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Original article

ENDOMETRIOSIS OF THE APPENDIX: WHEN TO PREDICT AND HOW TO MANAGE? MULTIVARIATE ANALYSIS OF 1,935 ENDOMETRIOSIS CASES

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Prècis

Appendiceal endometriosis was observed in 2.6% of patients with endometriosis, especially in presence of adenomyosis, large right endometrioma, deep pelvic lesions and ileo-cecal involvement

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Abstract

Study objective: To evaluate appendiceal endometriosis (AE) prevalence and risk factors in endometriotic patients submitted to surgery.

Design: Retrospective cohort study.

Setting: Tertiary level referral center, University hospital**.**

Patients: Consecutive 1935 patients who underwent surgical removal for symptomatic endometriosis**.**

Interventions: Electronic medical records of patients submitted to surgery over a 12-year period were reviewed. We assessed any correlation between demographic, clinical, and surgical variables and AE. In our center, appendectomy was performed using a selective approach. Appendix removal was performed in case of gross abnormalities of the organ, such as enlargement, dilation, tortuosity, or discoloration of the organ or presence of suspected endometriotic implants.

Measurements and Main Results: AE prevalence was 2.6% (50/1935), with only one false-positive at gross intra-operative evaluation. In multivariate analysis using a stepwise logistic regression model, independent risk factors for AE were: adenomyosis [aOR, 2.48, 95% confidence interval (CI), 1.32; 4.68], right endometrioma [aOR, 8.03, 95%CI, 4.08; 15.80], right endometrioma > or = 5cm [aOR, 13.90, 95% CI, 6.63; 29.15], bladder endometriosis [aOR, 2.05, 95% CI, 1.05; 3.99], deep posterior pelvic endometriosis (PPE) [aOR, 5.79, 95% CI, 2.82; 11.90], left deep lateral pelvic endometriosis (LPE) [aOR, 2.11, 95% CI, 1.10; 4.02], and ileo-cecal involvement [aOR, 12.51, 95% CI, 2.07; 75.75].

Conclusion: Among patients with endometriosis submitted to surgery, AE was observed in 2.6% and it was associated with adenomyosis, large right endometrioma, bladder endometriosis, deep posterior pelvic endometriosis, left deep lateral pelvic endometriosis and ileo-cecal involvement.

Keywords: deep infiltrating endometriosis, appendiceal endometriosis, appendectomy.

Introduction

The term “bowel endometriosis” is used when the endometrial-like glands and stroma infiltrate the bowel wall, reaching at least the muscular layer (1). It is estimated that 8-12% of patients with a diagnosis of endometriosis have bowel involvement. In particular, the rectum and sigmoid colon are responsible for approximately 90% of all intestinal lesions (2). Although appendiceal endometriosis (AE) is commonly considered an uncommon finding, in the Literature its prevalence varies widely (2-4).

Women with AE may complain of acute or chronic pelvic pain, fever, intussusception or lower gastrointestinal bleeding (3). Since AE have no pathognomonic symptoms and can be asymptomatic, this condition is more likely to be suspected during surgery on gross examination and diagnosed at histological examination of the appendix.

Abrao et al. (2) attempted to assess risk factors associated with AE, evaluating the relationship between it and the clinical presentation and co-localizations of endometriotic implants. They showed that women with AE had more widespread deep lesions and more frequent cyclic bowel symptoms.

Another study, conducted by Gimonet et al. (4), described an association between sigmoid, rectosigmoid, and right ureteral involvement and extrapelvic bowel endometriosis (EPBE), defined as the presence of an endometriotic lesion at the level of the ileum, appendix, or cecum.

Appendiceal involvement with endometriosis is a histological diagnosis after appendectomy. In the available Literature about AE, excision of the appendix was carried out using two different surgical strategies: selective appendectomy, in case of gross alterations of the appendix at intra-operative evaluation or preoperative imaging (2;5;6), or incidental appendectomy, defined as the surgical removal of the appendix at the time of a procedure unrelated to suspected appendiceal pathology (7).

The aim of the present study was to assess the prevalence of AE in our cohort of symptomatic patients with endometriosis submitted to surgery. Furthermore, we evaluated any clinical, surgical, and pathological risk factors for AE in our study group.

Materials and Methods

We conducted a retrospective cohort study on electronic medical records of consecutive patients who underwent surgical removal for symptomatic endometriosis at our referral center between August 2004 and October 2016. The only exclusion criterium was history of appendectomy for other pathologies. One thousand nine hundred and thirty-five (1,935) women were included in the study.

