THE USE OF GUM CHEWING IN POSTOPERATIVE CARE OF PATIENTS WITH ABDOMINAL SURGERY: DEVELOPING AN EVIDENCE-BASED CLINICAL PROTOCOL - PART I

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Abstract

Aim: The aim of the paper was to search for evidence that the use of gum chewing in the postoperative care of patients who had undergone abdominal surgery decreases the risk of paralytic postoperative ileus by significantly reducing the time to first flatus and time to first bowel movement. Methods: A literature review of selected meta-analyses and randomized control trials (RCT) was conducted to find the evidence that the use of gum chewing in the postoperative care of patients who had undergone abdominal surgery decreases the risk of paralytic postoperative ileus expressed as the time to first flatus and time to first bowel movement. The following databases were searched: OVID Medline®, CINAHL, and PubMed. The search focused on material published in English in peer-reviewed journals between the years 2002 and 2012. Weighted mean difference was the effect size abstracted from the meta-analyses of gum chewing on time to first flatus and time to first bowel movement. From the RCT, Cohen’s d effect sizes were calculated to determine the strength of the gum chewing intervention on time to first flatus and time to first bowel movement. Results: Four randomized controlled trials and two meta-analyses were selected and critically appraised. All six studies concluded that gum chewing has a statistically significant and very large to medium effect on time to first flatus and time to first bowel movement. Based on the effect sizes, the conclusion was drawn that chewing gum during the postoperative period leads to a clinically significant reduction in time to passage of first flatus and time to first bowel movement. Conclusion: Strong evidence supports the use of gum chewing in postoperative care of patients who have undergone abdominal surgery to reduce the risk of paralytic postoperative ileus. Key words: gum chewing, postoperative care, abdominal surgery, paralytic postoperative ileus, time to first flatus, time to first bowel movement.

Introduction

Despite numerous advances in surgical technique and perioperative care, paralytic postoperative ileus (PPOI) continues to be one of the most common and expected concomitants of abdominal surgery. PPOI can occur despite efforts to minimize surgical trauma and manipulation of the bowel (e.g., after laparoscopy), and it can occur after procedures that do not involve the bowel (e.g., hysterectomy and thoracic, knee, and other joint surgeries) (Senagore, 2007, p. S3). PPOI prolongs hospital stays, increases medical costs, may lead to hospital-acquired infections or complications and compromised pulmonary functioning, and poses increased burdens for patients and surgeons (Schuster et al., 2006, p. 174; Viscusi et al., 2006, p. 64). Patients with PPOI manifest symptoms of pain, distention, decreased or absent bowel sounds, inability to advance oral intake, and emesis. Treatment may be required, including nasogastric tube decompression, fluid and electrolyte replacement, and analgesia (Schuster et al., 2006, p. 174). Uncomplicated ileus following surgery resolves spontaneously within 2-3 days (Basaran, Pitkin, 2009, p. 2). The colon typically recovers motility in 3-5 days (Schuster, Montie, 2002, p. 465). When considering total hospital expenditures for a patient who develops PPOI after one of the 50 selected abdominal-related procedures, the cost of an average hospital stay of 11.5 days was $18,877. Applying this cost nationally results in a projected total hospital cost of $2.7 billion annually in the U.S. The projected cost of readmissions for coded PPOI was an additional $122.2 million annually for patients with...
coded PPOI on initial admission (Goldstein et al., 2007, p. 87).

Although the etiology of PPOI is multifactorial and not fully understood (Fitzgerald, Ahmed, 2009, p. 2558; Schuster, Montie, 2002, p. 466), research has suggested numerous contributing factors, including three major mechanisms: pharmacologic (opioids, general anesthetic), inflammatory causes (bowel manipulation, inflammatory mediator release), and neural reflexes (postoperative sympathetic overactivity or other inhibitory neuronal pathways) (Fitzgerald, Ahmed, 2009, p. 2558). In addition, perioperative fluid excess may prolong PPOI (Kehlet, 2008, p. 552). Many strategies have been applied to prevent and manage PPOI, ranging from changes in surgical techniques, supportive care, and patient-initiated activities, to pharmacological intervention (Johnson, Walsh, 2009, p. 644). Accelerated postoperative care, including early oral feedings, avoidance of nasogastric intubation, and early ambulation may hasten restoration of gut function, reduce morbidity, and shorten hospital stay (Goldstein et al., 2007; Mattei, Rombeau, 2006; Stewart et al., 1998). Additional techniques that can be combined in a multimodal approach to prevent and manage PPOI include opioid-sparing analgesia, use of regional anesthesia techniques, and administration of laxatives (Basse et al., 2001; Basse et al., 2005; Bauer, Boeckxstaens, 2004; Mattei, Rombeau, 2006).

