Stoma formation in Crohn's Disease and the likelihood of antidepressant use: a population-based cohort study

J. Blackwell[1,2,3], S. Saxena[3], N. Jayasooriya[1,2,3] I. Petersen[4,5], M. Hotopf[6,7], H. Creese[3], A. Bottle[3], R.C.G Pollok[1,2,3] – POP-IBD study group

[1] Department of Gastroenterology, St George's Univ. Hospitals NHS Foundation Trust, London, UK

[2]St George's University of London (SGUL), Institute for Infection and Immunity, London, UK

[3]School of Public Health, Imperial College London, London, UK

[4]Dept. Primary Care and Population Health, University College London, UK

[5]Dept. Clinical Epidemiology, Aarhus University, Denmark

[6]Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

[7]South London and Maudsley NHS Foundation Trust, London, UK

Corresponding author: Prof Richard Pollok

Address: St George's Hospitals NHS Foundation Trust, Dept. Gastroenterology, Level 2 Grosvenor Wing, Blackshaw Road, London, SW17 0QT, UK

Email: richard.pollok@nhs.net

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JB, SS, RP, NJ, IP, HC & MH conceived and designed this study. JB prepared the data and carried out statistical analysis supervised by IP and AB. All authors contributed to the development of the analysis, interpreting data and preparing the manuscript. RP will act as the guarantor for the study.

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ORCID number

JB	0000-0003-4278-3720
SS	0000-0003-3787-2083
NJ	0000-0003-1343-2446
IP	0000-0002-0037-7524
MH	0000-0002-3980-4466
HC	0000-0003-0431-7753
AB	0000-0001-9978-2011
RP	0000-0001-6452-6763

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Abstract

Background and Aims

The impact of a temporary or permanent stoma on mental health in Crohn's Disease (CD) is unknown.

Aim: To examine the association between intestinal surgery and stoma formation and subsequent antidepressant medication (ADM) use.

Methods: Using the Clinical Practice Research Datalink, we identified individuals with CD who underwent intestinal surgery between 1998-2018. We excluded individuals with a prescription for an ADM in the 6 months before surgery. Individuals were stratified into three groups: no stoma, temporary stoma, and permanent stoma. We used Kaplan-Meier curves to examine initiation of ADM after intestinal surgery and Cox regression to identify risk factors for ADM use after intestinal surgery.

Results: We identified 1,272 cases of CD undergoing their first intestinal surgery. Of these, 871 (68.5%) had no stoma, 191 (15.0%) had a temporary stoma and 210 (16.5%) had a permanent stoma. The 10-year cumulative incidence of ADM use was 26.4%, 33.4% and 37.3% respectively. Individuals with a permanent stoma were 71% more likely to receive an ADM than those with no stoma (HR 1.71, 95% CI 1.20-2.44). Individuals with a temporary stoma reversed within 12 months had a similar likelihood of ADM use to those without stoma formation (HR 0.99, 95% CI 0.64-1.53) whereas temporary stoma formation with late reversal after 12 months was associated with significantly greater likelihood of ADM use (HR 1.85, 95% CI 1.15-2.96).

Conclusion: Permanent stomas and temporary stomas with late reversal surgery are associated with increased ADM use after intestinal surgery, likely associated with increased anxiety and depression.

Keywords: Crohn's Disease; Stoma; Psychosomatic Medicine; Antidepressants

Abstract Word Count: 259/260

Introduction

More than three quarters of all patients with Crohn's Disease (CD) eventually develop complications of stricturing or penetrating disease.[1] As a consequence, one in two patients with CD require intestinal surgery within 10 years of receiving their diagnosis.[2] Each year 1.8% (95% CI: 1.62–1.91) of the CD population undergo surgery resulting in the formation of either a temporary or permanent stoma.[3] Fear of having an ostomy bag is frequently reported as one of the principal concerns of people living with Inflammatory Bowel Disease (IBD).[4–6] In discrete choice experiments, patients were willing to accept a >5% risk of death in order to avoid a permanent stoma.[7]

People living with stomas are more likely to report having a negative body image than those who had IBD related surgery without stoma formation.[8] Furthermore, 40% of people living with a stoma reported it had a negative impact on their sex life.[9] Despite this, most people living with a stoma reported it was much better than they had anticipated, and some people with temporary stomas elect not to have reversal surgery for this reason.[10]

