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Surgical Outcomes and Complications of Laparoscopic Hysterectomy for Endometriosis: a multicentric cohort study.

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Precis: Previous surgery for endometriosis or adenomyosis, younger age, and intraoperative complications increase the postoperative morbidity of laparoscopic hysterectomy for endometriosis; the administration of progesterone/estro-progestin preoperatively might reduce the risk of postoperative complications.

Abstract

Study Objective: To investigate the postoperative morbidity of laparoscopic hysterectomy (LH) for endometriosis/adenomyosis in terms of operative outcomes and complications.

Design: Retrospective multicentric cohort study.

Setting: Eight European minimally invasive referral centers.

Patients: Data from 995 patients with pathologically confirmed endometriosis and/or adenomyosis who underwent LH without concomitant urological and/or gastroenterological procedures from January 2010 to December 2020.

Interventions: Total laparoscopic hysterectomy.

Measurements and Main Results: Demographic patients' characteristics, surgical outcomes, and intraoperative and postoperative complications were evaluated. We considered major postoperative surgical-related complications any grade 2 or more events (Clavien-Dindo score) that occurred within 30 days from surgery. Univariate analysis and multivariable models fit with logistic regression were used to estimate the adjusted odds ratio (OR) and corresponding 95% CI for major complications. Median age at surgery was 44 years (28-54) and about half of them (505, 50.7%) were on medical treatment (estro-progestins, progestin or GnRh-analogues) at the time of surgery. In association with LH, posterior adhesiolysis was performed in 387 (38,9%) cases and deep nodule resection in 302 (30,0%). Intraoperative complications occurred in 3% of the patients and major postoperative complications were registered in 93 (9.3%). The multivariable analysis showed an inverse correlation between the occurrence of Clavien-Dindo >2 complications and age (OR 0.94, 95%CI 0.90-0.99), while previous surgery for endometriosis (OR 1.62, 95%CI 1.01-2.60) and intraoperative complications (OR 6.49, 95%CI 2.65-16.87) were found as predictors of major events. Medical treatment at the time of surgery has emerged as a protective factor (OR 0.50, 95%CI 0.31-0.81).

Conclusion: LH for endometriosis/adenomyosis is associated with non-negligible morbidity. Knowing the factors associated with higher risks of complications might be used for risk stratification and could help clinicians during preoperative counseling. The administration of estro-progestin or progesterone preoperatively might reduce the risks of postoperative complications following surgery.

Keywords

Hysterectomy, endometriosis, laparoscopic surgery, complications, morbidity, adenomyosis

Introduction

Although hysterectomy rates high-income countries are diminishing owing to a generally more conservative approach to benign gynecologic conditions, this operation remains the most common non-obstetric surgical procedure performed on women (1). In case of hysterectomies accomplished for benign conditions, the vaginal route has been described as the preferred surgical approach (2); however, laparoscopic hysterectomy (LH) has progressively become the favored route when surgery is performed in dedicated minimally invasive referral centers (3-5). The benefits related to LH, when compared to the open approach, have been largely demonstrated: reduced postoperative pain, shorter hospital stay, faster recovery, and a lower rate of surgical-related complications (6-7).

Even though mostly treated in dedicated centers, patients undergoing surgery for endometriosis are at higher risk of complications, especially those with deep infiltrating disease (8-9). Recently, endometriosis has been shown to represent an independent risk factor for major postoperative complications of LH (10), thus suggesting dedicated preoperative counseling about the increased risk of such events.

Several investigations have addressed the surgical-related morbidity of minimally invasive hysterectomy (11-13), while very few studies specifically focused on the risk factors for surgical complications of LH for adenomyosis/endometriosis (14-15). In the present study, we aimed to investigate the postoperative morbidity of LH for endometriosis and/or adenomyosis to risk stratify patients (in terms of increased risk of postoperative complication) based on demographic factors and prior medical/surgical treatment. A specific analysis of the factors associated with major postoperative events has been made and a detailed description of perioperative outcomes, intraoperative and thirty-days complications has been reported.