The treatment of PPOI has traditionally been supportive, with nasogastric decompression, intravenous fluids, and watchful waiting (Fitzgerald, Ahmed, 2009, p. 2558). However, the widespread introduction of enhanced patient recovery protocols has driven new research in this area focusing on mechanisms and treatments for this major cause of delayed discharge. One of these treatments is based on the physiologic theory of “sham feeding.” Gum chewing has been studied over the last decade as a form of sham feeding to stimulate bowel recovery after surgery. The presumed mechanism of action is vagal cholinergic (parasympathetic) stimulation of the gastrointestinal tract, similar to oral intake but with theoretically less risk of vomiting and aspiration (Johnson, Walsh, 2009, p. 645). Cephalic-vagal stimulation from chewing alone gives rise to propulsive and hormonal gastrointestinal activity similar to that seen with normal eating. Although early enteral feeding has also been shown to be beneficial, the effect on PPOI varies and patient intolerance is high, especially following gastrointestinal surgery. Gum chewing is an inexpensive, convenient, safe, effective, and physiologically sound method to use in enhancing the recovery of bowel function.

**Aim**

The aim of the paper was to search for evidence that the use of gum chewing in the postoperative care of patients who had undergone abdominal surgery decreases the risk of paralytic postoperative ileus by significantly reducing the time to first flatus and time to first bowel movement.

**Methods**

A literature review of selected randomized control trials (RCT) and meta-analyses was conducted to find the evidence that the use of gum chewing in the postoperative care of patients who had undergone abdominal surgery decreases the risk of paralytic postoperative ileus expressed as the time to first flatus and time to first bowel movement.

**Formulating the clinical question**

The following clinical question was formulated: For adult patients who have undergone abdominal surgery, does the use of gum chewing postoperatively reduce the risk of paralytic ileus in comparison with the usual care regimen? The question was related to prevention.

**Clinical question in PICO format**

P (population): adult abdominal surgical patients - adult patients greater than or equal to 18 years of age who have undergone abdominal surgery for any indication, and are able to chew gum in the postoperative setting, but are otherwise NPO (nothing by mouth).

I (intervention): gum chewing - chewing of sugar-free gum. Sugar-free chewing gum has met the American Dental Association (ADA) criteria for safety and effectiveness. Chewing sugar-free gum has been shown to increase the flow of saliva, thereby reducing plaque acid, strengthening the teeth, and reducing tooth decay. Of course, chewing sugar-containing gum also increases saliva flow, but it also contains sugar, which is used by plaque bacteria to produce decay-causing acids (ADA, 2013). Patients should be strongly discouraged from chewing sugar-containing gum, because it has definitely been shown to be cariogenic (Imfeld, 1999, p. 405).

C (comparison): usual care - usual postoperative NPO care.

O (outcome): the risk of paralytic postoperative ileus as measured by time to first flatus, time to first bowel movement. Paralytic postoperative ileus means ileus...
last lasting more than three days after surgery (Basaran, Pitkin, 2009, p. 2).

**Analyzed outcomes**

The following outcomes were used to compare patients with gum chewing intervention and patients with usual care after abdominal surgery: 1) time to first flatus and 2) time to first bowel movement.

**Search strategy**

Once the PICO question was crafted, a literature search was conducted to find evidence to support the proposed clinical protocol. The following databases were searched: OVID Medline®, CINAHL, and PubMed. Terms used in the search included: chewing gum, ileus, abdominal surgical patients, and postoperative ileus. The search focused on material published in English in peer-reviewed journals between the years 2002 and 2012. Inclusion criteria were: randomized controlled trials (RCT) and meta-analyses that included time to first flatus and time to first bowel movement as primary outcomes. Studies were excluded that treated other kinds of surgery than abdominal surgery, and other types of treatment or interventions than gum chewing. Each of the first six authors independently performed a literature search to locate appropriate materials. Each author chose at least one paper related to the PICO question. The seventh author, an expert in evidence-based practice, reviewed the material located and verified that six of the articles did indeed relate to the PICO question. Of the six articles, two were meta-analyses and four were RCT. The following data were collected from all eligible articles: year of publication, purpose, methodology (design type, random assignment, blinding, sample size, sampling plan, basic description of subjects, setting), variables, findings for PICO intervention on PICO outcome (type of statistical tests used, statistical findings, conclusion reached), and study strengths and weaknesses.