Prior to surgery, an accurate medical history was collected, and all patients underwent bimanual and speculum examinations as well as pelvic ultrasonography. When necessary, additional preoperative imaging methods were performed in order to plan surgery, including magnetic resonance imaging and multidetector computerized tomography enema. Pain symptoms related to endometriosis (chronic pelvic pain, dysmenorrhea, dyspareunia, dysuria, dyschezia) were assessed using a numerical rating scale (NRS) from 0 to 10. In particular, severe pain symptoms were considered as intensity equal or superior to 7 (8).

All surgical procedures were performed by a skilled team of surgeons with a consistent background in laparoscopic management of endometriosis.

In our center, appendectomy was performed in all cases using a selective approach. The decision of appendix removal was taken in case of gross abnormalities of the latter, such as enlargement, dilation, tortuosity, or discoloration of the organ or presence of suspected endometriotic implants. All patients with endometriosis were informed and counseled regarding the risk of selective appendectomy, in case of preoperative or intra-operative macroscopic alterations of the appendix. Video-laparoscopy was performed with a 10-mm laparoscope in the standard umbilical position and three 5-mm/10-mm suprapubic cannulas inserted under direct vision. An intra-operative abdomino-pelvic evaluation was performed, and a complete removal of all macroscopic endometriotic lesions was performed, as previously described (9;10).

The laparoscopic procedure usually began with systematic inspection of the upper abdomen, ileo-cecal junction, appendix and then the pelvis. Lysis of adhesions, stripping of any endometriomas

and ovarian suspension, isolation, and removal of deep implants of the anterior and posterior compartments, according to clinical and pathological aspects of the disease, were performed (10).

To perform the appendectomy, the cecum and appendix were mobilized, the mesoappendix was secured and cut, and the appendicular artery was isolated, coagulated and transected. Three endoloops were introduced through the right lower quadrant trocar and applied to the junction where the appendix extends into the cecum**.** Two ligatures were located at the base of the appendix 2 mm apart. The final ligature was placed approximately 7 mm above the last ligature, and then the area between the second and third ligature was coagulated and cut.

All specimens were submitted for pathological examination. The study population was divided into two groups according to histological confirmation of AE: endometriosis with or without appendiceal involvement. The two groups were compared in terms of demographic data (age, body mass index (BMI), previous surgery for endometriosis), clinical variables (medical therapy within 6 months before surgery, pain, and bowel symptoms) and surgical findings (associated endometriotic implants with maximum diameter and anatomical localizations). Data regarding associated endometriotic implants were retrieved from surgical reports completed by surgical team after the procedure.

Deep infiltrating endometriosis (DIE) was considered when infiltration of retroperitoneal tissue or pelvic organ wall was found during surgery. DIE was divided in: anterior pelvic endometriosis (APE) in case of bladder endometriosis; lateral pelvic endometriosis (LPE) in case of parametria and ureteral involvement; posterior pelvic endometriosis (PPE) in case of vaginal, recto-vaginal space, uterosacral ligaments, and recto-sigmoid tract infiltration by deep endometriotic lesions.

Due to the retrospective design of the study, institutional review board approval was not required, but a notification was performed, and the local ethics committee approved the collection of data for research purposes. All patients signed informed consent forms for the potential anonymous use of their data for research purposes.

Statistical analysis

Data were summarized using standard descriptive statistics. Differences between two groups were analyzed using the chi-squared test or Fisher's test and Mann–Whitney U test as appropriate. Univariate logistic regressions were performed to evaluate the association between predicting variables and AE. All variables with a p-value ≤ .05 were included in a multivariate stepwise backward logistic regression model. Correspondent odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Statistical significance was set to the conventional p-value ≤ .05. Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) software version 24.0 (IBM Corp., Armonk, NY, USA).

Results

Fifty-one patients underwent selective appendectomy for suspected AE. No patient was preoperatively diagnosed with AE. Pathological assessment confirmed AE in 50/51 samples (98%). The patient with a false diagnosis at macroscopic evaluation was found to have a faecolith. The prevalence of AE in our study population was 2.6% (50/1,935). The study group presented chronic inflammatory and fibrotic features in 22 women (44%), while acute inflammatory reactions were found in 28 women (56%). There was no correlation between pre-operative clinical presentation and histological features. No perioperative complications related to appendectomy were reported.

Table 1 reports the results of the univariate analyses to identify factors potentially associated with AE. Regarding preoperative symptoms, patients with AE more frequently complained of severe dyschezia (p= .003), constipation (p= .04), and pain in right iliac fossa (RIF) (p= .03). Concerning intra-operative findings, AE was associated with right endometrioma (p= <.001). In particular, the AE group presented a higher frequency of large right endometrioma (with maximum diameter equal or superior to 5 cm): 22 cases (44%) in the AE group versus 332 cases (17.6%) in the control group (p= <.001). Moreover, the AE group more often had concomitant adenomyosis (p= .005), bladder implants (p= <.001), right and left LPE (p= .04 and .006, respectively), PPE (p= <.001) and ileo-cecal involvement (p= <.001). Only three women with AE did not have a concomitant deep lesion and no patient had isolated AE.

