital has decreased since the late 90s and is now slightly more than 10 patients/year. For the crude failure rates in our institution, per decade, see table VI.

Year	Op / year	Failure (%)
1982-89	38	11.7
1990-99	27	7.4
2000-09	13	3.7

Table VI Crude failure rates at the Sahlgrenska University Hospital

Previously reported causes of failure are dominated by septical complications[233 234 241 297 298]. Crohn's disease is also mentioned in some studies as an important reason for failure[298], but in others the possible consequence of Crohn's disease (e.g. pouchitis, fistula, poor function) is designated as the primary reason[233 297]. Our proportion of "poor function" as a reason for failure is high compared to the 20-30% reported by others[233 234 297 298]. This could be due in part to the retrospective survey and also to the definition of poor function. Although the most probable causes of failure are presented in table V, some of the patients had more than one

possible reason. For example, three patients in the category "poor function" had experienced septic problems, but at the time of failure, the sepsis was assessed to be cured. For nine of the failure patients, Crohn's disease was a confirmed, or was at least a probable diagnosis. Three of these patients are classified (in the patient records/registry) as poor function, four as septic and the final two as pouchitis and fissure. It is also possible that anatomical problems lie behind a proportion of the "poor functions"; for seven patients, problems with evacuation of the pouch were a component of the poor pouch function.

Sexual function in pouch failure (III)

Both women and men in the failure group had lower score points compared to the control group for all domains and lower summary scores in the sexual function instruments used, however not statistically significant for either gender (summary score; women: p = 0.360, men: p = 0.229). 9/16 (56%) women and 7/13 (54%) men in the failure group had summary scores below the cut-off scores for sexual dysfunction. For the control group, corresponding figures were 32.5% and 31%, respectively. These differences were not statistically significant (women: p = 0.103, men p = 0.161).
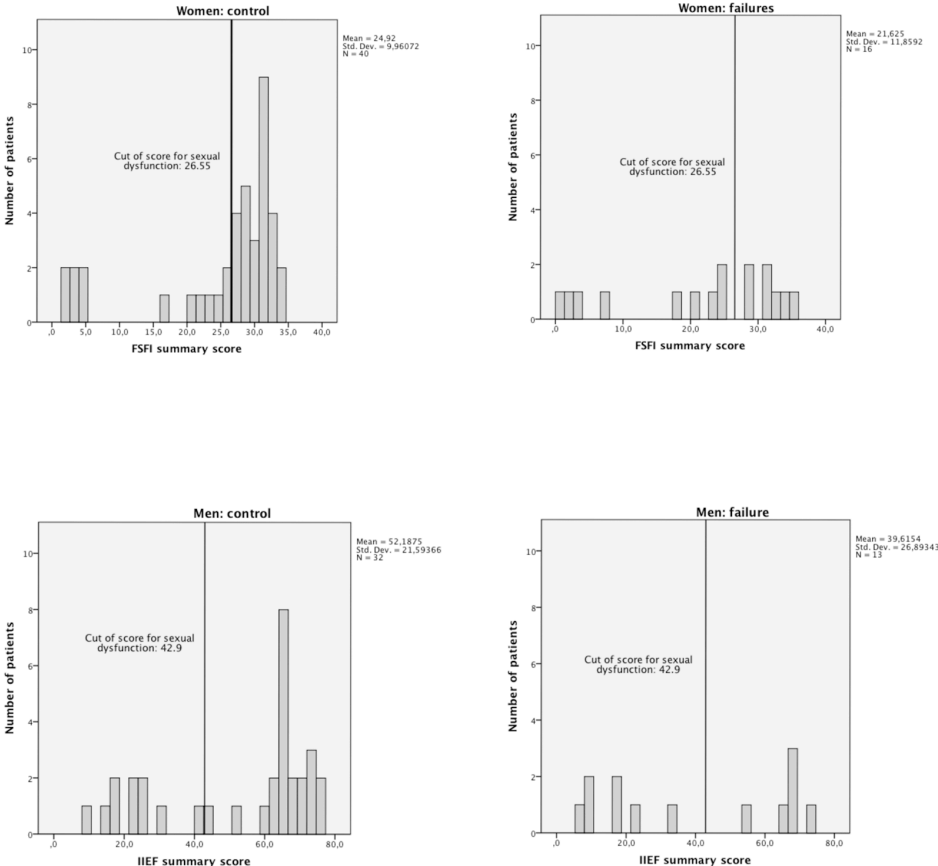