It remains unclear how stoma formation may contribute to the onset of mood disorders and the need for antidepressant medication. Stoma formation is associated with an increased risk of both anxiety and depression compared with stoma sparing surgery in CD, but it is unclear whether this applies to both permanent *and* temporary stomas.[11] Some patients believe it would be easier to cope with the idea of having a temporary stoma because it offers the possibility of reversal. However, it is unclear if this is the case.[10]

We designed a nationally representative population based cohort study to test the hypothesis that both permanent *and* temporary stomas are associated with an increased likelihood of antidepressant use following intestinal surgery for CD.

Methods

Data source and Ethical approval

Clinical Practice Research Datalink (CPRD) is one of the largest validated primary care research databases in the world. It contains longitudinal, patient-level, anonymised electronic health records of 18 million patients from more than 700 general practices and is representative of the United Kingdom (UK) population. Primary care physicians use Read codes to record diagnoses, surgical procedures and prescriptions. Data are audited to ensure accuracy and completeness. The database has been validated and used for research of long term conditions including IBD and depression.[12,13] We obtained ethical and scientific approval for our study from the Independent Scientific Advisory Committee (ISAC Protocol number: 15_018R).

Incident case definition

We defined incident CD cases as individuals with a first ever diagnosis Read code for CD at least one year after registering with an 'Up To Standard' practice for the period January 1st 1998 to May 1st 2016 in accordance with previously validated methods.[12]

Individuals were included in the cohort if they had a code for intestinal surgery. We excluded individuals who received an ADM prescription within the six-month period before the date of their surgery.

Exposure Variable

Stoma status following first intestinal surgery was the primary exposure variable. Individuals were classed as having `no stoma', a `temporary stoma' or a `permanent stoma'.

We used prescriptions of stoma bags to identify any patients who had stoma-forming surgery (Appendix A – Code List).

We defined patients as having no stoma if they did not receive a prescription for a stoma bag within three months of the date of their first intestinal surgery.

We defined patients as having a permanent stoma if they had a prescription for a stoma bag within three months of the date of their first intestinal surgery and had consecutive stoma bag prescriptions each year until the end of their follow-up.

We defined patients as having a temporary stoma if they had a prescription for a stoma bag within three months of the date of their first intestinal surgery but later had at least one year without any stoma bag prescriptions.

For patients with a temporary stoma we calculated the time to stoma reversal surgery. In a preliminary analysis we determined the median time between stoma bag prescriptions was 32 days (IQR 20-56). We therefore defined the time to stoma reversal surgery as the time from initial surgery to 32 days after the final stoma bag prescription. We subdivided individuals with a temporary stoma into those who had `early reversal' within a year and those who had `late reversal' after one year.

Outcome Measures

Our primary outcome measure was new ADM use following first intestinal surgery. We used antidepressant use as a surrogate marker for anxiety and depression since these conditions are known to account for the large majority of indications for antidepressant prescriptions.[14] We obtained prescription data for escitalopram, sertraline, citalopram, fluoxetine, paroxetine, venlafaxine and mirtazapine (Appendix B – Code List). We defined the date of new ADM use as the date of the first ADM prescription following intestinal surgery. Tricyclic antidepressants were rarely prescribed in our cohort at the dose required for mood disorders and we therefore excluded these from our outcome measure.

Covariates

We adjusted for covariates potentially associated with ADM use including: sex, age at surgery, era of surgery, smoking status, previous depression or anxiety, socio-economic status, time from diagnosis to surgery and perianal disease.

Age at surgery was included in regression models as a continuous variable.

We divided the study period into three eras (1998-2003, 2004-2010, 2011-2016) and adjusted for the era in which surgery took place.

Smoking is associated with depression and prognosis following intestinal resection in CD.[15] We defined individuals as `smokers', `ex-smokers' or `non-smokers' based on codes for smoking status. Individuals whose most recent code indicated active smoking were classed as `smokers', those with codes indicating previous but not current smoking were classed as `ex-smokers', and individuals who had *only* `non-smoker' codes were classified as `non-smokers'. Individuals without data on smoking are likely be either never-smokers or non-recent smokers and were therefore classed as `non-smokers'.[16]

Previous episodes of depression or anxiety are associated with the likelihood of further episodes and antidepressant use. We identified all individuals with a previous record of depression, anxiety or antidepressant medication use earlier than six months before the date of their surgery.

