

Significantly Increased Pregnancy Rates After Laparoscopic Restorative Proctocolectomy

A Cross-Sectional Study

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Objective: To assess the impact of a laparoscopic approach on female fecundity in ileoanal pouch surgery.

Background: Restorative proctocolectomy with ileal pouch anal anastomosis (IPAA) is associated with tubal factor infertility in female patients. Different studies showed less adhesion formation after laparoscopic colectomy. The relation between laparoscopic pouch surgery and fertility, however, has not been studied so far.

Methods: This cross-sectional study was carried out in 3 university hospitals in the Netherlands and in Belgium. Female patients older than 18 years that had IPAA under the age of 41 were eligible for inclusion (n = 179). We sent them a questionnaire addressing medical and fertility history. The primary endpoint was time to first spontaneous pregnancy after IPAA. This study has been registered with ISRCTN.org (ISRCTN85421386).

Results: Of 179 eligible patients, 160 (89%) returned the questionnaire. After IPAA, 50 (31%) patients attempted to conceive. Of these, 23 (46%) had undergone open and 27 (54%) had undergone laparoscopic IPAA. Patient characteristics were similar in both groups. Indications for surgery were ulcerative colitis (UC) in 37 patients, familial adenomatous polyposis (FAP) in 12 patients, and colonic ischemia in 1 patient. A Kaplan-Meier survival function was plotted for time to first spontaneous pregnancy and showed a higher pregnancy rate after laparoscopic IPAA (log-rank, $P = 0.023$). Similarly, subsequent survival analysis for all patients with UC showed an increased pregnancy rate for the laparoscopic group (log-rank, $P = 0.033$).

Conclusions: Pregnancy rates are significantly higher after laparoscopic IPAA. This makes the laparoscopic approach the method of choice in young women.

Keywords: colorectal surgery, familial adenomatous polyposis, fecundity, fertility, ileoanal pouch, laparoscopic surgery, lcerative colitis

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Restorative proctocolectomy with ileal pouch anal anastomosis (IPAA) is the preferred surgical treatment of intractable ulcerative colitis (UC) and familial adenomatous polyposis (FAP). Eventually,

up to 32% of patients with UC and virtually all patients with FAP are treated surgically. Many of these patients are young women in their reproductive years.^{1–3} In a large series of patients with FAP mean age at IPAA was 24 years, and in a series of patients with UC median age at IPAA was 27 years.^{1,4} It has been established that female patients face a significant reduction in fecundity after this procedure.^{5,6} The unfulfilled desire for a child leads to considerable emotional distress for the couples involved.⁷ Moreover, the costs for assisted reproductive technologies can be a financial burden for couples.⁸ Two Scandinavian studies showed a considerable decrease in fecundity after IPAA, down to 35% in patients with UC and down to 54% in patients with FAP, respectively.^{4,9} In a more recent study from the Netherlands, fecundity problems were documented in 15% of women after IPAA for FAP.¹ The reduction in fecundity is most likely attributed to adhesions of the Fallopian tubes caused by surgery in the pelvis, a so-called “tubal factor infertility.”^{4,9}

Over the last 2 decades, laparoscopy has been successfully introduced in colorectal surgery. In addition to the cosmetic advantages, laparoscopic IPAA has proved to be safe and feasible in both benign and malignant diseases.¹⁰ Recent studies demonstrated a significant decrease in adhesion formation after laparoscopic abdominal surgery.^{11,12} On the basis of those observations, it was hypothesized that a reduction in adhesions of the Fallopian tubes after laparoscopic IPAA could lead to better preservation of fertility in female patients. This relation between laparoscopic pouch surgery and fertility, however, has not been studied so far. Therefore, the aim of this study was to determine whether pregnancy rate was higher after laparoscopic IPAA than after open IPAA.