Fig IV Summary scores for the Female Sexual Function Index (FSFI) [261]. Vertical lines represent the level for sexual dysfunction[262].
Summary scores for the International Index of Erectile Function (IIEF)[253]. Vertical lines represent the level for sexual dysfunction[260].

Body image summary scores were significantly lower for both women and men in the failure group compared to the control group (women: p = < 0.001, men p = 0.002). For the item concerning possible dissatisfaction with the scar and/or stoma, there were no statistically significant differences between the groups (women: p = 0.534, men p = 0.177).

Both genders in the failure group had lower scores in all domains in SF-36 compared to the control group and an age and gender matched reference population, though statistically significant only in the social function domain for men.

Significant correlations between sexual function, body image and HQoL were not demonstrated.

Comments

Pouch failure is associated with a worse HQoL. An important component of HQoL is sexual function. Reports on sexual function for the patient with a functioning pouch varies from improved to deteriorated function (see Introduction). The consequences of pouch failure on sexual function are poorly investigated. The hypothesis that patients with pouch failure have a worse sexual function compared to patients with functioning pouches was not confirmed. Das et al. approached the problem in the study comparing excised and permanently diverted pouches, which is referred to above[242]. The study included 53 patients (36 women, no control group) with pouch failure. Men with excised pouches reported more problems to maintain erection than men with diverted pouches. A weakness of that study is that sexual function in women was not assessed.

In our study, body image was worse for both sexes in the failure group. Contrary to what has been reported by others[263 299], there was no correlation to an inferior sexual function.

A possible objection to our study is that it is a comparison of sexual function between patients with or without a stoma (and not between patients with or without pouch failure). The literature undeniably points to a worse sexual function for the ostomist, and also to the association of negative/inferior body image to a stoma[300]. Since the study did not include an additional control group with patients with terminal ileostomies, this issue was not explored in depth. Interestingly, the question concerning perception of scar and/or stoma was one of very few items in the study that did not demonstrate a clear difference between the groups.

Another criticism of the study could be the small study sample/size and the low response rate. However, all patients with pouch failure in the Gothenburg RPC cohort were asked to join the study and despite reminders by letter and then telephone calls to the non-responders, we did not manage to recruit more than 70% of the available patients. Furthermore, compared to other studies on sexual function in the context of RPC, a response rate of 70% is acceptable.

Probiotics in pouch disorders/disease (IV)

Randomization was successful and there were no differences concerning background characteristics, initial functional score, PDAI or levels of faecal biomarkers between the groups.

A tendency towards a larger difference (better functional score) was seen in the probiotics group, but it was not significant (table VII). There were furthermore no significant differences between the groups regarding PDAI or any of the biomarkers.

In an assessment of possible correlations at the baseline for functional score, the PDAI (incl. component scores) and the biomarkers were employed. Significant correlations were obtained for PDAI (including endoscopic and histological component scores) and for all biomarkers. The results for the PDAI summary score were: Calprotectin: $\rho = 0.52$, $p = 0.003$; Lactoferrin: $\rho = 0.57$, $p = 0.001$; MPO: $\rho = 0.52$, $p = 0.003$; ECP: $\rho = 0.50$, $p = 0.004$.

Parameter	Probiotics	Placebo	Comparison
	Diff median (range)	Diff median (range)	(p)
PFS	1 (-2 – 6)	0 (-6 – 2)	0.106
PDAI	1 (-4 – 5)	0 (-5 – 5)	0.276
Lactoferrin	-0.21 (-21.3 – 47)	-0.4 (-53 – 34)	0.739
Calprotectin	16 (-213 – 287)	-21 (-368 – 248)	0.101
MPO	-705 (-11757 – 36114)	-954 (-20702 – 15036)	0.430
ECP	-6 (-402 – 91)	0.5 (-92 – 194)	0.418

Table VII Differences for treatment effect within the groups. A positive difference implies a potential improvement. Comparison: differences between groups compared.