**Evaluation of the evidence**

Modified McMaster Quality Criteria (E. Schlenk, personal communication, October 2, 2012) were used to evaluate the evidence of individual studies. The modified U.S. Preventive Services Task Force (USPSTF) criteria were used to evaluate the evidence gathered from the entire set of studies (AHRQ, 2010).

**Statistical analysis**

Weighted mean difference was the effect size abstracted from the meta-analyses. In order to determine the strength of the gum chewing intervention on the outcomes in the RCT, Cohen’s d effect sizes were calculated. A web-based effect size calculator (Wilson, 2001) was used to calculate effect sizes. Forest plots were created to present effect sizes for postoperative times to first flatus and first bowel movement obtained from the four RCT.

**Results**

**Characteristics of the selected studies**

In Table 1, the characteristics of the two meta-analyses and four RCT are summarized. Four RCT were from different countries: Egypt, Japan, Korea, and USA. The two meta-analyses did not include information about setting. The modified McMaster Quality Criteria grades for the studies were as follows: two meta-analyses at level I and four RCT at level I. Level I means that the study was a meta-analysis or RCT without major limitations and with adequate power to answer the clinical question.

**Description of the studies**

Abd-El-Maeboud et al. (2009) published results from a RCT conducted at a University Hospital in Egypt over a period of seven months from July through January 2007 that evaluated the efficacy and safety of postoperative gum chewing on the recovery of bowel motility after Caesarean section (C-section). A convenience sample of patients undergoing routine scheduled C-section under general anesthesia was randomized to a treatment group and traditional care group.

Asao et al. (2002) published results from a prospective experimental clinical trial that studied the effect of gum chewing on Japanese patients with PPOI who had undergone laparoscopic colectomies. All patients in the study had colorectal cancer and underwent an elective laparoscopic colectomy. All patients received the same postoperative standard of care.

Choi et al. (2010) published results from a prospective randomized comparative study that examined the effect of chewing gum on bowel motility in patients undergoing radical cystectomy. The authors stratified patients with bladder cancer and subsequent radical cystectomy into two groups: those undergoing open cystectomy and those undergoing robot-assisted cystectomy. The study was conducted in the Kangbuk Samsung Hospital in Seoul, Korea from 2007 to 2009.

Schuster et al. (2006) published the results of a study on reducing ileus after elective open sigmoid colectomy by gum chewing. The purpose of this prospective RCT in a hospital in Santa Barbara, CA, was to compare patients who chewed gum after...
elective open colon resection with a control group and to measure the return of bowel function and appetite, length of hospital stay, and complications. The patients randomly pulled cards to determine their group assignment.

Schuster et al. (2006) published the results of a study on reducing ileus after elective open sigmoid colectomy by gum chewing. The purpose of this prospective RCT in a hospital in Santa Barbara, CA, was to compare patients who chewed gum after elective open colon resection with a control group and to measure the return of bowel function and appetite, length of hospital stay, and complications. The patients randomly pulled cards to determine their group assignment.

Fitzgerald and Ahmed (2009) performed a meta-analysis of RCT to examine the effect of chewing-gum therapy on PPOI. Seven studies were included with a total of 272 patients.

Vásquez et al. (2009) published a meta-analysis of RCT comparing the effect of gum chewing plus standard treatment vs. standard treatment on ileus after colorectal surgery. Six trials, published between 2002 and 2006, including 244 patients were analyzed. Patients underwent either elective open surgery or laparoscopy-assisted surgery, which included right hemicolectomy, transverse colectomy, left colectomy, sigmoidectomy, anterior resection, and/or abdominoperianal resection.