Table 2 reported uni- and multivariate logistic regression analysis evaluating factors predicting AE in our study population. By descending stepwise multivariate logistic regression analysis, independent risk factors for AE were: adenomyosis [aOR, 2.48, 95%CI, 1.32;4.68], right endometrioma [aOR, 8.03, 95%CI, 4.08;15.80], bladder endometriosis [aOR, 2.05, 95%CI, 1.05;3.99], PPE [aOR, 5.79, 95%CI, 2.82;11.90], left LPE [aOR, 2.11, 95%CI, 1.10;4.02] and ileo-cecal involvement [aOR, 12.51, 95%CI, 2.07;75.75]. Interestingly, aOR in case of large right endometrioma with maximum diameter ≥5 cm increased up to 13.90 [95%CI, 6.63;29.15]. Conversely, severe dyschezia, constipation, pain in RIF, and right LPE were not independent risk factors on multivariate analysis, although they were significantly associated with AE on univariate analysis.

Discussion

What is the prevalence of AE?

In our study, AE prevalence among patients who underwent surgery for symptomatic endometriosis was 2.6%. Several Authors had studied AE prevalence in women with endometriosis or other benign gynecological and non-gynecological diseases (i.e. fibroids, pelvic mass etc.). Tables 3 and 4 provide a summary of our data compared with 32 relevant full-text articles on this topic. The following key words were used to conduct a computerized search of PubMed/Medline: “endometriosis” AND “appendix” OR “appendectomy” OR “appendicitis”. Relevant full-text articles written in English from January 1955 to December 2018 containing a table of references were retrieved. All references were searched to identify other pertinent articles. Case reports or series with less than five patients were excluded.

In the available Literature, AE prevalence is highly variable (from 0.2 to 36,6%). This data is related to the wide heterogeneity of the studies concerning the population included and the surgical strategy adopted to perform appendectomy.

The AE prevalence in patients with histological diagnosis of endometriosis and in patients submitted to surgery for benign gynecologic and non-gynecological conditions was 2.5%

(186/7,338) and 1.2% (222/17,970), respectively. The AE prevalence in patients affected by endometriosis was 6.4% (102/1,606) adopting a selective approach and 1.9% (38/2,021) after an incidental approach. Concerning AE prevalence in patients with overall benign gynecologic and non-gynecological conditions, 3.7% (26/71) and 4.6% (106/2,280) were found with a selective and incidental approach, respectively.

Is it possible to predict AE?

Preoperative diagnosis of AE is difficult due to the lack of pathognomonic clinical or radiological findings. Therefore, it is crucial to suspect AE in patients who have one or more risk factors for appendiceal involvement.

In our cohort population, AE was independently associated with PPE, ileo-cecal, and bladder endometriosis. These results are in agreement with findings from Abrao et al. (2).

We also observed a significant association between the presence of right endometrioma and AE, especially in case of large ovarian cyst. This association could be due to the proximity of the two organs and characteristic clockwise peritoneal fluid circulation pattern. Several studies showed a different distribution of endometriotic lesions between the two sides of the abdomino-pelvic cavity, correlating it with the anatomical differences between the two hemipelvises and the circulation of the peritoneal fluid (11-13).

In contrast to Gimonet et al. (4), we did not observe a significant association between AE lesions and right ureter, but with left ureter and parametrium. This can be simply a statistical finding. However, the high frequency of ureteral involvement in case of posterior deep nodule and the asymmetric distribution of ureteral lesion could explain our data (12).

Appendectomy: incidental or selective approach?

There is no consensus regarding the management of occult AE in women with endometriosis.

According to several authors, incidental appendectomy could allow complete disease eradication, full symptom relief, and abolition of potential complications related to AE (i.e., intussusceptions or lower gastrointestinal bleeding) (14-19).

On the contrary, among patients with endometriosis the rate of negative histological findings for AE after incidental appendectomy is higher than the selective approach [86.8% (92/106) and 69.0% (224/326), respectively]. Our study confirmed a low rate of negative histological findings for endometriosis after selective appendectomy in women affected by endometriosis (2%; 1/51).

Furthermore, the clinical importance of microscopic foci of this chronic benign disease remains uncertain. Indeed, the role of incidental appendectomy in the post-operative improvement of pain symptoms or disease recurrence has not been elucidated yet. Lastly, incidental appendectomy during abdominal procedures was associated with increased risk of postoperative wound complications and overall morbidity during elective surgery (13). Complications related to appendectomy for occult AE were poorly reported, except for Moulder et al. (14), who observed two cases (2/395, 0.5%) of bowel injuries. Therefore, the lack of data on surgical complications and clinical outcomes related to appendectomy for AE did not allow researchers to balance risks and benefits of the incidental appendix excision in women with endometriosis.