Comments

Probiotics have been studied in a multitude of clinical settings in the GI-tract, including inflammatory bowel disease, IBS and pouchitis. There are relatively good indications of the beneficial effects of probiotics as primary prophylaxis for pouchitis and for the maintenance of induced remission[169-171]. Furthermore, probiotics have been used as a primary treatment of acute pouchitis[172-174 301]. These data, together with the potential beneficial effects in patients with IBS[274 275], formed the rationale for the current study. Probiotics for functional pouch disorders have not, to our knowledge, been previously attempted.

The hypothesis that a 3-week course of probiotics would offer a better pouch function in terms of a decrease in the functional score was not confirmed. The interpretation of this result should be seen in the light of the study sample size. The power calculation was based on a difference in functional score of two score points as clinically relevant. However, the dispersion of the effect variable showed up to be too wide, with a concomitant loss of power. The recorded difference in functional score was, however, only one score point and even if this were a true difference, the clinical significance could be questioned.
Another potential criticism of the study is the choice to include patients both with and without pouchitis. However, the cut-off level of the PDAI at 7 can be, and has been, challenged. To increase the sensitivity of the score, some authors have suggested a cut-off level of 5 to be more accurate[132]. With regard to the PDAI, several authors have reported a poor correlation for the symptom component and the histo- and endo-components, respectively[132 188 249]. Furthermore, it is possible to obtain a pouchitis diagnosis (PDAI ≥ 7) using the PDAI score, with minimal points on endoscopy and histology. Consequently, it has been proposed to omit the symptom component for a more objective score[248]. It is also well known that pouch function varies for the individual patient. With a rigid limit for pouchitis, a single patient can be considered to suffer from pouchitis at one occasion and from a functional disorder a couple of days later. In this context, it seems additionally important to emphasize that PDAI is a poorly validated instrument.

Another point for discussion is the choice of probiotics strain(s). Neither of the two studied strains has been used in the setting of pouchitis or in functional gastrointestinal disorders.

However, both species are included in VSL#3 and *B.infantis* is the probiotic with the best evidence for a beneficial effect in IBS[274 275]. The obvious argument against this reasoning is the danger of extrapolating the benefits of one probiotics strain to another[276].

It could be argued that the 3-week study period is too short to detect the possible effects on pouch function. However, in previous studies with the aim to assess probiotics as primary treatment of pouchitis, a marginally longer study period was used[301 302]. The same length or somewhat longer periods are valid for some studies on IBS[274]. It could only be speculated on whether an additional week would have yielded different results. However, it is shown that probiotics colonize (temporarily) the intestine within weeks[303]. There is also evidence for a prompt effect on the immune system and consequently a possibility to detect changes in at least the faecal biomarkers within the study period[304]. However, the time to a functional response is uncertain.

As proposed by others, this study lends some support for the use of faecal biomarkers as an aid in the management of pouch disorders[248 282]. However, when sensitivity and specificity were calculated for Calprotectin and Lactoferrin, the results were inferior compared to those obtained in earlier studies (for this comparison, a cut-off for Calprotectin at 92.5 was used according to the study by Johnson et al.[248]).

Biomarker	PDAI	Sensitivity (%) [other study]	Specificity (%) [other study]
Calprotectin	≥7	70 [90]	75 [76.5][248]
Lactoferrin	≥7	70 [100]	60 [85][282]