Table 2 presents the results and Table 3 shows the effect sizes from the six studies. Cohen’s $d$ effect sizes with 95% confidence intervals (CI) were calculated from the results of the four RCT (Abd-El-Maeboud et al., 2009; Asao et al., 2002; Choi et al., 2011; Schuster et al., 2006). In three of the trials (Abd-El-Maeboud et al., 2009; Asao et al., 2002; Schuster et al., 2006), gum chewing was shown to have a very large to large effect on time to first flatus and time to first bowel movement; in one study (Choi et al., 2011) gum chewing was shown to have a medium effect. Weighted mean differences with 95% CI were abstracted from the two meta-analyses (Fitzgerald, Ahmed, 2009; Vásquez et al., 2009) as a measure of effect size.
The use of gum chewing in postoperative care of patients with abdominal surgery

**Table 2 Brief summary of research findings**

<table>
<thead>
<tr>
<th>Authors, year of publication</th>
<th>Gum chewing group</th>
<th>Control group</th>
<th>Time to first flatus</th>
<th>Time to first bowel movement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abd-El-Maeboud et al., 2009</td>
<td>Gum chewing group (n=93)</td>
<td>Control group (n=107)</td>
<td>17.9±4.6</td>
<td>24.4±7.1</td>
</tr>
<tr>
<td>Asao et al., 2002</td>
<td>Gum chewing group (n=10)</td>
<td>Control group (n=9)</td>
<td>2.1±0.5 (d) *(50.4±12) h</td>
<td>3.2 ±0.9 (d) *(76.8±21.6) h</td>
</tr>
<tr>
<td>Choi et al., 2011</td>
<td>Gum chewing group (n=30)</td>
<td>Control group (n=30)</td>
<td>57.1 (43-78)</td>
<td>69.5 (51-92)</td>
</tr>
<tr>
<td>Schuster et al., 2006</td>
<td>Gum chewing group (n=17)</td>
<td>Control group (n=17)</td>
<td>89.4±24</td>
<td>80.2 ±19.1</td>
</tr>
<tr>
<td>Fitzgerald, Ahmed, 2009</td>
<td>Gum chewing group (n=144/122)</td>
<td>Control group (n=128/107)</td>
<td>12.60 h (17% reduction)</td>
<td>14.00 h reduction</td>
</tr>
<tr>
<td>Vásquez et al., 2009</td>
<td>Gum chewing group (n=132/93)</td>
<td>Control group (n=112/74)</td>
<td>14.00 h reduction</td>
<td>24.99 h reduction</td>
</tr>
</tbody>
</table>

h=hours; d=days; *days from the original study were converted into hours; †M±SD except Choi et al. (2011), which reported medians and ranges.

**Table 3 Effect sizes**

<table>
<thead>
<tr>
<th>Authors, year of publication</th>
<th>Effect size: Time to first flatus</th>
<th>Effect size: Time to first bowel movement</th>
<th>Magnitude of effect sizes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abd-El-Maeboud et al., 2009</td>
<td>$d = -1.0712$ 95% CI: -1.3682 to -0.7742</td>
<td>$d = -1.3085$ 95% CI: -1.6145 to -1.0025</td>
<td>Very large</td>
</tr>
<tr>
<td>Asao et al., 2002</td>
<td>$d = -1.5350$ 95% CI: -2.5593 to -0.5107</td>
<td>$d = -1.5805$ 95% CI: -2.6118 to -0.5493</td>
<td>Very large</td>
</tr>
<tr>
<td>Choi et al., 2011</td>
<td>$d = -0.7052$ 95% CI: -0.1686 to -1.2418</td>
<td>$d = -0.7052$ 95% CI: -0.1686 to -1.2418</td>
<td>Medium</td>
</tr>
<tr>
<td>Schuster et al., 2006</td>
<td>$d = -0.8662$ 95% CI: -1.5693 to -0.1631</td>
<td>$d = -1.5062$ 95% CI: -2.2678 to -0.7446</td>
<td>Large / very large</td>
</tr>
<tr>
<td>Fitzgerald, Ahmed, 2009</td>
<td>WMD = -12.60 95% CI: -21.49 to -3.72</td>
<td>WMD = -23.11 95% CI: -34.32 to -11.91</td>
<td>-</td>
</tr>
<tr>
<td>Vásquez et al., 2009</td>
<td>WMD = -14.00 95% CI: -23.45, -4.55</td>
<td>WMD = -24.99 95% CI: -42.31, -7.66</td>
<td>-</td>
</tr>
</tbody>
</table>

$d= $Cohen’s $d$ effect size; CI=confidence interval; WMD=weighted mean difference

Figures 1 and 2 are forest plots depicting effect sizes for postoperative times to first flatus and first bowel movement obtained from the four RCT. Both graphs display intervention to the left side of the “line of no effect”.