Methodology

Data of consecutive patients who underwent LH with or without concomitant salpingo-oophorectomy for pathological-confirmed endometriosis and/or adenomyosis at eight tertiary minimally invasive centers between January 2010 and December 2020 were reviewed. Institutional Review Board approval was obtained (approval ID 35/2020, November 17th, 2020). Patients with concomitant surgical procedure beyond hysterectomy, such as bowel surgery (i.e. shaving, discoid resection, segmental resection) and urinary-tract surgery (i.e. resection and bladder resection) were excluded from the present study. Conversely, we included in the analysis patients who have had the following concomitant surgical procedures: endometrioma enucleation, ureterolysis, deep nodule resection, posterior adhesiolysis and upper colpectomy. Hysterectomies, simple or radical (in case of parametrial resection), were all accomplished in standard fashion as described elsewhere (2,5,10); vaginal cuff closure was performed either transvaginally or laparoscopically as per the surgeon's preference.

Evaluated baseline characteristics included body mass index (BMI), uterine weight (grams), and age at the time of surgery. Data about parity, previous abdominal surgery, prior cesarean section, and medical treatment at the time of the hysterectomy were also collected.

For this study the following perioperative outcomes were evaluated: intraoperative blood loss (mL), operative time (minutes), hospital stay (days), intraoperative and postoperative blood transfusion, and occurrence of intraoperative complications (any unintentional injury to organs or structure beyond the uterus). Conversion to open surgery was reported but not considered *per se* as a complication. The severity of endometriosis was graded in accordance with the rAFS score (16), and the sites of endometriotic disease were reported as follows: peritoneal, ovarian, deep, and not specified. Regarding final histology data of uterus weight (grams) and presence of adenomyosis were reported. Postoperative complications were reported in accordance with the Clavien-Dindo classification (17) and also described in detail. Same hospital readmissions and reoperations that occurred within 30 days from surgery were reported.

Statistical analysis:

Descriptive statistics have been reported as absolute numbers (mean and standard deviation or median and range) for continuous variables and rate and percentage (%) for categorical variables. D'Agostino-Pearson test has been run to determine whether sample data followed a Gaussian distribution. Patients who had any grade 2 (or more) postoperative complication were compared with those who had uneventful postoperative follow-up or grade 1 postoperative complication. Associations with the occurrence of major complication (Clavien-Dindo grade 2 or more) were explored using chi-square test or Fisher's exact test for categorical variables, and the Student's t-test or Wilcoxon rank-sum tests for continuous variables, as appropriate. All calculated p-values were 2-sided, and $p < 0.05$ was considered statistically significant. Multivariable models were fit with logistic regression to estimate adjusted odds ratio (OR) and corresponding 95% CI for major complications. Statistical analysis was performed using JMP® Pro 13.0.0 (SAS Institute, Inc.)

Results

We analyzed data of 995 consecutive patients who underwent LH for pathologically proven endometriosis / adenomyosis; 871 (87.5%) and 124 (12.5%) had simple and radical LH, respectively. Conversion to open abdominal surgery occurred in 14 (1.4%) cases. The median age at surgery was 44 years (28-54), and most of the patients presented with normal BMI (median 24; 15.4-48.8). About half of the patients (505, 50.7%) were on medical treatment for endometriosis at the time of surgery (estro-progestins 21.3%, progestin 24.6%, GnRh-analogues 4.8%). Details on baseline patients' characteristics and specific sites of the endometriotic lesions have been shown in Table 1. In regard to surgery, 818 patients had concomitant surgical procedures beyond hysterectomy; in particular posterior adhesiolysis was performed in 387 (38,9%) cases and deep nodule resection in 302 (30,0%), Table 2.