Table VIII Sensitivity and specificity for Calprotectin and Lactoferrin

General discussion

Soon after its introduction more than 30 years ago, RPC emerged as the principal alternative for reconstruction after proctocolectomy in patients with UC and FAP. The main argument for the procedure is the avoidance of a permanent stoma and thereby the ability for normal defecation. RPC has proved to be possible with a very low operative mortality, and with a short-term morbidity in the same range as that of comparable major surgery. Pouch function stabilizes during the first few months following surgery. A satisfactory (at least according to the surgeon) functional outcome after RPC is 4-5 bowels a day, and zero or sporadic night time defecations, no urgency, no problems with evacuation, full continence and no restrictions in everyday life. A small price to pay for the majority of patients is the use of antidiarrhoeic medication and often minor restrictions of food/timing of meals. Several studies report a decline in function in the long-term (10-20 years after surgery), but still with overall satisfaction for the majority of patients. A massive volume of evidence also points to an HQoL for the majority of RPC patients well in parity with the background population.

However, even if the vast majority of patients fares well, a substantial portion experiences complications that in various ways affect their daily lives in a negative way and for some ultimately leads to pouch failure. As this type of surgery has the main objective of improving quality of life, it is of uttermost importance that the frequency of complications, also in the long-term perspective, must be as low as possible. The majority of patients are young and have an expected remaining length of life of 40-60 years. In this context it is essential to study the long-term effects of RPC; this is the focus of this thesis.

Pouch function

Study I deals with pouch function in the long-term perspective and confirms deterioration in terms of a pouch functional score and a concomitant impairment in nearly all pouch physiological parameters. The impairment of the functional score was a median of 1.5 score points; how well this translates into a clinically significant deterioration is debatable. This is not only a question of the weight of the different items in the score, but also the fact that the individual items vary in importance between patients. For example, intermittent soiling at night could be considered by one patient as devastating and by another as trivial. It is also possible that the measured deterioration of functional score in this cohort of patients should be seen as fairly small in relation to normal ageing.

Of the evaluated *physiological parameters*, only pouch volume correlated to the functional score. Öresland et al. showed that pouch volume was the only predictive factor for subsequent pouch function. However, only approximately 20% of the variability in functional score could be explained by volume and pouch compliance[39]. It is still not clear how much pouch physiology contributes to the functional outcome in the long-term compared to the relative impact of other factors such as patients age, underlying disease (UC, FAP), pelvic anatomy, general small bowel function, patient personality/psychology and "surgeon factors" (including impact of the institution). In this context it is important to state that "pouch physiology" in practice is what is measurable and that the study (I) only has focused on a few physiological parameters that we were able to record.

Increased age as a determinator for pouch function was demonstrated (I), thus confirming the finding of previous studies that state that function, particularly continence, deteriorates with increased age; however, the interpretation of these results varies[67 74]. Another important issue in this context is if there should be an upper age limit for construction of RPC. Some authors have reported on this issue; the functional results may be inferior compared to patients in younger age groups, but this does not seem to translate in to markedly inferior HQoL[289 305]. The general conclusion appears to be that RPC could be an option in the well informed medically fit patient even in the 70:th or 80:th decades of life[289 305]. However, this standpoint is debatable, as it is likely that an apparently healthy septuagenarian has more limited resources than the younger patient to handle possible morbidity that inevitably follows major surgery. Interestingly, the Scandinavian experience seems to be limited on this issue.

Concerning *patient personality*, an interesting study from Wienryb et al. indicated differences in outcome (aspects of HQoL) depending on the pre-operative personality. Preoperative problems with a perfectionist body image and poor frustration tolerance predicted a worse HQoL beyond pouch function alone. Interestingly, alexithymia was associated with a better outcome [306].

An interesting issue is the relative impact of *the diagnosis* (UC) on the functional outcome. Patients with FAP (and RPC) are in many ways the ideal control group in this context. The available data points to a functional result similar to that of the UC patients, but with (the well-known) lower incidence of pouchitis[131 307]. In a study by Lovegrove et al. where meta-analytical technique was employed, the only functional parameter that demonstrated a significant benefit for FAP, was a minor reduction in 24 hour stool frequency[308]. Furthermore, significantly more fistulas were seen after surgery for UC, as well as pouchitis. No other adverse events differed significantly between the groups.