METHODS

Participants and Study Design

This cross-sectional study was performed in 3 university hospitals in the Netherlands and in Belgium. Hospital databases were searched for IPAA from 1993 to 2009. Eligible participants were all living female patients who were at least 18 years old at the time of the study and who had IPAA under the age of 41. There were no limitations as to indications for the surgery. The study protocol was approved by the institutional review board of the University Hospitals of the Catholic University in Leuven (B32220109939). All potential participants were contacted for consent. They then received a questionnaire (Supplemental Digital Content, available at <http://links.lww.com/SLA/A236>), and if it was not returned within 3 weeks a reminder was sent. In case of incomplete or unclear answers, participants were contacted to further clarify the data. The study was carried out between February 2010 and February 2011.

The questionnaire had been developed by the Department of Obstetrics and Gynaecology and the Department of Surgery at the Academic Medical Center, Amsterdam. It addressed patients' general medical history, their desire for children and their fertility and obstetric history both before and after IPAA. Specific questions regarding potential confounding factors such as smoking at the time of conception attempt, a history of pelvic inflammatory disease, and

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a history of extrauterine gravidity were included. All self-reported patient data were subsequently verified and completed by checking the available medical records. *Pregnancy* was defined as a “clinical pregnancy,” that is, the presence of a fetus with a heartbeat demonstrated by ultrasound. *Time to pregnancy* was defined as the number of months between the time the patients stopped birth control and the first day of the last menstrual period. The menstrual cycle was considered regular if its duration was between 28 and 35 days. *Subfertility* was defined as unsuccessfully trying to conceive for at least 12 months. Several patients reported more than 1 pregnancy, but only the time to first pregnancy was used in this study. Primary endpoint was time to first spontaneous pregnancy after IPAA.

Surgical Techniques

Single-stage IPAA was carried out in one surgical procedure, with or without creation of a loop ileostomy. Two-stage IPAA consisted of a (sub) total colectomy at first, leaving a rectal stump and an end ileostomy in situ. After the patients sufficiently recovered, a completion proctectomy with creation of the IPAA was carried out, with or without the creation of a loop ileostomy. In both the open and the laparoscopic techniques the ovaries were left unimpaired; that is, the ovaries were not attached to the abdominal wall, nor were antiadhesive materials used in any of the patients.

Laparoscopic and Open Techniques

Laparoscopic IPAA was performed either as a totally laparoscopic colectomy or as a hand-assisted colectomy with the aid of a hand-port inserted in a Pfannenstiel incision. The proctectomy and IPAA construction were then carried out via the Pfannenstiel incision. A close or wide (in the mesorectal plane) rectal dissection was performed. In selected cases, a loop ileostomy was created. In the open technique, the entire procedure was done via a midline incision. Proctocolectomy and creation of the IPAA were carried out in exactly the same way as described previously.

Statistical Analysis

All patients who had attempted to conceive after IPAA were included in the analysis and categorized as laparoscopic or open IPAA according to treatment. One patient had a midline laparotomy for postoperative complications after a laparoscopic IPAA. She was therefore included in the open group. Categorical data were reported as counts and percentages and continuous data as mean with standard deviation or median with interquartile range. For dichotomous outcomes, laparoscopic and open IPAA groups were compared with χ^2 method and Fisher exact test where appropriate. To compare means, the independent *t* test was used. The primary endpoint time to spontaneous pregnancy was plotted in a Kaplan-Meier survival function for both groups and compared with the log-rank test. The time to pregnancy period could also end in censoring instead of pregnancy for one the following reasons: end of couples' relationship, restarting birth control, pregnancy by in-vitro fertilization (IVF), and end of follow-up period (at the time of data collection). An important confounder is UC as indication for IPAA. Patients with UC are known to have worse fecundity after IPAA than patients with FAP. Therefore, survival analyses were carried out on UC separately. Auxiliary survival analysis was done for time to any pregnancy. In this analysis, IVF pregnancies were also included. All tests were 2-sided, and *P* values of less than 0.05 were deemed significant. Statistical analyses were performed with PASW Statistics for Windows (version 18). This study is registered with ISRCTN.org (ISRCTN85421386).

