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**Laparoscopic treatment of endometriosis and predictors of major complications:
a retrospective cohort study**

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ABSTRACT

Introduction: Patients with advanced endometriosis may be at an increased risk of surgical complications following laparoscopic treatment of endometriosis; however, this relationship has not been examined. We sought to identify predictors of major complications following laparoscopic treatment of endometriosis. **Material and methods:** A retrospective cohort study of women who underwent laparoscopic treatment of suspected endometriosis between 2009 and 2016 within the Division of Minimally Invasive Gynecologic Surgery at Brigham and Women's Hospital, Boston, MA, USA. Predictors of major perioperative complications were assessed by comparing the characteristics of women who had any major intraoperative or postoperative complication to those of women who had no complication. **Results:** A total of 397 women underwent laparoscopic treatment of suspected endometriosis including excision of superficial endometriosis (55.4%), excision of deep-infiltrating endometriosis (24.9%), fulguration of endometriosis (38.3%), hysterectomy (23.2%), ovarian cystectomy (35.5%), salpingectomy (18.6%), oophorectomy (15.1%) and bowel resection (1.0%). Women were followed for 60 days following surgery, over which time eighteen women (4.5%) had a major perioperative complication. Patient characteristics and preoperative imaging were similar between women with and without complications. Women with advanced endometriosis, including stage III or IV endometriosis, deep-infiltrating endometriosis, or rectovaginal disease, were more likely to have a complication, though this did not reach statistical significance (77.8% of women with a complication versus 56.7% of women without a complication had advanced endometriosis, $p=0.077$). Women who had a complication were more likely to have undergone adhesiolysis or ureterolysis (88.9% of women with a complication versus 52.5% without a complication underwent adhesiolysis, $p=0.002$; and 61.1% of women with a complication versus 28.8% without a complication underwent ureterolysis, $p=0.003$). The total number of procedures was greater for women who had a complication (4.3 ± 1.2 vs. 3.2 ± 1.5 , $p=0.003$). All other procedure characteristics were similar between women with and without complications.

Conclusions: Complications following laparoscopic treatment of suspected endometriosis could not be predicted by preoperative patient characteristics or surgical findings of advanced endometriosis. Adhesiolysis, ureterolysis and an increased number of total procedures may be predictive of

perioperative complications suggesting that surgical complexity as measured by the procedures performed, rather than the disease severity, may increase the risk of a complication compared to women who do not undergo these procedures.

Keywords

endometriosis, endoscopic surgery, laparoscopy, complication, deep-infiltrating endometriosis

Abbreviations:

ASRM American Society for Reproductive Medicine

DIE deep-infiltrating endometriosis

Key message

Major complications following laparoscopic treatment of suspected endometriosis are infrequent and difficult to predict by patient characteristics, preoperative imaging, or disease severity at the time of surgery. Certain procedures including adhesiolysis and ureterolysis, as well as the total number of procedures performed, may be predictive of major complications.

INTRODUCTION

Endometriosis is defined as the presence of endometrial glands and stroma outside the uterus. It is a complex disease that is estimated to affect 5% to 10% of reproductive age women [1]. Symptoms are highly variable with some women largely asymptomatic and others severely debilitated by pain or infertility associated with the disease. Surgical treatment, usually by laparoscopy, is used in symptomatic women who have shown poor response to medical therapy or have clinical or radiographic findings suggestive of advanced disease such as an endometrioma or deep-infiltrating lesions [2,3]. Women with advanced endometriosis are surgically complex due to the potential for dense adhesions, inflammation, distorted pelvic anatomy, and gastrointestinal or genitourinary tract involvement [4]. Surgical treatment in these women often requires extensive dissection and in some cases, bowel, bladder, or ureteral surgery, all of which may increase the risk of surgical complications [5-8].