As for other low-frequent surgery, the question of impact of *caseload and surgical experience* on outcome is of great interest. The number of studies on this issue is small. However, data indicates that both surgical experience and institutional volume correlates to failure and to reoperation rate[309 310]. In one of the two available studies, there was also shown that low and high volume centres differed in case-selection, which in turn probably affects results[309]. Since RPC is a relatively complex procedure with a non-negligible morbidity rate, it seems reasonable to allocate the surgery to centres with a certain caseload. A number of at least ten procedures per year are proposed in the ECCO guidelines, though this figure is arbitrarily chosen[311]. If this argument is valid for the standard RPC, it seems reasonable to even further centralize salvage surgery.

Still unknown are the functional results in the truly long-term perspective. Considering an expected length of life with the pouch of around 30-60 years, some of the results reflect only mid-term perspective and there are only a few studies that have explored a longer perspective[68]. A possible perspective for the ageing pouch patient is a further deterioration of pouch physiology in conjunction with the age dependent impairment of anal sphincter function[312 313], reflected in a worse function and ultimately a rising frequency of pouch failure. Since failure includes the creation of an (sometimes high flow) ileostomy, it seems reasonable to believe that the management of this situation can be very difficult in an old patient with considerable comorbidity.

Pochitis and poor pouch function

Probably more than half of the patients with RPC will at some point present with symptoms indicating possible pouchitis. However, symptoms as the sole criteria for pouchitis have a relatively low specificity and as much as half of the symptomatic patients do not fulfil criteria for pouchitis. Different strategies have been explored for handling this problem. As the majority of patients with a manifest pouchitis will respond promptly to a short course of antibiotics, it *is probably a very common* practice to use this treatment to confirm the "diagnosis". An obvious objection to this approach is the substantial number of patients undergoing an incorrect treatment with the concomitant risk for adverse effects and the general consequences of increased antibiotic exposure.

The other principal approach in this situation is endoscopy with confirming biopsies before treatment. The need for use of these more costly resources is a drawback. The use of a biomarker as a tool for selecting patients for endoscopy has been previously explored and both Calprotectin and Lactoferrin seem promising. Our own results give some support for this , but it needs to be confirmed in a larger study. Furthermore, the conventional cut off levels for the biomarkers must be confirmed and related to optimal criteria for pouchitis. When patients with PDAI <7 and ≥7 were assessed separately, the correlations to the biomarkers remains significant in both groups (IV). This points to the potential problem with the current PDAI cut-off. Thus, a proportion of patients will not fulfil the PDAI criteria for pouchitis but nevertheless seems to have inflammatory alterations in their pouch. Cost-effectiveness is another aspect of the management of pouchitis that should be evaluated.

The patients with verified pouchitis who do not respond to, or frequently relapse on antibiotic treatment, is another clinical issue. In this setting, the work-up should be considerably more extensive in order to exclude other causes than idiopathic pouchitis. Broad evaluation of the rest of the bowel (MR enterography, wireless capsule endoscopy, biopsies for exclusion of celiac disease etc.), assessment of pelvic anatomy in detail (MR) and repeated biopsies of the pouch including the afferent limb could be considered. It is our and others impression that a relatively large number of the patients with frequent relapses could be managed with maintenance antibiotic therapy, titrated to the lowest effective, continuous or intermittent, dose[171]. There are also indications that a subset of patients with antibiotic refractory disease (not only with verified CD), will benefit from immunomodulatory therapies[218 314]. A close cooperation with the gastroenterologist is important in this situation.

An even larger problem, at least in terms of numbers, are the patients with poor function without any obvious macro- or microscopical evidence of *acute* inflammation (chronic inflammation in the pouch is a common finding, but without obvious correlation to pouch function[44]) that did not respond to dietary changes or antidiarrhoeal medication. Symptomatic similarities to IBS led Shen et al. to introduce the concept of the irritable pouch syndrome - IPS[188]. Due to the high prevalence (10-15%) of IBS in the general population[315 316], it seems reasonable to assume that at least part of these patients actually have IBS. Another observation that could support this hypothesis is the observed high prevalence of IBS-like symptoms in patients with IBD in remission (i.e. no objective signs of ongoing inflammatory activity). The pathogenesis of IBS is unclear, but there are indications of an underlying low-grade inflammation, at least in a subgroup of patients. One hypothesis is that this subgroup could have an altered immunological function, maybe combined with dysbiosis that affects the regulation of the brain-gut axis[317]. It would be of interest to further explore the impact of IBS in patients with poor pouch function, especially since IPS has been proposed as a "new"

disorder.

