Treatment of inflammatory bowel disease: medical and surgical aspects
Eshuis, E.J.

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THE EFFECT OF APPENDECTOMY ON THE DISEASE COURSE OF ULCERATIVE COLITIS, A SYSTEMATIC REVIEW

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ABSTRACT

Aim
Previous studies showed significantly lower appendectomy rates in ulcerative colitis patients compared to healthy controls. Since then, evidence indicating the appendix has an immunomodulatory role ulcerative colitis has been accumulating. Aim was to examine the latest evidence on the effect of appendectomy on the disease course in patients with ulcerative colitis.

Methods
PubMed, the Cochrane library, and EMBASE were searched. Primary endpoints were number of relapses, use of steroids, number of hospital admissions and colectomies.

Results
The search resulted in 6 observational studies totalling 2,532 patients; 5 case control studies and 1 cohort study. Due to clinical heterogeneity, no meta-analysis could be conducted. One study found lower relapse rates in patients appendectomized before onset of ulcerative colitis (absolute risk reduction 21.5%; 95% confidence interval -1.71% - 45.92%). Another 2 studies found a reduced requirement for immunosuppression in appendectomized patients (absolute risk reduction 20.2%; 95% confidence interval 9.67% - 30.46% and absolute risk reduction 21.4%; 95% confidence interval 10.32% - 32.97%). In addition, one study found lower colectomy rates in non-appendectomized patients (absolute risk reduction 8.7%; 95% confidence interval -1.29% - 18.66%), 2 studies found lower colectomy rates in appendectomized patients (absolute risk reduction 21.4%; 95% confidence interval 13.17% - 28.79% and absolute risk reduction 18.7%; 95% confidence interval 7.50% - 29.97%).

Conclusions
There is limited and conflicting data available regarding the effect of appendectomy on the disease course of ulcerative colitis. Most studies suggest a beneficial effect, the minority find no or a negative effect. A prospective randomized trial evaluating the disease modifying effect of appendectomy on the disease course of ulcerative colitis is therefore justified.
Background

Ulcerative Colitis (UC) diffusely affects the colonic mucosa, and is characterized by episodes of relapse and remission. UC should be regarded as a multifactorial disease involving an interaction between genetic and environmental factors that give rise to an inappropriate immunologic response. The disease activity is confined to the colon, and almost always involves the rectum. From there it may extend continuously to more proximal segments of the colon. Patients can be classified as having proctitis (disease limited to the rectum), left-sided colitis (disease activity extending to proximal but not beyond the splenic flexure), or pancolitis (with disease activity extending from the rectum proximally to the cecum). The majority of UC patients can be treated effectively with medical therapy, such as 5-aminosalicyclic acids (oral and/or topical) as first line therapy, but frequently topical and/or systemic corticosteroids are needed. More refractory patients need immunosuppression with thiopurines, calcineurin inhibitors and/or TNF alpha blockers. Ulcerative colitis refractory to medical management is treated surgically, mostly by means of a proctocolectomy with ileal J-pouch anastomosis. Up to 30%-40% of patients with UC ultimately require surgery depending on local medical culture and availability of biologic therapies. The surgical procedure can be complicated by the development of anastomotic leakage requiring reoperation and by pouchitis, high stool frequency, faecal incontinence and reduced fertility. A meta-analysis of complications showed pouch failure in 0.5-1% per year, pelvic sepsis in 9.5% and severe, mild and urge faecal incontinence in 3.7%, 17% and 7.3%, respectively.

The triggering factor for the development of UC is still unknown. However, cytokine imbalance and the production of inflammatory mediators by activated CD4+ T cells are considered to play an important role in the pathogenesis of UC. T-helper type 2 cells and their cytokines, particularly interleukin (IL)-4, have been suggested to enhance the development of UC. The cytokine production within the appendix has been proposed to trigger an immunological cascade in the colorectum. The appendix is therefore suggested to be a potential priming site in the development of UC.

There is growing evidence in the literature inversely linking prior appendectomy with the subsequent risk of developing ulcerative colitis. This inverse association was first reported in 1987 as an unexpected finding in a study of childhood determinants of inflammatory bowel diseases. Only when another study reported a low incidence of 0.6% of appendectomy in UC patients compared to an incidence of more than 25% in controls from orthopaedic clinics, this inverse relation drew major attention. Since then, various epidemiological and case control studies have investigated the association between appendicitis, appendectomy and the risk of developing UC. Furthermore, a study with a T-cell receptor α chain knockout mouse model of colitis showed that the development of inflammation was suppressed in those animals that underwent appendectomies, particularly at 3-5 weeks of age. Together with the findings that periappendiceal inflammation with cecal patch occurs commonly as a skip lesion in UC, even in left-sided colitis, the appendix is suggested to be closely related to the pathogenesis of UC and may therefore offer a potential therapeutic target.