Prior work evaluating women with American Society for Reproductive Medicine (ASRM) stage III or IV endometriosis suggests that complications may be more likely to occur when concomitant bowel surgery or a hysterectomy is performed [9,10]. Studies of women with deep-infiltrating endometriosis (DIE) have also shown that major complications are more likely to occur when the bowel is involved and/or bowel surgery becomes necessary, in particular when segmental resection is performed [5,7]. For women with bowel endometriosis, laparoscopic bowel resection results in fewer complications compared to open bowel resection [11]. A study of women with ureteral endometriosis also reported an increased risk of complications with a greater number of intraabdominal incisions such as a vaginotomy or cystotomy [12]. While these studies suggest that women with advanced stage, deep-infiltrating, bowel or ureteral endometriosis have an increased risk of complications with certain concomitant procedures, no study has investigated predictors of complications in all women undergoing laparoscopic treatment of endometriosis. We sought to examine all women undergoing surgical treatment of presumed as well as pathologically-confirmed endometriosis to determine if any unique patient or procedure characteristics could predict major complications, thereby aiding in surgical planning or perioperative counseling. We hypothesized that women with advanced

endometriosis, defined in our study as ASRM stage III or IV endometriosis, deep-infiltrating endometriosis (DIE), or rectovaginal endometriosis, were more likely to have a complication given the increased complexity of their disease.

MATERIAL AND METHODS

This retrospective cohort study included all women referred to the Minimally Invasive Gynecologic Surgery Division at Brigham and Women's Hospital in Boston, MA, USA for laparoscopic treatment of endometriosis between January 2009 and September 2016. Surgeries were performed by three Minimally Invasive Gynecologic Surgeons within the division. Inclusion criteria were all women who underwent laparoscopic treatment of endometriosis during the study period as recorded by the primary surgeon in the operative report. This included excision and/or fulguration of presumed and/or pathologically-confirmed disease. All surgeons in this study performed fulguration by means of bipolar electrosurgical desiccation of endometrial implants. Women who underwent laparoscopic treatment of endometriosis were included regardless of the primary indication for the procedure or final pathology in order to identify predictors of complications unique to the surgical treatment of suspected endometriosis. Women who underwent laparoscopic treatment of endometriosis and did not have pathologic confirmation of disease were not excluded as the surgical procedure, rather than the histopathology, was felt to place women at risk of a surgical complication. Accordingly, women who underwent fulguration of endometriosis without excision and did not have a pathology specimen available, were also included. Women undergoing surgical treatment of a known gynecologic malignancy were excluded.

Patient characteristics were collected from the medical record including age, race, body mass index, parity, prior surgical history, prior medical and surgical treatment of endometriosis, symptoms and preoperative imaging findings. Procedural characteristics were collected including surgical findings, surgical procedures, operative time and estimated blood loss. The total number of concomitant procedures performed at the time of surgery was also determined. Women were classified as having advanced endometriosis if they had stage III or IV endometriosis, DIE, or rectovaginal endometriosis.

ASRM staging was determined by surgeon report when available, or by review of the detailed surgical findings in the operative report. DIE was determined from the surgeon report whenever the terms “deep-infiltrating” or “nodule” were used to describe the disease. Rectovaginal endometriosis was determined by the surgeon’s report of endometriosis in this space. The surgical pathology was collected when specimens were available for examination. Major perioperative complications within 60 days of the procedure were collected from the medical record. These were defined as conversion to laparotomy, estimated blood loss greater than or equal to 500 mL, transfusion, pelvic infection, inadvertent or delayed organ injury, venous thromboembolism, intensive care unit admission, readmission or reoperation. Only complications that were documented in the medical record were included. Complications that occurred at an outside facility were included, if known, otherwise they were not available to report.

Statistical analyses

Patient and procedure characteristics were compared for women who had at least one major complication and women who did not have any major complications using the chi-square test, Student’s t-test and Wilcoxon rank-sum test, as appropriate. The association between advanced endometriosis and a major complication was evaluated using a multivariable logistic regression model, controlling for age, race, body mass index, prior surgery, and the performance of a myomectomy or hysterectomy during the procedure. Myomectomy and hysterectomy were included in the regression as these procedures are independent of endometriosis severity but may impact the likelihood of a complication. Statistical significance was determined at a p-value less than 0.05 for the final model and all p-values were two-sided. All statistical analysis was performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

A subgroup analysis was also performed including only those patients with advanced endometriosis in order to determine if any unique predictors of complications were present in this cohort. Similar statistical methods were applied to this subgroup including a univariate analysis comparing patient and procedure characteristics for those women with advanced endometriosis who did and did not have

a major perioperative complication, followed by a multivariable logistic regression model controlling for the factors mentioned.