Estimated intraoperative blood loss was minimal with a median of 100 mL (10-2000); 2.3% of the patients required perioperative blood transfusions. Overall intraoperative complications occurred in 3% of the patients, including 7 ureteral injuries (0,7%), 8 bladder injuries (0,8%), 9 bowel lesions (0,9%) and 6 intraoperative bleeding requiring blood transfusions. Postoperative complications were registered in 137 (13.8%) cases and 93 patients (9.3%) had a major event. A detailed report of postoperative complications within 30-days from surgery have been reported in Table 3. According

to the Clavien-Dindo classification, no patients experienced Grade 4 (or more) events, while 4.4% had grade 1 complications, 5.4% and 3.9% had grade 2 and grade 3 complications, respectively.

At the univariate analysis, among the factors evaluated for major postoperative complications, increased operative time, younger age at surgery, previous surgery for endometriosis and the occurrence of intraoperative complications were associated with Clavien-Dindo grade 2 (or more) complication. Conversely, ongoing medical treatment for endometriosis/adenomyosis at the time of surgery resulted to play a protective role.

The multivariable analysis for factors associated to Clavien-Dindo $\geq$2 complication confirmed the inverse correlation with age (Odds ratio 0.94, 95%CI 0.90-0.99). Conversely a direct correlation has been found with previous surgery for endometriosis (Odds ratio 1.62, 95%CI 1.01-2.60) and with the occurrence of intraoperative complications (Odds ratio 6.49, 95%CI 2.65-16.87). The protective role of medical treatment at the time of surgery has also been confirmed (Odds ratio 0.50, 95%CI 0.31-0.81). (Table 4).

Discussion

In the present study, we found that the occurrence of intraoperative complications represented a huge risk factor for postoperative grade 2 (or more) complications. Younger patients and those who had prior surgery for endometriosis were also most likely to experience major postoperative complications within 30 days from surgery. Conversely, we found that medical treatment for endometriosis at the time of surgery played a protective role.

The presence of endometriosis has been described as an independent risk factor for major complications at the time of laparoscopic hysterectomy (10). Such events were registered in about one out of ten patients in our study, and this rate is in accordance with what is reported in the most recent literature (7,18). Knowledge of factors associated with major complications allows us to further improve our practice and counsel patients more effectively. Endometriosis and adenomyosis represent only about 5% of the indications of benign LH (10); however, considering the large number of patients who undergo hysterectomy every year, even a modest decrease in the complication event rate might be of significant relevance.

Although the overall intraoperative complication rate for LH in this cohort is low at 3 %, these events resulted to be strongly associated with postoperative major complications. Although it is not possible to define the reason behind this finding, we might hypothesize that patients experiencing intraoperative complications (e.g. intraoperative bleeding) might be more likely to have postoperative disorders, such as vaginal cuff bleeding or dehiscence. Even if there is no scientific way to define surgical skills, it is reasonable to hypothesize that treating patients with suspected endometriosis and adenomyosis in referral centers should offer them the most appropriate cure, potentially reducing the risks of intraoperative adverse events. In this scenario, an accurate preoperative work-up is crucial to properly select the cases. In this study, we also found that prior surgery for endometriosis was a significant independent contributor to the increased risk of postoperative complications. This observation corroborates what was previously reported in other studies (19), where women with a surgical history of endometriosis undergoing gynecologic surgeries had a higher risk of surgical complications. Conversely, age was inversely correlated to the risk of postoperative complications. Of note, we were not able to address the reasons for this finding, but it is reasonable to hypothesize the more aggressive surgical treatment in young patients to avoid a possible risk of recurrence related to conservative surgery might have driven subsequent higher complication rates.

Of extreme interest, in our population, we noted that women under medical treatment at the time of surgery had a reduction of risk of major complications by approximately a half. A possible explanation could be the anti-inflammatory effects of estro-progestin and progesterone. These properties have been previously demonstrated; specifically, authors reported that they may reduce the inflammatory state generated by the metabolic activity of the ectopic endometrium, and the consequent immune response effects, both in-vitro and in-vivo (20). However, these remain only speculations, and further investigations are needed to confirm our findings. Moreover, it must be acknowledged that there might be other patients-related characteristics which could have biased this result since the inherit limits of the non-randomized study design.