The aim of this systematic review was to examine the latest evidence on the effect of appendectomy on the disease course in patients with UC.
METHODS

Search Strategy and study selection
The electronic databases PubMed, the Cochrane library, and EMBASE were searched up to 2 August 2010 by a clinical librarian. The search was performed with both keywords and MeSH terms. The search consisted of: ulcerative colitis OR colitis, ulcerative [MESH] AND (appendix OR appendectomy OR appendicectomy OR appendiceal).

Two reviewers (TG&EE) independently screened titles and abstracts for their relevance. In case of disagreement between the two reviewers, a third reviewer (WB) was involved. Additionally, the reference lists of all included articles were hand searched for other relevant references.

Studies designed to evaluate the effect of appendectomy on the disease course in patients with UC were included. No limits were applied to the reason for appendectomy or timing of appendectomy in UC patients. Cases were defined as patients with UC who had undergone an appendectomy at any time. Controls were defined as UC patients who had not undergone an appendectomy. Editorials and commentaries were excluded, as well as animal studies. All controlled trials and observational studies designed to investigate this effect were selected. Inclusion was not otherwise restricted by study size, language, or publication type.

Outcome measures
Primary outcomes considered were the number of relapses, the number of hospital admissions, the use of steroids, and the number of colectomies. These measures were selected because of their clinical relevance. The number of relapses reflects the increase of disease activity, which can be measured in the outpatient clinic. The number of hospital admissions indicates a severe increase in activity of UC. The need for steroids is a good clinical marker for severe disease. Colectomy rates show patients with UC refractory to medical management.

Data extraction and assessment of methodological quality
Data was extracted by two reviewers independently and included the study design (cohort vs. case control), patient characteristics, total number of persons in each comparison group, disease specifications, duration of disease, medication type, potential confounders used for adjustment (e.g. smoking) and the four different outcome measurements compared between the appendectomized and non-appendectomized patients. Inconsistencies between the data extractions were resolved by consensus. Data reporting conforms to the Meta-Analysis of observational Studies in Epidemiology (MOOSE) group guidelines.

The methodological quality of the studies included was assessed by two reviewers independently using the Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, including the recruitment of cases and controls, the assessment of disease state, description of potential confounders, and other forms of potential bias. In this assessment points can be allocated for every item. Three broad perspectives are judged: the selection of the study groups (maximum 4 points); the comparability of the groups (maximum 2 points); and the ascertainment of either the exposure or outcome of interest (maximum 3 points).
The assessment of methodological quality and the data extraction was performed by two reviewers independently. SPSS version 18.0 for Windows® (SPSS Inc, Chicago, Illinois) was used for statistical analysis. Results for continuous data were expressed as median with range or mean ± standard deviation (SD). Results for the primary outcome measurements were expressed as absolute risk reduction (ARR) with 95% confidence interval (CI).

**RESULTS**

A total of 359 potentially relevant titles were identified from the literature search in the aforementioned electronic databases, of which 63 were considered relevant based on title and abstract. Hereafter, 22 articles were excluded because they were commentaries, seven articles were excluded because they did not present new data, and 23 articles were excluded because they reported on the inverse association between appendectomy and UC, not on the effect on the disease course of patients with UC.

Five articles were case reports or case series and were therefore not included in the analysis. However, the main results of these articles are shown in this review to give a complete view of all available data on this subject. One of these articles was only available in Korean; this was translated by a native speaker.

A total of six full text articles remained for final analysis and data extraction 18–23. Details of the search are shown in Figure 1.

*FIGURE 1: FLOW CHART OF ARTICLE INCLUSION*
Description of studies

Naganuma et al. performed a case control study with UC patients from seven different hospitals. Both the studies from Radford-Smith et al. and Florin et al. collected patients with UC from a clinical database from the period 1995-1999 and 1995-2002, respectively. Selby et al. included consecutive patients from a single practice. Hallas et al. collected incident UC cases that were appendectomised from a national hospital registry from the period 1977-1999 and matched these by sex, age and age at diagnosis with UC patients who did not have had an appendectomy (controls). Each control case was assigned an index date corresponding to the appendectomy date of the matched case and disease activity of both cases and controls in the periods before and after this index date was compared. Cosnes et al. included a cohort of consecutive patients with UC from 1997-2000 and retrospectively studied the patients who had undergone appendectomy before disease onset and prospectively studied patients who had an appendectomy after onset of UC.