We used the Index of Multiple Deprivation (IMD), a postcode-linked measure of socio-economic deprivation, to assign individuals to 1 of 5 groups using IMD quintiles, from IMD group 1 (least deprived) to 5 (most deprived).

The peri-diagnostic period of CD is associated with an increased risk of incident depression and this may be compounded with early surgery.[11,17] We adjusted for the time from diagnosis of CD to surgery.

Perianal disease is a risk factor for depression following intestinal surgery for CD.[11] We defined patients as having perianal disease if they had a Read code for perianal surgery in their medical records.

Statistical Analysis

Baseline characteristics of cohort were summarised using frequencies and percentages.

We used Cox regression to calculate hazard ratios and 95% confidence intervals for the risk of first antidepressant use by stoma status (i.e. no stoma, temporary stoma and permanent stoma).

In a further analysis we aimed to determine whether the timing of reversal surgery for a temporary stoma affected the likelihood of antidepressant use. We subdivided individuals with a temporary stoma into those who had reversal surgery within a year and those who had reversal surgery after one year and compared these groups with individuals who had no stoma. In these models we adjusted for sex, age at surgery, smoking status, previous depression or anxiety, socio-economic status, perianal disease and time from diagnosis to surgery.

We generated Kaplan Meier curves to examine the incidence of antidepressant use following surgery by stoma status.

As disease course after the first surgery may have an impact on the likelihood of subsequent antidepressant medication use we performed a sensitivity analysis where we adjusted for further corticosteroid use and surgery as proxies for ongoing disease activity and severity.

All analyses were performed using STATA 16 (Statacorp LP, USA).

Results

Between 1st January 1998 and 1st May 2016, we identified 1,272 incident cases of CD who underwent intestinal surgery. Of these 68.5% had no stoma (n=871), 15.0% had a temporary stoma (n=191) and 16.5% had a permanent stoma (n=210). Median follow-up after the surgery date was 5.2 years. Individuals who received a permanent stoma were more likely to be more than 39 years old at the time of their surgery than those with no stoma or a temporary stoma (61.4% vs 46.3% vs 47.6%, Table 1). The median time to stoma reversal for individuals with a temporary stoma was 7.5 months (IQR 3.6-15.7 months). The median observed time living with a stoma for individuals with a permanent stoma was 45 months (IQR 11.1-95.7). All Cox regression models met the proportional hazards assumptions.

Stoma status and the likelihood of antidepressant use

The cumulative 10-year incidence of antidepressant use following intestinal surgery was 26.4%, 33.4% and 37.3% for patients with no stoma, a temporary stoma and a permanent stoma, respectively.

Before adjusting for covariates the likelihood of antidepressant use for patients who received a temporary stoma was not statistically significantly higher than those who had no stoma (HR 1.35, 95% CI 0.96-1.88). By contrast, patients with a permanent stoma were significantly more likely to receive an antidepressant following surgery compared with those with no stoma (HR 1.70, 95% CI 1.21-2.37, Figure 1).

After adjusting for the covariates listed, a temporary stoma continued to be associated with a similar likelihood of antidepressant use relative to those with no stoma (HR 1.27, 95% CI 0.90-1.79, Table 2). A permanent stoma, however, was associated with a significantly higher likelihood of antidepressant use compared with no stoma (HR 1.71, 95% CI 1.20-2.44).

Women were more likely to receive a new antidepressant prescription following intestinal surgery than men (HR 1.54, 95% CI 1.17-2.03).

Previous depression, anxiety or antidepressant use was associated with a significant increase in the likelihood of initiating an antidepressant medication following surgery (HR 2.20, 95% CI 1.66-2.93).

Age at surgery, smoking status, socio-economic status, time from CD diagnosis to surgery, and perianal disease were not associated with antidepressant use following intestinal surgery for CD.