RESULTS

Between 1993 and 2009, 570 patients underwent IPAA, of whom 179 patients were eligible for inclusion in the study (Fig. 1).

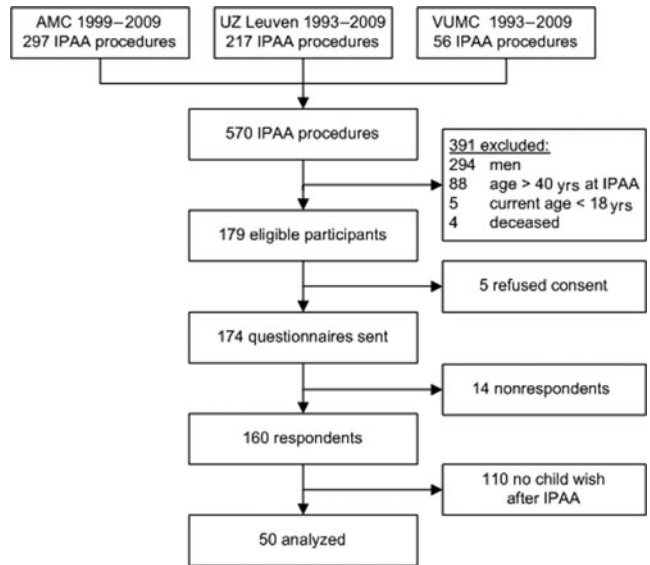


FIGURE 1. Participant flow chart.

Of all eligible patients, 67 (37%) had open and 112 (63%) had laparoscopic IPAA. Indications for IPAA were FAP in 45 patients, UC in 132 patients, slow transit constipation in 1 patient, and colonic ischemia in 1 patient. Fifty patients had attempted to conceive after IPAA and were included in the analysis. Twenty-three (46%) had open and 27 (54%) had laparoscopic surgery. Mean follow-up was 9.4 (standard deviation = 5.0) years postoperatively. Patient characteristics, details on the operation, and presence of potential confounding factors that could influence fecundity did not differ between the groups (Table 1). More patients in the open group had IVF treatment.

Overall, in the laparoscopic group, 19 (70%) patients became pregnant spontaneously and 1 patient had IVF successfully. In the open group, 9 (39%) patients became pregnant spontaneously and 4 after IVF. Figure 2 shows time to spontaneous pregnancy for both groups. There was a significant difference in favor of the laparoscopic group ($P = 0.023$). In the same figure, time to any pregnancy is shown, that is, including pregnancies after IVF. Here a trend is seen in favor of the laparoscopic group ($P = 0.061$). In the laparoscopic group, 15 (56%) patients conceived spontaneously within 12 months, compared to 7 (30%) in the open group. There were no IVF pregnancies within 12 months. Subfertility was observed in 10 (37%) patients in the laparoscopic group and in 15 (65%) patients in the open group (χ^2 test $P = 0.053$).

Subgroup analysis was done for time to spontaneous pregnancy for UC patients (Fig. 3). In 37 patients with UC, the significant difference remained in favor of the laparoscopic group ($P = 0.033$). Of the patients with UC, in the laparoscopic group 11 (55%) became pregnant within 12 months of attempting in comparison with 6 (35%) in the open group.

DISCUSSION

The results of this study show that, compared to open IPAA, laparoscopic IPAA leads to a better preservation of fertility and a higher postoperative pregnancy rate. In subset analysis, this significant effect remained for patients with UC who had had laparoscopic IPAA. This is the first study to report on fecundity after laparoscopic IPAA. Previous studies reported a reduction in pelvic adhesions after laparoscopic surgery.^{11–14} For patients, pregnancy and time to pregnancy are far more relevant outcomes. The improved preservation of