Ethical approval

This study was approved by the Partners Institutional Review Board (IRB protocol no: 2016P002058/BWH on 11/3/2016).

RESULTS

A total of 397 patients were identified from medical records as having undergone laparoscopic treatment of endometriosis in our division between 2009 and 2016. Three surgeons performed the procedures over varying time intervals, with one surgeon performing 316 of the procedures, the second surgeon performing 76 of the procedures, and the third surgeon performing 27 of the procedures in the cohort. All three surgeons were high-volume surgeons performing over 100 complex laparoscopic procedures annually. Characteristics for all women who underwent laparoscopic treatment of endometriosis, displayed by the presence or absence of a major perioperative complication, are shown in Table 1. Patient characteristics including age, body mass index, parity, prior surgical history, symptoms, medical treatment of endometriosis, symptoms and preoperative imaging were similar between women with and without complications.

Of the 397 women, 319 (80.4%) had pathology-confirmed endometriosis. The remaining women underwent surgical treatment of suspected endometriosis without pathologic confirmation. Most of these women exclusively underwent fulguration of disease, lysis of adhesions, or removal of an uninvolved specimen such as the uterus or adnexa to treat their disease. Only 37 (9.3%) of women had suspected endometriosis tissue excised that returned negative for endometriosis on final pathology.

Eighteen (4.5%) women had a major perioperative complication. There was one intraoperative bowel injury and two intraoperative bladder injuries. There were 11 postoperative cases of major infection,

four of which were pelvic abscesses treated with percutaneous drainage by Interventional Radiology. There were seven reoperations within 60 days of surgery, 13 readmissions within 60 days of surgery, two intensive care unit admissions, two blood transfusions, one bowel injury diagnosed postoperatively, one rectovaginal fistula and one ureterovaginal fistula. There were no cases that converted to laparotomy, no cases with an estimated blood loss greater than or equal to 500 mL, and no cases of a venous thromboembolism.

Procedure characteristics for women with and without a major complication are shown in Table 2. A total of 229 (57.5%) women had advanced endometriosis. On univariate analysis, women who had a major complication were more likely to have advanced endometriosis (77.8% versus 56.7%); however, this was not statistically significant ($p=0.077$, OR 2.67, 95% CI 0.86 to 8.26). Women who had a complication were also more likely to have one of the subtypes of advanced endometriosis (ASRM stage 3 or 4, deep-infiltrating, and rectovaginal endometriosis), though no subgroup reached statistical significance.

Various concomitant procedures were performed and are reported in Table 2. On univariate analysis, procedures that were more common amongst women who had a complication were lysis of adhesions (88.9% versus 52.5%, $p=0.002$), and ureterolysis (61.1% versus 28.8%, $p=0.003$). The mean total number of procedures was greater in those women who had a complication (4.3 ± 1.2 versus 3.2 ± 1.5 , $p=0.003$). Operative time was also longer for women who had a complication (119 ± 51 vs. 89 ± 53 min, $p=.017$).

Upon multivariate logistic regression analysis (controlling for age, race, body mass index, any prior surgery, myomectomy and hysterectomy) only adhesiolysis, ureterolysis, and the total number of procedures performed intraoperatively were predictive of a complication (Table 3). Advanced endometriosis was not predictive of a complication (OR 1.41, 95% CI 0.83 to 2.40). All other procedure characteristics were similar between women with and without complications.

A subgroup analysis was also performed on 229 patients with advanced endometriosis. Of the women with advanced endometriosis, 14 (6.1%) had a major perioperative complication. This is compared to 4 (2.4%) of women without advanced endometriosis who had a major perioperative complication. Upon univariate analysis, women with advanced endometriosis and a major complication were more likely to report dyspareunia preoperatively (57.1% versus 30.2%, $p=0.038$) and undergo lysis of adhesions during surgery (100% versus 69.8%, $p=0.013$). Interestingly, only dyspareunia remained statistically significant upon multivariable logistic regression (OR 1.84, 95% CI 1.03 to 3.26, $p=0.038$).