In a sensitivity analysis we also adjusted for events after the first surgery, namely corticosteroid use and further surgery, not including stoma reversal, as markers of ongoing disease activity and severity. Corticosteroid use after surgery was associated with an increased likelihood of initiating an antidepressant medication, as was further surgery (Corticosteroid: HR 1.39, 95% 1.06-1.81, Further Surgery: HR 1.55, 95% CI 1.12-2.16). Adjusting for these did not significantly alter the main findings (Appendix C).

Timing of stoma reversal surgery and the likelihood of antidepressant use

Of the 191 individuals who had a temporary stoma, 131 (69%) had `early' stoma reversal surgery within one year and 60 (31%) had `late' stoma reversal surgery after one year.

The cumulative 10-year incidence of antidepressant use was 26.4% in individuals with no stoma formed at surgery (n=871), 25.6% in those with a temporary stoma formed at surgery which was reversed within one year, and 45.3% in those with a temporary stoma reversed after one year ($p<0.001$, Figure 2).

After adjusting for the listed covariates, the likelihood of antidepressant use in individuals with early reversal of their stoma was similar to that in individuals who had no stoma formation at the time of their intestinal surgery (HR 0.99, 95% CI 0.64-1.53, Table 3). However, individuals with late reversal of their stoma had significantly increased likelihood of antidepressant use following their initial surgery

compared with individuals who had no stoma formation at the time of their surgery (HR 1.85, 95% CI 1.15-2.96, Table 3).

Discussion

Main findings

We found individuals with CD and a permanent stoma after intestinal surgery were 74% more likely to start using an antidepressant compared with individuals who had surgery without stoma formation. Individuals with a temporary stoma reversed within a year of formation had a similar likelihood of using an antidepressant after surgery as individuals without a stoma. However, individuals with a temporary stoma for more than a year were significantly more likely to receive an antidepressant medication than individuals who had surgery without stoma formation.

Findings in relation to previous studies

We found permanent stoma formation is associated with increased rates of antidepressant use after intestinal surgery for CD compared with non-stoma surgery. This is in keeping with the findings of Ananthakrishnan et al. that stoma formation is associated with an increased risk of depression in individuals with CD (OR 1.73, 95% CI 1.05-2.85).[11]

The association between stoma formation and subsequent antidepressant use is likely to be a result of multiple factors. Individuals undergoing stoma formation may have more severe CD, which is associated with increased rates of anxiety and depression.[18] Other studies suggest stoma formation may also result in psychiatric morbidity given individuals are more likely to report having a negative body image following stoma formation.[9] Furthermore, four out of ten individuals with a stoma report it negatively affects their sex life, and some report being stigmatised for having a stoma and become socially isolated as a result.[8–10] Four out of five individuals report they had to change their job and diet as a consequence of having a stoma, and half of those questioned changed their clothing style. Most individuals living with a stoma report it took more than 6 months to feel comfortable with the daily

care of their stoma.[19] Furthermore, a common concern of people living with a stoma is that the bag may leak or smell, potentially resulting in low self-esteem and withdrawal from social situations.

Previous research examining the association between depression and stoma formation made no distinction between temporary and permanent stomas.[11] There are several potential explanations for our finding that permanent stomas are associated with an increased likelihood of antidepressant use whereas temporary stomas with early reversal surgery are not. Qualitative research has found some patients believe they could cope better with a temporary stoma because it offers the hope of reversal surgery and the potential to return to `normality'.[10] We found the timing of temporary stoma reversal was associated with the likelihood of antidepressant use. Individuals who were reversed within 12 months of stoma formation had a similar likelihood of ADM use compared with those undergoing intestinal surgery without stoma formation, however those reversed after 12 months were significantly more likely to be prescribed an ADM. Many patients anticipate early stoma reversal surgery, and it is possible that when their expectations are disappointed this results in increased rates of anxiety or depression.[10] Stoma reversal surgery is often delayed if CD remains active, and it is therefore possible these individuals are more likely to start an antidepressant medication on account of having more active CD, which is associated with increased rates of depression and anxiety.[18]

We found women were more likely than men to start an ADM following surgery. This is in keeping with previous studies that found women have lower quality of life scores after stoma formation than men. It is also likely our results reflect a broader gender disparity, with men being relatively undertreated with antidepressants compared with women.[20,21]

Strengths and Limitations

To our knowledge this is the first population-based study to examine the association between temporary and permanent stoma formation in CD and subsequent antidepressant use. Data were drawn from a large nationally representative validated research database, free of referral centre and

participant selection biases. Data were recorded at the time of consultation or prescription and are therefore not subject to recall bias.