TABLE 1. Characteristics of All Patients Who Attempted to Conceive After IPAA

	Open IPAA (n = 23)	Laparoscopic IPAA (n = 27)	P
Baseline characteristics			
IPAA indication			0.734†
Familial Adenomatous Polyposis	5 (22%)	7 (26%)	
Ulcerative Colitis	17 (74%)	20 (74%)	
Other	1 (4%)	—	
Age at IPAA (yrs)	25.6 (5.7)	26.2 (3.7)	0.653‡
Previous midline laparotomy	2 (9%)	0 (—)†	0.207†
Surgery			
1 stage: 2 stage procedures	15:8	23:4	0.183‡
Anastomotic leakage	3 (13%)	2 (7%)	0.412‡
Reoperation	4 (17%)	2 (7%)	0.283‡
Fertility			
Age at start attempt to conceive (yrs)	29.8 (4.4)	28.3 (4.0)	0.237‡
Smoking at time of attempt	6 (26%)	2 (7%)	0.121†
Pelvic inflammatory disease in history	1 (4%)	0 (—)	0.460†
Extra-uterine gravidity in history	2 (9%)	1 (4%)	0.588†
Known male fertility factor present*	3 (13%)	0 (—)	0.273†
Tried IVF/ICSI for first pregnancy after IPAA	9 (39%)	3 (11%)	0.044†
Attempted to conceive before IPAA	4 (17%)	11 (41%)	0.121†
Pregnant before IPAA (naturally)	4 (17%)	7 (26%)	0.515†
Pregnant before IPAA (treatment)	0 (—)	0 (—)	—

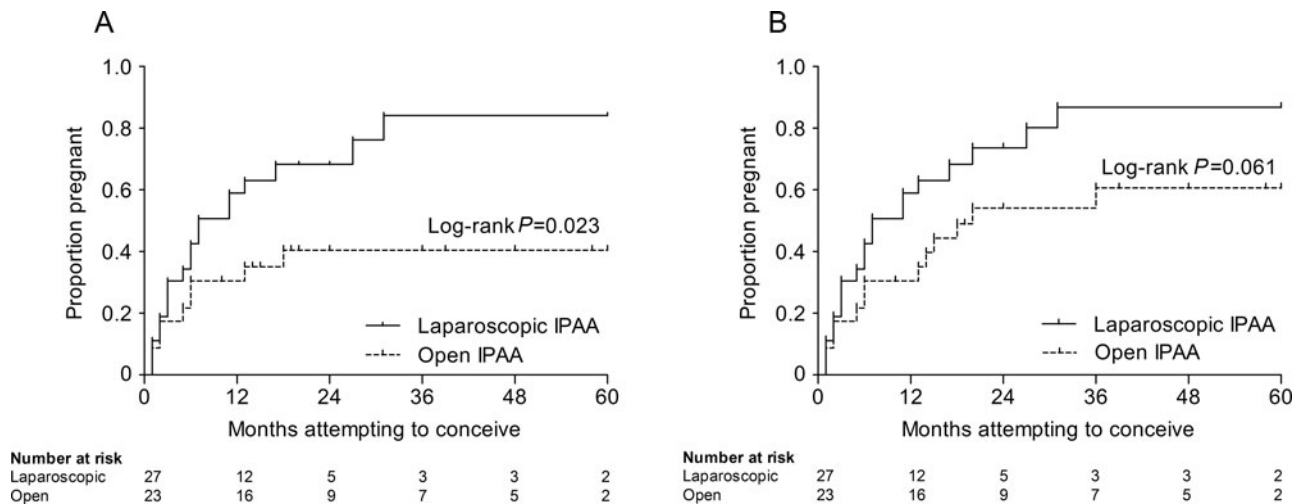
Data are n (%) and mean (SD).

*Tested in 14 and 8 partners, respectively.

†Fisher's exact test.

‡Independent *t* test.

ICSI indicates intracytoplasmic sperm injection.

**FIGURE 2.** Kaplan-Meier estimates of time to spontaneous pregnancy (A) and time to any pregnancy, including in vitro fertilization (B) treated by laparoscopic and open IPAA.

fecundity after laparoscopy in this study is most likely the result of a reduction in adhesions to the tuboovarian complex.