Methodological quality of studies

The methodological quality of the six included studies has been summarized in Table 1. The overall quality of the studies was moderate. Of the 6 studies included for this review, 5 were case-control studies and 1 was a cohort study. The studies varied in the selection of cases and controls. Often there was no independent validation of cases and no statement of potential selection bias. Also differences in comparability were present. A number of studies did not report any adjustment; in other studies adjustment was limited to age, sex and smoking or age, smoking status, immunosuppression and duration of disease, duration of disease alone or adjustment was extensively reported. The exposure measurement was in all studies illustrated by the statement that medical charts, national registers, interviews and/or questionnaires were used.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study type</th>
<th>Selection</th>
<th>Comparability</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naganuma et al</td>
<td>2001</td>
<td>Case control</td>
<td>σ</td>
<td>σ</td>
<td>σ</td>
</tr>
<tr>
<td>Radford-Smith et al</td>
<td>2002</td>
<td>Case control</td>
<td>σσ</td>
<td>σσ</td>
<td>σ</td>
</tr>
<tr>
<td>Selby et al</td>
<td>2002</td>
<td>Case control</td>
<td>σσσσσ</td>
<td>σσσσσ</td>
<td>σσσσσ</td>
</tr>
<tr>
<td>Florin et al</td>
<td>2004</td>
<td>Case control</td>
<td>σσσ</td>
<td>σσσσσ</td>
<td>σσσσσ</td>
</tr>
<tr>
<td>Hallas et al</td>
<td>2004</td>
<td>Case control</td>
<td>σσσσσ</td>
<td>σσσσσ</td>
<td>σσσσσ</td>
</tr>
<tr>
<td>Cosnes et al</td>
<td>2002</td>
<td>Cohort study</td>
<td>σσσσσ</td>
<td>σσσσσ</td>
<td>σσσσσ</td>
</tr>
</tbody>
</table>

In the assessment of methodological quality, three perspectives are judged: the selection of the study groups (maximum 4 points); the comparability of the groups (maximum 2 points); and the ascertainment of either the exposure or outcome of interest (maximum 3 points).

Outcome of studies

An outline of the results is shown in Table 2. Meta-analysis was not feasible because the studies were heterogeneous in terms of variation in outcome measures, timing of appendectomy and timing of measurements.
### TABLE 2: OVERVIEW OF INCLUDED STUDIES

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Study type</th>
<th>N</th>
<th>N</th>
<th>Appendectomy patients</th>
<th>N</th>
<th>N</th>
<th>Appendectomy controls</th>
<th>Age (mean)</th>
<th>Duration of disease</th>
<th>Medical therapy</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naganuma et al.</td>
<td>2001</td>
<td>Japan</td>
<td>case control</td>
<td>325</td>
<td>325</td>
<td>21 (6,5%)</td>
<td>53</td>
<td>16,3%</td>
<td>38,9 (±13,7)</td>
<td>39,4 (±14,2)</td>
<td>all localizations</td>
<td>NA, ASA, CS</td>
<td>NA</td>
</tr>
<tr>
<td>Radford-Smith et al.</td>
<td>2002</td>
<td>Australia</td>
<td>case control</td>
<td>307</td>
<td>1016</td>
<td>21 (6,8%)</td>
<td>286</td>
<td>28,1%</td>
<td>32,7 (±10,85)</td>
<td>33,6 (±10,38)</td>
<td>all localizations</td>
<td>NA, ASA, CS, IM</td>
<td>NA</td>
</tr>
<tr>
<td>Selby et al.</td>
<td>2002</td>
<td>Australia</td>
<td>case control</td>
<td>259</td>
<td>280</td>
<td>12 (4,6%)</td>
<td>70</td>
<td>25%</td>
<td>43,1 (±10,89)</td>
<td>41,1 (±10,82)</td>
<td>all localizations</td>
<td>NA, ASA, CS, IM</td>
<td>NA</td>
</tr>
<tr>
<td>Florin et al.</td>
<td>2004</td>
<td>Australia</td>
<td>case control</td>
<td>294</td>
<td>1016</td>
<td>19 (6,5%)</td>
<td>275</td>
<td>27,1%</td>
<td>32,7 (±10,86)</td>
<td>33,6 (±10,38)</td>
<td>all localizations</td>
<td>NA, ASA, CS, IM</td>
<td>NA</td>
</tr>
<tr>
<td>Hallas et al.*</td>
<td>2004</td>
<td>Denmark</td>
<td>cohort</td>
<td>202</td>
<td>808</td>
<td>202 †</td>
<td>0</td>
<td>0%</td>
<td>38,6 (±18,0)</td>
<td>38,7 (±17,7)</td>
<td>all localizations</td>
<td>NA, ASA, CS, IM</td>
<td>19y</td>
</tr>
<tr>
<td>Cosnes et al.**</td>
<td>2002</td>
<td>France</td>
<td>retrospective</td>
<td>638</td>
<td>NA</td>
<td>49 (8%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>all localizations</td>
<td>NA, ASA, CS, IM</td>
<td>25y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>prospective</td>
<td>507</td>
<td>NA</td>
<td>41 (8,1%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>all localizations</td>
<td>NA, ASA, CS, IM</td>
<td></td>
</tr>
</tbody>
</table>