In common with all observational studies using routinely collected data, inaccuracies in coding and completeness may occur. We were unable to ascertain the indication for intestinal surgery or the severity of CD leading up to it, which may have influenced the likelihood of ADM use afterward.

We used ADM use as a surrogate marker for mood disorders, namely depression or anxiety, and extracted data for the most commonly prescribed ADMs in our study period. We were unable to directly determine the indication for ADM prescriptions; previous studies demonstrated that the large majority of ADM prescriptions are for either depression or anxiety, and this is particularly true of SSRIs which comprised the majority of ADM prescriptions in our study.[14] Some individuals may have had mood disorders but did not receive an ADM prescription, potentially choosing to pursue an alternative treatment such as cognitive behavioural therapy, which was not captured in this study. This is likely to have affected our exposure groups equally, though it may have resulted in underestimation of the rates of mood disorders. CPRD contains only limited data on biologic prescriptions as these are prescribed almost exclusively in hospital settings and we were therefore unable to adjust for these.

We used stoma bag prescriptions as a surrogate marker for a stoma but were unable to definitively determine the indication for these prescriptions. It is highly likely stoma bags indicated either an ileostomy or colostomy had been formed during intestinal surgery as our analysis required stoma bags to have been prescribed within 3 months of the date of intestinal surgery.

Implications

We found individuals with CD who receive a permanent stoma following intestinal surgery had a significantly increased likelihood of subsequent ADM use compared with individuals who had intestinal surgery without stoma formation.

Among patients who had a temporary stoma formed, those who had stoma reversal surgery within 12 months had a similar likelihood of subsequent ADM use to individuals with non-stoma surgery, but those reversed later than 12 months after their initial surgery were 73% more likely to receive an ADM.

In keeping with previous studies, we found that stoma formation is associated with significant psychiatric morbidity and recommend that patients should be counselled regarding this before undergoing surgery. However, this association is not necessarily causative. It is likely such individuals have more complicated disease and this may account for their increased ADM use, rather than the fact they are living with a stoma. We adjusted for subsequent corticosteroid use and further surgery as proxies for ongoing disease activity and found both were associated with more antidepressant use. However, permanent stoma formation and late reversal of a temporary stoma remained associated with increased subsequent antidepressant use. This study demonstrates that such individuals are at significant risk of psychiatric morbidity, and therefore clinicians should ensure they screen for mood disorders and ensure treatment is available when required.

Finally, engagement with a stoma support group may improve psychological adaptation to life with a stoma, and individuals undergoing stoma formation should be signposted to these resources.[10]

Conclusions

Permanent stoma formation and temporary stomas with late reversal are associated with significantly increased rates of ADM use after intestinal surgery, which is likely to be indicative of anxiety and depression. Clinicians should be vigilant regarding the higher rate of anxiety and depression in this patient group and consider applying approaches to integrate mental and physical healthcare provision.

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Table 1: Baseline Characteristics of Cohort

	No Stoma	Temporary Stoma	Permanent Stoma
n=	871	191	210
Demographics			
Male (%)	393 (45)	92 (48)	120 (57)
Age at diagnosis (%)			
<20	59 (7)	10 (5)	17 (8)
20-39	408 (47)	90 (47)	64 (30)
>39	404 (46)	91 (48)	129 (61)
Social deprivation (%)			
IMD 1-3	388 (45)	71 (37)	64 (30)
IMD 4-5	230 (26)	48 (20)	43 (20)
Unknown	253 (23)	72 (38)	103 (49)
Smoking status (%)			
Never-Smoker	588 (68)	125 (65)	126 (60)
Ex-Smoker	107 (12)	15 (8)	46 (22)
Smoker	176 (20)	51 (27)	38 (18)
Disease duration before surgery - Months (Range)	17 (0-170)	22 (0-166)	22 (0-164)
Perianal Disease (%)	109 (13)	36 (19)	57 (27)
Corticosteroids (%)	498 (57)	120 (63)	129 (61)
Thiopurines (%)	389 (45)	95 (50)	103 (49)
Era of surgery (%)			
1998-2003	242 (28)	31 (16)	43 (20)
2004-2010	381 (44)	92 (48)	86 (41)
2011-2016	248 (28)	68 (36)	81 (39)

IMD – Index of Multiple Deprivation.