As with all observational studies on treatment effect, the most important potential bias to consider is confounding by indication. Strikingly, we did not find any significant differences in any of the patient characteristics studied. Nevertheless, there are many factors to influence fecundity and not all could be explored. For instance, it was observed that patients could not report if they had had a regular menstrual cycle when attempting to conceive. In a study using questionnaires, a certain level of recall bias is to be expected. However, several studies have shown that on a population level recall of time to pregnancy has been deemed very reliable up to several years.^{15,16}

The direction of the recall bias effect is unpredictable, but it is not expected to be different in any of the 2 treatment groups.

Another factor to potentially influence the outcome is time. The first IPAA in this series was done in 1993, but the first laparoscopic IPAA in this series was not done until 1995. It is hard to predict how this would influence fecundity. The open procedures were all carried out by experienced colorectal surgeons from 1993 onwards. The series of laparoscopic pouches includes the learning curve, but all laparoscopic pouches were done by surgeons with extensive experience in open pouch surgery. Despite the learning curve present in the laparoscopic series, superior fecundity was seen. Finally, an important difference was to be expected in patients with UC. In earlier

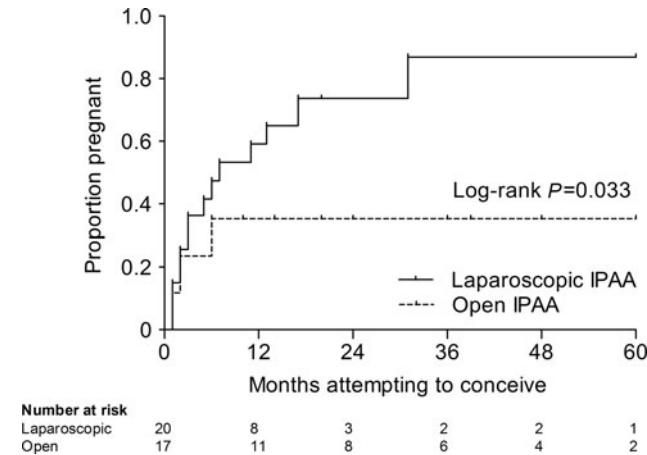


FIGURE 3. Kaplan-Meier estimates of time to spontaneous pregnancy for all patients with ulcerative colitis (n = 37) by laparoscopic and open IPAA.

studies, patients with UC were described to have a worse fecundity outcome after IPAA than those with FAP, albeit the potential effect of laparoscopy was never considered.^{4,9,17} For this reason, survival analyses were stratified for patients with UC.

Reduction in fecundity in patients having had open IPAA in comparison to healthy women has been well reported.⁶ In our study, this was also observed, with 1-year pregnancy rates of 30% for the open group and 56% for the laparoscopic group. For comparison, in a cross-sectional study of 3300 Dutch women, the 6-month and 1-year pregnancy rates for 29-year-olds were 64% and 85%, respectively.¹⁸ It is common clinical practice to refer female patients with an IPAA to a gynecologist for fertility treatment within the first year of attempting to conceive. Even with a better fertility preservation after laparoscopy, this should remain the standard of care.

The high response rate of 89% makes this study representative for all young female patients who need IPAA. Nonetheless, it would be very interesting to study the potential fecundity benefit of laparoscopy prospectively, preferably in a large multicenter study. Imaging of the Fallopian tubes by hysterosalpingography to detect tubal occlusion or diagnostic laparoscopy with a dye test to study the pick-up function of the Fallopian tubes would further strengthen the hypothesis of fertility reduction as an effect of pelvic adhesions.

To date, evidence for the advantages of laparoscopic IPAA has not been decisive. In a well-conducted systematic review, Ahmed et al¹⁰ concluded that laparoscopic IPAA is safe and feasible but it has mainly limited short-term and cosmetic advantages. In a recent large series, a reduction in short-term complications is corroborated.¹⁹ Studies focusing on long-term outcomes, that is, a possible reduction of incisional hernias and adhesion-related complications are yet to be published. With the results of this study, there is now an important

argument that all young female patients should have a laparoscopic IPAA.

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