ASA=salicylates, CS= cortical steroids, IM= immunomodulatory, B= biological (α-TNF); All appendectomies were performed before onset of Ulcerative Colitis (UC), those with † were performed after onset of UC; NA= data not applicable

** Significantly more female patients in appendectomy group.

### TABLE 3: OUTLINE OF RESULTS OF UC PATIENTS

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Relapse</th>
<th>A+ patients</th>
<th>A- patients</th>
<th>Hospital admissions</th>
<th>A+ patients</th>
<th>A- patients</th>
<th>Steroid use</th>
<th>A+ patients</th>
<th>A- patients</th>
<th>Colectomy</th>
<th>A+ patients</th>
<th>A- patients</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naganuma et al.</td>
<td>2001</td>
<td></td>
<td>12 (57,1%)</td>
<td>42 (78,6%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>relapse=hospitalization or increase in clinical activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radford-Smith et al.</td>
<td>2002</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>4 (4,8%)</td>
<td>71 (25%)</td>
<td>0 (0%)</td>
<td>60 (21,4%)</td>
<td>* Immunosuppression (AZA,6MP, MTX, MCP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selby et al.</td>
<td>2002</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>4 (33,3%)</td>
<td>43 (18,0%)</td>
<td>2 (16,7%)</td>
<td>1 (12,5%)</td>
<td>* Immunosuppression (AZA,6MP, MTX, MCP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Florin et al.</td>
<td>2004</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1 (5,3%)</td>
<td>74 (27%)</td>
<td>1 (5,3%)</td>
<td>67 (24%)</td>
<td>* Immunosuppression (AZA,6MP, MTX, MCP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallas et al.</td>
<td>2004</td>
<td>NA</td>
<td>171/1171*</td>
<td>631/424</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>9 (4,5%)</td>
<td>42 (5,2%)</td>
<td>* N° of admissions before/after appendectomy or index date</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cosnes et al.</td>
<td>2002</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>33 (67%)</td>
<td>412 (70%)</td>
<td>7 (14,3%)</td>
<td>33 (5,6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All appendectomies were performed before onset of Ulcerative colitis (UC), those with † were performed after onset of UC

A+ = appendectomy, A- = non appendectomy, AZA = azathioprine, 6MP = 6-mercaptopurine, MTX = methotrexate, MCP = mycophenolate, NA= data not applicable
Of the four outcome measurements, Naganuma et al. studied the relapse rates of UC (Table 3). In this study, a relapse was defined as hospitalization or increase in clinical activity of UC. The study found a lower relapse rate in patients who had an appendectomy before onset of UC (57.1%) compared with controls who had not undergone appendectomy (78.6%, ARR 21.5%; 95% CI -1.71% - 45.92%).