The present study is one of the largest to date to assess the risk of postoperative complications of LH for endometriosis. Data of consecutive patients treated in tertiary referral centers by dedicated

minimally-invasive surgeons guarantee the appropriateness of the treatment. Postoperative adverse events were manually collected from patients' hospital notes and clinical charts, and reported in detail. The postoperative complications were collected within 30 days from LH and precisely graded in accordance with a specific severity grading of surgical complications (17). The number of patients included in this project, together with the relatively high rate of postoperative complications offered the chance to properly explore the factors associated with a higher risk of major events.

This study has several limitations which need to be addressed. First, the retrospective study design with inherent weaknesses could have impacted the external validity of our investigation, in particular, selection bias might have influenced our results. Indeed, patients included in this study might be not fully representative of the population undergoing LH for endometriosis. In particular, we acknowledge that the vast majority of the patients included in this study had a normal BMI at the time of the surgery, thus making our findings not fully representative for all patients with endometriosis undergoing hysterectomy. Second, all patients have been treated in tertiary minimally invasive gynecology referral centers, reflecting a reduction of the generalizability of our findings. Third, since we lack different-hospital readmission data, we may have underestimated postoperative complications and readmission rates. However, it has to be underlined that it is common practice at our institutions to advise discharged patients to present to the same hospital in case they experience complications to prevent discontinuity of care.

Conclusions

In patients affected by endometriosis surgery might be challenging and associated with non-negligible morbidity. Knowing the factors associated with higher risks of complications could be extremely helpful during preoperative counseling to make patients aware of potential scenarios, risks, and side effects of the treatment. In patients undergoing LH for endometriosis, the administration of estro-progestin or progesterone preoperatively might reduce the risks of postoperative complications following surgery.

Attestation Report:

Jvan Casarin: Conceptualization, Methodology, Formal analysis, Writing - Original draft preparation; Antonella Cromi: Formal Analysis, Writing - Original draft preparation; Giorgio Bogani: Formal analysis, Writing – Review & Editing; Fabio Ghezzi: Conceptualization, supervision. All other authors: data curation, Writing – Review & Editing.

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Tables

Table 1. Demographic and disease-related characteristics of the study population.

Laparoscopic hysterectomy for endometriosis	N=995
Age at surgery (years)	44 (28-54)
BMI (kg/m2)	24 (15.4-48.8)
Nulliparous	413 (41.5%)
Previous cesarean section	278 (27.9%)
Previous abdominal surgery, n (%) *Previous surgery for endometriosis*	699 (70.2%) *443 (44.5%)*
Medical treatment at time of surgery - *Estro-progestins* - *Progestins* - *GnRh analogues*	505 (50.7%) *212 (21.3%)* *245 (24.6%)* *48 (4.8%)*
Site of endometriotic disease - Peritoneal - Ovarian - Deep - Not specified	 271 (27.7%) 136 (13.7%) 5 (2.6%) 225 (22.6%)
Adenomyosis at final pathology	778 (78.2%)
Uterus weight (grams)	100 (35-2510)
r-ASRM score	18 (1-178)

Legend: Data is expressed as median and range for continuous variables, and absolute number and percentage for categorical variables. BMI=Body Mass Index [weight (kg)/ height (m^2)].

Table 2. Surgical data of the treated cohort.

Procedure details	
Type of Hysterectomy - Simple (TLH) - Radical (RH)	 871 (87,5%) 124 (12,5%)
Salpingo-oophorectomy - Unilateral - Bilateral	 150 (15,1%) 267 (26,8%)
Endometrioma enucleation	110 (11,1%)
Ureterolysis	267 (26,8%)
Deep nodule resection	302 (30,0%)
Posterior adhesiolysis	387 (38,9%)
Upper colpectomy	32 (3,2%)
TLH and BSO (only)	177 (17,8%)

Surgical outcomes	
Operative time (min)	113 (27-365)
Blood loss (mL)	100 (10-2000)
Blood transfusion	23 (2,3%)
Conversion to open surgery	14 (1,4%)
Intraoperative complications	30 (3,0%)
Postoperative complications	137 (13,8%)
Hospitalization (days)	3 (1-44)
Reoperations	33 (3,3%)
Readmissions	31 (3,1%)

Legend: Data is expressed as median and range for continuous variables, and absolute number and percentage for categorical variables.
Deep nodule resection was considered in case of torus and/or uterosacral ligament and/or vaginal fornix nodule resection

Table 3. Details of postoperative complications occurred within 30-days from surgery.