It is also in the context of poor pouch function *and* IBS that treatment with probiotics is of particular interest. Evidence for beneficial effects of probiotics in IBS exist, but are not absolutely convincing. We could not demonstrate an effect of probiotics in the form of *Lactobacillus plantarum* 299 and *Bifidobacterium infantis* on pouch function as assessed with the PFS. The study was not dimensioned for an evaluation of the effect in the subgroup with poor function, but without acute inflammation. It would be of interest to further explore the role of probiotics in this group.

Excise or divert?

The failure rate, about 10%, in the Gothenburg cohort is within the range of previous reports. The reasons for failure, dominated by septical complications and poor function, are also in accordance with the literature.

The optimal management in situations of failure is an unsolved issue. One concern with indefinite diversion is the possible risk of neoplastic transformation in the deviated pouch. None of the patients in our study (II) had dysplasia. Dysplasia was also not present in the only other study on consequences of permanent pouch diversion[296]. However, 5/13 patients in our and 5/20 in the study by Das et al. were graded with changes comparable to Type C according to Veress, indicating a risk for dysplasia. The conclusion in both studies was that these findings warranted further follow-up.

The concern of neoplastic transformation in an excluded part of the intestine partly emanates from the observation of an 50-100 times increased risk for small bowel cancer in Crohn's disease[318]. A substantial proportion (around 25%) was found in a bypassed segment[319]. However, if this observation is valid, the situation in terms of defunctioned pouches is difficult to foresee.

Another focus was an assessment of the clinical consequences of leaving the failed pouch *in situ*. The majority of the patients had no problems (leakage, pain etc.) related to their defunctioned pouches, and only minor stoma related complaints. HQoL was not assessed in this study (II); however, these patients are part of the failure group in the study by Berntdsson et al. mentioned above, where an inferior HQoL among the patients with failure was demonstrated[65]. There was also a tendency for a worse HQoL for the patients with failure (including patients in study II) in study III, compared to patients with functioning pouches. It is therefore reasonable to presume a worse HQoL compared to patients with functioning pouches. There are most likely several explanations to this impairment, e.g. an (sometimes high output) ileostomy, disappointment with years spent on complications, missed opportunities for education or career advancement due to periods of protracted illness etc.

The principal argument *for* leaving the failed pouch *in situ* is the risk associated with further pelvic surgery (e.g. nerve damage due to altered anatomy and/or scarring) and subsequent healing problems. Another potential benefit for women with indefinite diversion is that the pouch still remains in the pelvis as a support for the uterus and vagina, thereby lessen the risk of dyspareunia and vaginal discharge[81]. Our hypothesis regarding a worse sexual function in patients with pouch failure was not confirmed (IV). Furthermore, when we compared the patients with diverted and excised pouches, there were no obvious differences concerning sexual function. Das et al.[242] compared the outcome after failure between patients with excised and diverted pouches and reported indications of increased bladder and sexual

problems among the patients with pouch excision. They recommended diversion (if there was no absolute indication for excision) as the procedure of choice.

However, in a number of patients with failure, there is no other option than excision, mainly due to an ongoing perineal septic complication. For some patients, excision is not the solution to the perineal problems. Conversely, a well-known complication to pouch excision is morbidity associated to the perianal wound[235 240]. In our material, 17/34 with pouch excision had perianal healing problems; 14 patients required at least one surgical procedure. The longest time to documented healing was 36 months.

There is a lack of information regarding the actual frequencies of excision versus diversion in clinical practice. It could be concluded that both alternatives are common. Interestingly, in a major cohort from Finland, all patients with failure seemed to be managed by excision[241].
To conclude; if the option to choose between excision and diversion is possible, the arguments for leaving the pouch *in situ* outweighs those for excision.