Table 2: Risk of antidepressant use after first intestinal surgery for Crohn's Disease

	Unadjusted		Adjusted	
n=	1,272		1,272	
	HR	95% CI	HR	95% CI
Stoma status				
No Stoma	1	-	1	-
Temporary Stoma	1.35	0.96-1.88	1.27	0.90-1.79
Permanent Stoma	**1.70**	**1.21-2.37**	**1.71**	**1.20-2.44**
Sex				
Male	1	-	1	-
Female	**1.62**	**1.24-2.12**	**1.54**	**1.17-2.03**
Age at surgery	1.00	0.99-1.00	1.00	0.99-1.00
Social deprivation				
IMD 1-3	1	-	1	-
IMD 4-5	1.20	0.86-1.67	1.03	0.74-1.44
Unknown	1.15	0.86-1.55	1.10	0.81-1.49
Smoking status				
Never-Smoker	1	-	1	-
Ex-Smoker	0.90	0.60-1.37	0.81	0.52-1.27
Smoker	1.17	0.86-1.61	0.93	0.65-1.30
Days from diagnosis to surgery	1.06	0.80-1.40	1.00	0.99-1.00
Perianal Disease	1.34	0.97-1.84	1.31	0.94-1.83
Previous depression or anxiety	**2.37**	**1.82-3.10**	**2.20**	**1.66-2.93**
Era of surgery				
1998-2003	1	-	1	-
2004-2010	**1.56**	**1.13-2.14**	1.37	0.96-1.94
2011-2016	**1.90**	**1.29-2.80**	**1.58**	**1.02-2.93**

IMD – Index of Multiple Deprivation.

Table 3: Risk of antidepressant use among individuals with Crohn's Disease and temporary stomas with early and late reversal surgery

	Unadjusted		Adjusted	
n=	1,062		1,062	
	HR	95% CI	HR	95% CI
Stoma status				
No Stoma	1	-	1	-
Early Stoma Reversal	1.06	0.69-1.63	0.99	0.64-1.53
Late Stoma Reversal	**1.97**	**1.24-3.11**	**1.85**	**1.15-2.96**
Sex				
Male	1	-	1	-
Female	**1.65**	**1.22-2.22**	**1.54**	**1.13-2.10**
Age at surgery	0.99	0.99-1.00	0.99	0.98-1.00
Social deprivation				
IMD 1-3	1	-	1	-
IMD 4-5	1.19	0.84-1.69	0.99	0.70-1.42
Unknown	0.94	0.67-1.32	0.91	0.64-1.29
Smoking status				
Never-Smoker	1	-	1	-
Ex-Smoker	0.76	0.45-1.29	0.75	0.44-1.30
Smoker	1.10	0.77-1.56	0.88	0.60-1.29
Days from diagnosis to surgery	1.00	0.99-1.00	1.00	0.99-1.00
Perianal Disease	**1.50**	**1.05-2.16**	1.40	0.96-2.04
Previous depression or anxiety	**2.26**	**1.67-3.05**	**2.12**	**1.54-2.92**
Era of surgery				
1998-2003	1	-	1	-
2004-2010	**1.53**	**1.08-2.17**	1.34	0.91-1.96
2011-2016	**1.78**	**1.15-2.75**	1.50	0.92-2.43

No Stoma – Intestinal surgery for Crohn's Disease without stoma formation.
Early Stoma Reversal – Temporary stoma reversed within a year of formation.
Late Stoma Reversal – Temporary stoma reversed more than one year after formation.
IMD – Index of Multiple Deprivation

Figure 1: Antidepressant medication use following first intestinal surgery for Crohn's disease by stoma status

Figure 2: Antidepressant medication use following first intestinal surgery for Crohn's Disease among individuals with temporary stomas with early and late reversal surgery

No Stoma – Intestinal surgery for Crohn's Disease without stoma formation.
Temporary Stoma: Early Reversal – Reversed within a year of formation.
Temporary Stoma: Late Reversal – Reversed more than one year after formation.