The use of steroids in both the appendectomy and non-appendectomy patients was investigated in 4 of the 6 studies. Radford-Smith et al. and Florin et al. found a lower requirement for immunosuppression (defined as therapy with azathioprine, 6-mercaptopurine, methotrexate or mycophenolate) in the UC patients who had an appendectomy (4.8 and 5.6%) compared to the controls (25% and 27%; ARR 20.2%; 95% CI 9.67% - 30.46% and ARR 21.4%; 95% CI 10.32% - 32.97%, respectively). Selby et al. found no differences in ongoing immunosuppression requirement (defined as therapy with azathioprine, 6-mercaptopurine, or cyclosporine) between patients who had an appendectomy before onset of UC (33.3%), patients who had an appendectomy after onset of UC (12.5%) or the control group (18%). The study of Cosnes et al. found no difference in the necessity for oral steroids in the appendectomised (67%) and non-appendectomised (70%) patients.

In the study by Hallas et al. the number of hospital admissions in patients with UC before and after the appendectomy compared to hospital admissions in controls before and after the index date were reported. The number of hospital admissions in the appendectomy group was 171 before and 117 after appendectomy (47% decrease). The number of admissions in the control group was 631 before and 424 after the index date (49% decrease).

In five studies the colectomy rate was investigated. Both Selby et al. and Hallas et al. found no differences in colectomy rates between the patients who had an appendectomy before onset of UC (12.5% and 4.5%, respectively), patients who had an appendectomy after onset of UC (16.7% in the study by Selby et al.) or the control group (8.8% and 5.2%, respectively). In the study by Cosnes et al. a higher proportion of appendectomised patients required colectomy (14.3%) compared to the non-appendectomised patients (5.6%; ARR for non-appendectomised patients 8.7%; 95% CI -1.29% - 18.66%). Radford-Smith et al. and Florin et al. both found a lower colectomy rate in the appendectomy group (0% and 5.3%, respectively) compared to the non-appendectomy group (21.4 and 24%, ARR 21.4%; 95% CI 13.17% - 28.79% and ARR 18.7%; 95% CI 7.50% - 29.97%, respectively).

Case reports and case series

Two case reports and three case series are published regarding the effect of appendectomy on the disease course in patients with UC (Table 4). Okazaki et al. described a patient with distal ulcerative colitis, whose symptoms resolved after appendectomy, and was asymptomatic after three years of follow up. Kim et al. described a case with severe pancolitis, whose symptoms decreased after appendectomy and was able to end the use of steroids. Jarnerot et al. performed a pilot study on laparoscopic appendectomy in 10 patients with refractory UC. This pilot study was stopped after six patients because of the difficulties in interpreting the results caused by confounding factors. These involved difference in medication used and duration of disease. No firm conclusions were drawn by Jarnerot et al.
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study type</th>
<th>N</th>
<th>Disease</th>
<th>Disease localization</th>
<th>Disease duration (range)</th>
<th>Medical therapy</th>
<th>Disease activity</th>
<th>Full</th>
<th>Col.</th>
<th>FU</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okazaki et al.</td>
<td>2000</td>
<td>case report</td>
<td>1</td>
<td>distal ulcerative colitis</td>
<td>3y</td>
<td>none</td>
<td>Matt’s grade IV*</td>
<td>Matt’s grade II*</td>
<td>1 (100%)</td>
<td>0</td>
<td>3 y</td>
<td>*microscopic grade</td>
</tr>
<tr>
<td>Jarnerot et al.</td>
<td>2001</td>
<td>case series</td>
<td>6</td>
<td>refractory UC</td>
<td>median 2.5 y (4 mo-12 y)</td>
<td>ASA, CS, IM</td>
<td>NA</td>
<td>NA</td>
<td>2 (33%)</td>
<td>0</td>
<td>2-4 y</td>
<td>study stopped due to difficulties in interpreting the results</td>
</tr>
<tr>
<td>Jo et al.</td>
<td>2003</td>
<td>case series</td>
<td>9</td>
<td>all localizations (mild)</td>
<td>median 49.4 mo (9-168 mo)</td>
<td>ASA, CS, T</td>
<td>UCAI 147.2 (±29)</td>
<td>UCAI 118.8 (±29)</td>
<td>0</td>
<td>0</td>
<td>6 mo</td>
<td>UCAI decrease was transient, only significant at 4 weeks after appendectomy</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>2006</td>
<td>case report</td>
<td>1</td>
<td>pancolitis</td>
<td>2 y</td>
<td>ASA, CS</td>
<td>severe*</td>
<td>mild*</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>*activity was measured by using the UCAI, however exact scores could not be retraced</td>
</tr>
<tr>
<td>Bolin et al.</td>
<td>2009</td>
<td>case series</td>
<td>50</td>
<td>ulcerative proctitis</td>
<td>median 5y (8 mo-30 y)</td>
<td>ASA, CS, IM, B and T</td>
<td>SCCA 9 (range 7-12)</td>
<td>SCCA 2 (range 0-12)</td>
<td>15 (30%)</td>
<td>0</td>
<td>14 mo</td>
<td></td>
</tr>
</tbody>
</table>