DISCUSSION

Among a diverse set of referral patients, 57.5% of whom had advanced endometriosis, the overall major perioperative complication rate for laparoscopic treatment of endometriosis was 4.5%. While our study did not detect any patient characteristics that could predict complications preoperatively, procedure characteristics including adhesiolysis, ureterolysis, or a greater number of total procedures performed intraoperatively, were associated with an increased risk of major perioperative complications. Contrary to our hypothesis, women with advanced endometriosis, including stage III or IV endometriosis, DIE, and rectovaginal disease, were not more likely to have a major complication.

Previous studies have focused on women with advanced stage endometriosis and reported intraoperative complication rates ranging from 0.4 to 5% and a postoperative complication rate ranging from 1.0 to 37.9% [9,10,13]. Magrina et al retrospectively investigated 493 women with stage III and IV endometriosis who underwent laparoscopic treatment of endometriosis and reported 2 (0.4%) intraoperative complications, 3 (0.6%) conversions to laparotomy, and 5 (1%) major postoperative complications [10]. Brudie et al reviewed 80 women with stage IV endometriosis who underwent laparoscopic treatment and found a 5% conversion rate and 5% perioperative complication rate [13]. A study by Minelli et al reviewed 1363 women with stage IV endometriosis who underwent

radical and nonradical laparoscopic excision and found an intraoperative complication rate of 1.9% and postoperative complication rate of 37.9%, including several minor events [9]. With regards to DIE, Kondo et al reviewed 568 women who underwent laparoscopic excision of DIE and found a 1.1% major intraoperative complication rate, and 4.6% major postoperative complication rate [5]. Byrne et al prospectively assessed 4721 women with rectovaginal endometriosis who underwent laparoscopic excision and found an overall perioperative complication rate of 6.8% [14]. Our complication rate of 4.5% included major perioperative complications in all women undergoing laparoscopic treatment of endometriosis. It is difficult to compare our complication rate to prior work given the different patient populations examined (different subtypes of endometriosis) and varying definitions of a complication (major versus minor, intraoperative versus postoperative) across the literature. Of note, most studies, including ours, included high-volume surgeons at specialized referral centers which could impact the complication rate. The literature is also susceptible to publication bias whereby high complication rates may go unreported.

Similar to prior studies, we found that certain concomitant procedures predict perioperative complications. In the study by Magrina et al concomitant hysterectomy and longer operative time were associated with an increased risk of postoperative complications [10]. Each additional 60 minutes incurred a 57% increased odds of a postoperative complication [10]. Our study also found that operative time was significantly longer in those patients who had a perioperative complication, though it is unclear if this was the cause or result of the complication as intraoperative complications were also included in our analysis. A retrospective study by Minelli et al found that the risk of an intraoperative complication was nearly threefold higher when a bowel resection was performed, and studies by Abo et al and Kondo et al found that the risk of a postoperative complication was significantly greater among women who underwent a segmental bowel resection compared to bowel shaving [5,7,9]. A prospective study by Meuleman et al showed no difference in postoperative complication rates for women who did or did not undergo a bowel resection [15]. A study by Alves et al found that in women with ureteral endometriosis, increasing number of intraabdominal incisions, including vaginotomy and cystotomy, were associated with a significantly increased risk of complications (OR 2.08 and 8.77, respectively) [12]. Unlike our study, no prior study examined

women with all subtypes of endometriosis. Our study identified adhesiolysis, ureterolysis, and the total number of procedures as unique predictors of complications in all women undergoing laparoscopic treatment of endometriosis. It is important to note that while these procedures were more likely to have been performed in patients who had a complication, the act of adhesiolysis or ureterolysis may not be the direct cause of the complication. In fact, ureterolysis is routinely performed at our institution in cases of DIE or rectovaginal endometriosis in order to isolate and protect the ureter from injury. These procedures may instead be surrogates for surgical complexity or the extent of tissue dissection. In a subgroup analysis including only those patients with advanced endometriosis, only preoperative dyspareunia was predictive of a complication, though it is difficult to draw conclusions from a small subgroup.