All four studies show a statistically significantly better outcome (time to first flatus) with intervention (gum chewing) than with usual postoperative care.
All four studies show a statistically significantly better outcome (time to first bowel movement) with intervention (gum chewing) than with usual postoperative care.

*Evaluate the overall evidence using modified USPSTF criteria*

In evaluating the overall evidence using the modified U.S. Preventive Services Task Force (USPSTF) criteria (AHRQ, 2010), we would rate the level of certainty regarding net benefit as high, which means that the available evidence usually includes consistent results from well-designed, well-conducted studies in representative populations. These studies assess the effects of the interventions on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.

![Forest plot of effect sizes on postoperative time to first flatus](image1)

**Figure 1** Forest plot of effect sizes on postoperative time to first flatus

![Forest plot of effect sizes on postoperative time to bowel movement](image2)

**Figure 2** Forest plot of effect sizes on postoperative time to first bowel movement
Discussion

Consistent and inconsistent results among the studies, range of effect sizes

All six studies significantly supported the effect of the PICO intervention of gum chewing on the PICO outcomes, which strongly indicates the usefulness of the intervention. The outcomes were clearly defined and consistent across all the studies. In three RCT, the effect size was very large to large for gum chewing on time to first flatus and time to first bowel movement; in one study, the effect size was medium (Table 3). These minor inconsistencies may be due to the sample sizes of the studies.

Strengths and weaknesses of research designs and methods in the studies

The strengths and weaknesses of the research designs and methods can have a large impact on the analysis and interpretation of results. Two studies (Fitzgerald, Ahmed, 2009, p. 2558; Vásquez et al., 2009, p. 650) were meta-analyses of RCT, which produce the strongest evidence, and four studies (Abd-El-Maeboud et al., 2009, p. 1335; Asao et al., 2002, p. 30; Choi et al., 2011, p. 884; Schuster et al., 2006, p. 175) were RCT (Table 1). Another strength was a variety of settings across the studies. Most studies involved patients from different countries and different types of abdominal surgery, which improves the external validity of the overall evidence. All six studies had random assignment to groups.

The weaknesses in the studies included some variation in the methods. Sample size varied, though most of the RCT reported small or moderate sample sizes. The meta-analyses included a small number of studies. Slight to moderate differences were observed in the postoperative protocols, as well as in the precise way in which gum chewing was integrated into postoperative care. For example, one regimen involved chewing sugar-free gum for 30 minutes, 3 times daily until first flatus and first oral intake (Choi et al., 2011, p. 884). Another regimen involved chewing one stick of sugar-free gum for 15 minutes every 2 hours starting 2 hours after the end of surgery, continuing this every 2 hours of the day while the patients were awake. Gum chewing stopped with passage of flatus and resumption of oral intake (sips of water), which for both groups started at 12 hours postoperative (Abd-El-Maeboud et al., 2009, p. 1335).

Another weakness was a lack of standardization or description of perioperative care regimens. In the meta-analyses, the demographic data were not provided. In three RCT, the mean age was approximately 60 years, with a slight prevalence of men over women, although in one RCT, the sample consisted of 200 women after C-section, obviously with a lower mean age (26 years).

Applicability to patient population and setting

The study findings are applicable to the patient population and setting for the PICO question. All but one of the studies included adults aged 18 years or older who underwent abdominal surgery. In the meta-analysis by Vásquez et al. (2009, p. 650), subjects were aged 15 years and above. Studies did not provide information about the evaluation and screening of the cognitive function of the patients. The applicability of the findings may vary slightly between patient populations based on the type of surgery performed. The effect of chewing gum on bowel motility was examined in patients undergoing radical cystectomy (Choi et al., 2011, p. 884), elective open colon resection (Schuster et al., 2006, p. 175), laparoscopic colectomy for colorectal cancer (Asao et al., 2002, p. 30), C-section (Abd-El-Maeboud et al., 2009, p. 1335), elective open or laparoscopic gastrointestinal surgery for any indication (Fitzgerald, Ahmed, 2009, p. 2558), and elective open or laparoscopic colorectal surgery (Vásquez et al., 2009, p. 650). Setting locations were not reported in either meta-analysis. The four RCT were conducted in Japan (Asao et al., 2002), Egypt (Abd-El-Maeboud et al., 2009, p. 1335), Korea (Choi et al., 2011, p. 884) and a U.S. community hospital (Schuster et al., 2006, p. 175). Although the studies involved slightly different patient populations and settings, the results are still generalizable to the PICO clinical question. Differences in health care delivery systems notwithstanding, PPOI are a common complication of abdominal surgeries.