FU= Follow up; ASA=salicylates, CS= cortical steroids, IM=immunomodulatory, B=biological (a-TNF); UCAI= ulcerative colitis activity index; SCCA= simple clinical colitis activity index; NA= data not applicable; Col. = colectomy numbers
Jo et al. conducted a trial in 9 patients that were compared to nine historical control patients (retrospectively matched). They found a transient decrease in Ulcerative Colitis Activity Index (UCAI), which was only significant after 4 weeks ($p < 0.05$).

In a case series by Bolin et al. 50 patients with ulcerative proctitis underwent appendectomy. The Simple Clinical Colitis Activity index (SCCA) improved significantly from a median of 9 to a median of 2 ($p < 0.0005$) in 40 patients (80%). From these patients, 15 patients (30%) had no need for continuing medical therapy. The index remained unchanged in 10 of 50 patients (20%). The initial clinical response has been maintained in 37 of 40 patients (93%) for up to three years. Moreover, the appendiceal histology showed ulcerative appendicitis in 25 patients (50%).

**DISCUSSION**

This review shows there is limited and even inconsistent data available regarding the effect of appendectomy on the disease course of UC. Of the six studies, one found a lower relapse rate in patients who had an appendectomy before onset of UC. Two studies found a reduced requirement for immunosuppression in appendectomised patients. However, another two studies found no differences in the requirement for immunosuppression. In addition, two studies found no significant differences in colectomy rates between the appendectomised and non-appendectomised patients, 1 study actually found higher colectomy rates in appendectomised patients, and two studies found lower colectomy rates in appendectomised patients.

The results from this systematic review show the difficulties associated with case control and cohort studies. The methods to recruit cases and controls was different among all the studies, varying from UC cases identified in databases, consecutive UC patients from one clinic or from different hospitals, and controls from the community, from outpatient clinics or from twin databases. To establish comparability, cases and controls should be matched and/or confounders must be adjusted for in the analysis. The adjustment for confounders was insufficiently reported in all studies. Also, the median duration of follow up and median duration of disease was not always readily available. For this review, four endpoints were chosen to identify the effect of appendectomy on the disease course of UC. At least one or more of these endpoints was investigated by the included studies. Nonetheless, methodology was too heterogeneous therefore pooling of data from the studies was not possible.

Several other studies have described the effect of appendectomy on the influence of the disease course of UC. Okazaki et al. and Kim et al. both reported a case where appendectomy after UC onset beneficially influenced the clinical course of UC in a patient with distal ulcerative colitis and pancolitis, respectively. Jo et al. concluded that their period of observation was too short to conclude whether appendectomy was beneficial. They also stated that periappendiceal inflammation in UC is a consequence of UC, rather than non-specific inflammation. This suggests that the appendix is a site possibly involved by UC. In a case series by Bolin et al. 80% of the 50 patients experienced significant improvement in clinical activity with 30% having a complete remission of symptoms after appendectomy, without the requirement of any pharmacological treatment for up to three years of follow-up. Moreover, the appendiceal histology showed ulcerative appendicitis in 25 patients (50%). In these incident reports, one should be aware of the possible presence of publication bias, since failed attempts of appendectomy as therapy for UC may not have been reported.
With the aforementioned remarks to the quality and comparability of the studies included for the review, the clinical relevance of the differences found in the studies remains controversial. As illustrated by the prospective series published by Jarnerot et al. 26 and Jo et al. 27, a major shortcoming in the studies published so far is the divergence of patients and endpoints that were analyzed. The patients differ with regards to duration and localisation of disease, medication used, and whether the appendectomy was performed before or after UC was diagnosed. In addition, different endpoints were analysed in the studies, varying from histological and disease-activity endpoints to the unspecific endpoint of admission rate.

All these aspects make it difficult to draw conclusions, but the studies by Naganuma et al., Radford-Smith et al., Florin et al. and Bolin et al. do suggest that appendectomy in patients with UC may have a beneficial effect on the disease course of UC. It is evident that more rigorous and prospective data is needed. A prospective randomized trial evaluating the disease modifying effect of appendectomy on the disease course of UC is therefore justified.
Reference list