Our study is unique in that it investigated major intraoperative and postoperative complications for all women referred for laparoscopic treatment of endometriosis, regardless of disease severity. A broad case mix of patients and procedures were included to reflect the full spectrum of endometriosis surgery and to provide a thorough assessment of potential predictors of complications, including the potential contribution of advanced disease. Advanced endometriosis was also defined using three categories of disease severity to encompass the different features that make endometriosis surgery complex. All patients undergoing surgical treatment of suspected endometriosis, including a few patients with excised tissue that was ultimately negative for endometriosis, were included in order to identify surgical complications pertinent to the procedure, rather than the histopathology alone.

A limitation of this study is its retrospective design with inconsistencies in surgeon reporting of endometriosis staging, tissue penetration and organ involvement as retrieved from the operative note. Data was retrieved from the institutional medical record as available and it is possible that certain patient or procedure characteristics were not captured. While most patients presented to our institution for follow-up it is also possible that complications diagnosed at an outside facility were not reported to the surgeon and are therefore not accounted for. Our study also includes a heterogenous group of patients, procedures, and complications, which may limit our ability to find associations between patient and procedure characteristics and the occurrence of any complication. Some of the women

without pathology-proven endometriosis may not truly have endometriosis which may bias our findings to include surgical risk pertinent to the procedure but not the disease. Major complications were defined broadly and it is possible that certain complications have unique predictors. For example, all organ injuries occurred in women with advanced endometriosis suggesting that advanced disease may be a risk factor for this type of complication. Furthermore, the results apply to referral patients operated on by a small group of surgical subspecialists and may not be generalizable to all patients undergoing endometriosis surgery. Lastly, our study may be insufficiently powered to detect a difference in complication rates for some patient or procedure characteristics. For example, some less common procedures such as bowel resection (n = 4), were likely too infrequent to detect a difference in the occurrence of a complication. The total number of patients with any complications was also relatively small (n = 18) which limits the statistical power of our findings.

CONCLUSION

In summary, major complications following laparoscopic treatment of suspected endometriosis are infrequent and are difficult to predict preoperatively. Surgical complexity as measured by the procedures performed, rather than disease severity, may increase the risk of a perioperative complication. These results should be interpreted with caution, however, as certain disease characteristics that may increase the risk of a major perioperative complication may not be sufficiently represented in our cohort.

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Table legends

Table 1. Patient characteristics

Table 2. Procedure characteristics

Table 3. Predictors of complications

Table 1. Patient Characteristics

	No complication (N=379)	Major complication ^a (N=18)	<i>P</i> -value
Age (mean ± SD)	35.7 ± 8.2	35.3 ± 5.0	0.834
Race			
Caucasian	293 (77.3%)	12 (66.7%)	0.039
Black	18 (4.8%)	4 (22.2%)	
Asian	33 (8.7%)	--	
Hispanic	21 (5.5%)	1 (5.6%)	
Other	14 (3.7%)	1 (5.6%)	
BMI (mean ± SD)	26.6 ± 6.8	27.9 ± 5.8	0.435
Parity (mean ± SD)	0.7 ± 1.0	0.6 ± 0.9	0.466
Surgical history			
Any prior laparoscopy	236 (62.3%)	12 (66.7%)	0.807
Any prior laparotomy	110 (29.0%)	7 (38.9%)	0.370
Prior hysterectomy	31 (8.2%)	3 (16.7%)	0.193
Prior surgery for endometriosis	200 (52.8%)	8 (44.4%)	0.762
Symptoms ^b			
Pelvic pain	352 (92.9%)	18 (100.0%)	0.241
Dysmenorrhea	347 (91.6%)	18 (100.0%)	0.199
Dyspareunia	124 (32.7%)	8 (44.4%)	0.306
Dyschezia	60 (15.8%)	3 (16.7%)	0.932
Dysuria	41 (10.8%)	2 (11.1%)	0.972
Infertility	22 (5.8%)	2 (11.1%)	0.299
Prior medical management			
Hormones	123 (32.5%)	6 (33.3%)	0.956
GnRH agonist	37 (9.8%)	4 (22.2%)	0.069
Imaging			
US or MRI with endometrioma	140 (36.9%)	7 (38.9%)	0.867
US or MRI with implant	40 (10.6%)	2 (11.1%)	0.940

^a Conversion to laparotomy, estimated blood loss ≥ 500 ml, transfusion, pelvic infection, inadvertent or delayed organ injury, venous thromboembolism, intensive care unit admission, readmission or reoperation within 60 days postoperatively.