Risks and benefits of the treatment to patients

Gum chewing is a form of sham feeding, which could encourage gastrointestinal motility through cephalic-vagal stimulation (Noble et al., 2009, p. 100). The gum chewing intervention could significantly shorten the time to first flatus and time to first bowel movement. Additional benefits of the gum chewing intervention are that it is inexpensive, well tolerated, widely available, physiologically based, and effective (Fitzgerald, Ahmed, 2009, p. 2558). The content of maxitols in sugar-free chewing gums may play a role in the amelioration of ileus after surgery due to their potential to affect gastrointestinal motility and to
their effect as osmotic laxatives (Tandeter, 2009, p. 39).

Despite all these benefits, there are some risks associated with gum chewing. The risks of gum chewing are swallowing of gum or aspiration of gum as a foreign body. Although gum is designed to be chewed and not swallowed, it generally is not harmful if swallowed. If gum is swallowed, the gum base simply passes through one’s gastrointestinal system as other roughage does. This process normally takes only a few days. Factors that increase the risk of foreign material aspiration in adults include underlying primary neurological disorders, such as senile dementia, mental retardation, seizures, strokes, and Parkinsonism. Conditions that cause coma or depress the central nervous system and the gag reflex, such as alcohol, narcotics, barbiturates, or benzodiazepines, can also increase likelihood of aspiration. Other predisposing and facilitative factors to foreign body aspiration include institutionalization, old age, poor dentition, impaired swallow reflex, impaired cough reflex, loss of consciousness, and maxillofacial trauma (Njau, 2004). Without the presence of these predisposing factors, the risk of aspiration is minimal. Further, the quantity of gum used is very small and would not occlude the whole trachea, though sleeping with gum in the mouth can be dangerous and should be avoided.

Overall, the risks of gum chewing are minor when compared to its benefits. It is important to carefully choose the patients eligible for this intervention. Patients eligible for gum chewing are those who have had abdominal surgery, are able to follow instructions about gum chewing, have normal dentition, and are able to stay awake while chewing gum.

The results of other meta-analyses (Chan, Law, 2007; de Castro et al., 2008; Marwah, Singla, Tinna, 2012; Noble et al., 2009; Purkayasatha et al., 2008) also support these findings. In addition to shortening the time to first flatus and to first bowel movement, gum chewing has also been associated with other benefits such as a reduction in hospital stay (Chan, Law, 2007; Fitzgerald, Ahmed, 2009, p. 2559) in some of these studies.

**Limitations**

A limitation of this review is the small number of studies. Although only six studies were chosen and critically appraised, the designs were strong and the findings were consistent. Overall, the limitations of the studies themselves do not prevent using the results in the development of the clinical protocol.

**Conclusion**

PPOI is a common complication of abdominal surgeries, leading to increased hospital stays and healthcare costs. Gum chewing is an inexpensive, convenient, safe, effective, and physiologically based intervention that significantly reduces PPOI and may make the patient more comfortable. Strong evidence supports the use of gum chewing in the postoperative care of patients who have undergone abdominal surgery in order to reduce the risk of paralytic postoperative ileus. This intervention should be considered for routine use to prevent PPOI. Therefore a clinical protocol should be developed.

The purpose of the literature review was to gather evidence to support the development of a clinical protocol that would mandate the inclusion of gum chewing in the postoperative orders of eligible patients who had abdominal surgery in order to prevent PPOI. The clinical protocol itself will be presented in Part II of the article.

**Ethical aspects and conflict of interest**

There is no conflict of interest to be disclosed. Because the review did not involve human subjects, medical records, or human tissues, Institutional Review Board approval was not required.

**Contribution to authorship**

All of the authors made substantial contributions to the conception and design of the review, and all were involved in the literature search, analysis and interpretation of the data, and in the drafting and revising the paper. E. Schlenk supervised the course project and critiqued the final draft of the paper.

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