Postoperative complications	
Severity (Clavien-Dindo score) - Grade 1 - Grade 2 - Grade 3 - Grade 4 (or more)	 *44 (4.4%)* *54 (5.4%)* *39 (3.9%)* *0 (0.0%)*
Vaginal cuff bleeding	18 (1.8%)
Vaginal cuff dehiscence	14 (1.4%)
Fever	39 (3.9%)
Lower urinary tract infections	27 (2.7%)
Bladder disfunction - *Need for self-catheterization*	22 (2.2%) *3 (0.3%)*
Pelvic ascess	8 (0.8%)
Fistula - *Urogenital fistula* - *Enterogenital fistula*	10 (1.0%) 7 3

Legend: Data is expressed as median and range for continuous variables, and absolute number and percentage for categorical variables.
Deep nodule resection was considered in case of torus and/or uterosacral ligament and/or vaginal fornix nodule resection

Table 4. Analysis of the factors influencing major (Clavien-Dindo ≥ 2) postoperative complications.

	Univariate Analysis			Multivariable Analysis	
	Complications: No (n=902)	Complications: Yes (n=93)	P value	Odds Ratio (95% CI)	P value
Age at surgery (years)	44 (28-50)	43 (29-54)	0,01	0,94 (0,90-0,99)	0,01
BMI (kg/m2)	24 (15,6-48,8)	23,5 (15,4-47,6)	0,74		
Nulliparous	372 (41,2%)	41 (44,1%)	0,66		
Previous cesarean section	250 (27,7%)	28 (30,1%)	0,63		
Previous abdominal surgery	628 (68,6%)	71 (76,3%)	0,19		
Previous surgery for endometriosis	393 (43,6)	50 (53,8)	0,06	1,62 (1,01-2,60)	0,04
Medical treatment at the time of surgery	467 (52,3%)	38 (41,3)	0,04	0,50 (0,31-0,81)	0,01
Uterus weight (grams)	150 (35-2510)	150 (50-900)	0,87		
Site of endometriotic disease - Peritoneal - Ovarian - Deep	 250 (27,7%) 121 (13,4%) 327 (36,3%)	 21 (22,6%) 15 (16,1%) 36 (38,7%)	0,70		

- Not specified	204 (22,6%)	21 (22,6%)			
Radical Hysterectomy	113 (12,5%)	11 (11,8%)	0,84		
Hysterectomy + bilateral salpingo-oophorectomy (no associated procedures)	157 (17,4%)	20 (21,5%)	0,32		
Adenomyosis	713 (79,1%)	65 (59,9%)	0,09	0,64 (0,439-1,05)	0,21
Endometrioma enucleation	97 (10,7%)	13 (14,0%)	0,34		
Ureterolysis	242 (26,8%)	25 (26,9%)	1,00		
Deep nodule resection	273 (30,3%)	29 (31,2%)	0,91		
Posterior adhesiolysis	353 (39,1%)	34 (36,6%)	0,66		
Upper colpectomy	28 (3,1%)	10 (4,3%)	0,53		
Operative time (min)	110 (27-365)	120 (50-360)	0,06	1,01 (0,99 -1,02)	0,45
Conversion to open surgery	14 (1,6%)	0 (0,0%)	0,23		
Intraoperative complications	18 (2,0%)	12 (12,9%)	<0,001	6,49 (2,65-15,87)	<0,001

Legend: Data is expressed as median and range for continuous variables and absolute number and percentage for categorical variables. Significant predictors at p-value < 0.1 in the univariate analysis were exported to the multivariable logistic regression model.