^b Not mutually exclusive

GnRH, gonadotropin-releasing hormone; US, ultrasound; MRI, magnetic resonance imaging.

Table 2. Procedure Characteristics

	No complication (N=379)	Major complication (N=18)	p-value
Surgical findings			
Advanced endometriosis	215 (56.7%)	14 (77.8%)	0.077
ASRM Stage 3 or 4	169 (44.6%)	12 (66.7%)	0.066
Deep-infiltrating endometriosis	92 (24.3%)	7 (38.9%)	0.169
Rectovaginal endometriosis	83 (21.9%)	7 (38.9%)	0.093
Endometrioma	136 (35.9%)	5 (27.8%)	0.483
Location of the excised nodule			
Rectovaginal space	51 (13.5%)	5 (27.8%)	0.088
Uterosacral ligament	37 (9.8%)	3 (16.7%)	0.409
Bowel	6 (1.6%)	--	0.591
Bladder	5 (1.3%)	--	0.624
Ureter	3 (0.8%)	--	0.591
Abdominal wall	6 (1.6%)	--	1.000
Procedures			
Excision of superficial endometriosis	210 (55.4%)	10 (55.6%)	0.990
Excision of deep endometriosis	92 (24.3%)	7 (38.9%)	0.161
Fulguration of endometriosis	148 (39.1%)	4 (22.2%)	0.151
Myomectomy	34 (9.0%)	3 (16.7%)	0.272
Hysterectomy	88 (23.2%)	4 (22.2%)	0.922
Ovarian cystectomy	131 (34.6%)	10 (55.6%)	0.069
Oophorectomy	57 (15.0%)	3 (16.7%)	0.851
Salpingectomy	70 (18.5%)	4 (22.2%)	0.690
Bowel shaving	16 (4.2%)	1 (5.6%)	0.785
Bowel excision	7 (1.8%)	--	0.561
Segmental bowel resection	4 (1.1%)	--	0.661
Appendectomy	17 (4.5%)	--	0.358
Bladder excision	2 (0.5%)	--	0.757
Ureteral excision	1 (0.3%)	--	0.827
Lysis of adhesions	199 (52.5%)	16 (88.9%)	0.002
Ureterolysis	109 (28.8%)	11 (61.1%)	0.003

Total number of procedures	3.2 ± 1.5	4.3 ± 1.2	0.003
EBL (mL) (mean ± SD)	55.3 ± 66.3	85.3 ± 103.4	0.069
Operative time (min) (mean ± SD)	88.8 ± 52.9	119.3 ± 50.6	0.017
Same-day discharge	357 (100%)	7 (38.9%)	<0.001

ASRM, American Society for Reproductive Medicine; EBL, estimated blood loss.

Table 3. Multivariable logistic regression for predictors of major complications

	Odds ratio ^a	95% Confidence Interval	p-value
Surgical findings			
Advanced endometriosis	1.41	0.83-2.40	0.200
ASRM Stage 3 or 4	1.39	0.85-2.28	0.193
Deep-infiltrating endometriosis	1.44	0.89-2.33	0.134
Rectovaginal endometriosis	1.62	1.00-2.62	0.051
Procedures			
Lysis of adhesions	2.09	1.07-4.08	0.030
Ureterolysis	1.93	1.11-3.34	0.019
Total number of procedures	1.58	1.07-2.33	0.022

^aAdjusted for age, race, BMI, prior surgery, and the performance of a myomectomy or hysterectomy during the procedure.

ASRM, American Society for Reproductive Medicine.