Follow-up?

What about surveillance of patients with functioning pouches? It is decidedly wise to plan for one or two visits during the first year when there is a successive stabilization of pouch function. A planned follow-up for the well functioning pouch after that is probably a waste of resources. The exception could be the situation with suggested risk factors for neoplastic transformation, i.e. dysplasia or cancer in the excised rectum or colon, or confirmed dysplasia in the pouch. However, it could be questioned if the number of reported cancers related to ileal pouches actually exceeds the background frequency of small bowel cancer.

Alternatives to RPC

It should be evident from this thesis that there is a relative magnitude of problems associated to RPC. But what are the alternatives?
Proctocolectomy and conventional ileostomy is one viable option. The patients who choose this alternative is spared from problems directly associated with the pouch (septical problems, poor function and pouchitis). Ostomy appliances have improved compared to 30 years ago and are still in constant development. However, in spite of this, the majority of patients consider a permanent ileostomy as a "non-alternative", principally due to the effects on body image.
Another option is the *ileorectal anastomosis*. Compared to RPC, it is a technically less demanding procedure with relatively low morbidity and a functional outcome in the same range. Besides this, the largest benefit is probably the minimized risk for impaired fertility and for deteriorated sexual function. The obvious drawback of the ileorectal anastomosis is the need for surveillance for development of dysplasia. It is probably wise to recommend all patients without contraindications, to maintain treatment with 5-ASA preparations in order to reduce the grade of proctitis and (likely) the development of dysplasia[311]. An unsolved problem is the lack of solid criteria for the selection of the right patients for ileorectal anastomosis. The most important determinant is likely rectal compliance. The decision is relatively straightforward in a patient with either a pronouncedly inflamed, non-compliant or a macroscopically normal rectum. The issue, however, is the more common situation with

moderate inflammation and some grade of decreased compliance. Furthermore, it is common that this evaluation has to be done on the defunctioned rectum. The decision making in this situation is ultimately based on a discussion between the surgeon and the well-informed patient. However, in the case of failure of the ileorectal anastomosis, there is often an option of RPC.

Finally, the continent ileostomy remains an option for the small/minor subset of patients in whom RPC or ileorectal anastomosis are not is possible. This rare construction offers an alternative to the conventional ileostomy that not should be forgotten.

There has also been expectations that the introduction of *laparoscopic* or laparoscopy assisted RPC should aid in the reduction of complications/morbidity. Reported results indicate that the procedure(s) is feasible and safe. As in other forms of surgery, there is an association with a faster postoperative recovery after laparoscopic surgery and perhaps a more a favourable cosmetic result. However, the functional outcome and complications/morbidity in the long-term data is lacking[320].

In spite of the unknown functional outcome in the truly *long-term* perspective, RPC is, and probably will be, the preferred surgical alternative for reconstruction for the foreseeable future. However, at least in Sweden, IRA has turned up as the first choice for suitable patients, especially in women with the prospect of future pregnancy.

Conclusions

Pouch function, as assessed by a functional score, deteriorates with time. The change is statistically significant, however the clinical relevance is unclear.

Pouch physiology, in terms of manovolumetric characteristics, shows significant deteriorations in the mid long-term perspective in all parameters, with the exception of resting anal pressure.

The risk of and reasons for pouch failure in the Gothenburg RPC cohort are in accordance with what has been reported by others.

Patients with pouch failure and the pouch left in situ encounter few complaints from the diverted pouch, or from the ileostomy.

Dysplasia was not found in the indefinitely diverted pouches. However, the observational time was relatively short and the patient cohort was small.

We were unable to demonstrate statistically significant deterioration of sexual function in patients with pouch failure compared to patients with functioning pouches.

Patients with pouch failure demonstrated a significantly worse body image compared to patients with functioning pouches.

A short course of probiotics did not improve pouch function in patients with poor function.

The grade of pouch inflammation correlated with the assessed faecal biomarkers of inflammation.

Acknowledgements

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