Potential limitations of the present study could be its retrospective design and the heterogeneity of the pre-surgical investigations. However, the high number of patients, the statistical methodology including data obtained after surgical excision and histological confirmation, can represent strength points.

Conclusion

Among patients with endometriosis surgically treated, appendiceal endometriosis is observed in 2.6% and it is associated with adenomyosis, large right endometrioma, bladder endometriosis, deep posterior pelvic endometriosis, left deep lateral pelvic endometriosis and ileo-cecal involvement. It is mandatory to counsel the patient with endometriosis scheduled for surgery about the risk of appendix excision and to be surgically prepared to perform selective appendectomy, especially in the presence of these risk factors. Further prospective randomized studies are needed to evaluate and compare benefits and risks of selective and incidental appendectomy for AE.

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Table 1: Comparison of pre-operative data and intra-operative findings between women with and without appendiceal endometriosis

Characteristics	Endometriosis with appendiceal endometriosis (n= 50)	Endometriosis without appendiceal endometriosis (n= 1,885)	p-value
-Demographic data:			
Age (years)	36.4 +/- 7.5	35.7 +/- 6.8	0.7
BMI (Kg/m^2)	22.4 +/- 4.4	22.2 +/- 3.6	0.8
Previous surgery for endometriosis	22 (44)	1,332 (70.7)	<0.001
Preoperative medical therapy	48 (96)	1,800 (95.5)	0.9
-Clinical data:			
History of infertility	12 (24)	679 (36)	0.08
Severe CPP	12 (24)	400 (21.2)	0.6
Severe dysmenorrhea	31 (62)	973 (51.6)	0.2
Severe dyspareunia	17 (34)	506 (26.8)	0.3
Severe dysuria	3 (6)	101 (5.4)	0.8
Severe dyschezia	18 (36)	364 (19.3)	0.003

Rectal bleeding	2 (4)	54 (2.9)	0.7
Constipation	14 (28)	316 (16.8)	0.04
Diarrhea	4 (8)	103 (5.5)	0.4
Abdominal bloating	2 (4)	82 (4.3)	1
Pain in RIF	3 (6)	24 (1.3)	0.03
-Surgical data:			
Laparoscopic route	49 (98)	1,881 (99.7)	0.2
Adenomyosis	27 (54)	652 (34.6)	0.005
Peritoneal	39 (78)	1301 (69)	0.2
Left endometrioma	8 (16)	705 (37.4)	0.002
Right endometrioma	29 (58)	619 (32.8)	<0.001
Right endometrioma > or = 5 cm	22 (44)	332 (17.6)	<0.001
Bladder endometriosis	17 (34)	280 (14.8)	<0.001
Left LPE	21 (42)	470 (24.9)	0.006
Right LPE	16 (32)	380 (20.2)	0.04
PPE	37 (74)	659 (35)	<0.001
Ileocecal endometriosis	3 (6)	4 (0.2)	0.001
Maximum diameter of the main DIE lesion (cm)	3.01 +/- 0.22	2.97 +-/ 0.48	0.9

Data are shown as mean +/- standard deviation or n (%). Severe pain symptoms had numeric rating scale score ≥ 7.

Abbreviations: BMI: body mass index; CPP: chronic pelvic pain; LPE: lateral pelvic endometriosis; PPE: posterior pelvic endometriosis; RIF: right abdominal fossa; DIE: deep infiltrating endometriosis

Table 2: Factors predicting presence of appendiceal endometriosis in our study population

	Univariate analysis		Multivariate analysis	
Variable	OR (95%CI)	p-value	aOR (95%CI)	p-value
BASELINE CHARACTERISTICS				
Age (year)*	1.02 (0.98-1.06)	0.5	-	-
BMI (Kg/m^2)*	1.02 (0.95-1.09)	0.7	-	-
Previous surgery for endometriosis	0.33 (0.18-0.57)	<0.001	0.38 (0.21-0.71)	0.002
PRE-OPERATIVE SYMPTOMS				
Severe dysmenorrhea	1.53 (0.86-2.73)	0.2	-	-
Severe dyspareunia	1.40 (0.78-2.54)	0.3	-	-
Severe CPP	1.17 (0.61-2.26)	0.6	-	-
Severe dysuria	1.13 (0.34-3.68)	0.8	-	-
Severe dyschezia	2.35 (1.30-4.23)	0.004	1.47 (0.75-2.91)	0.3
Hematochezia	1.41 (0.33-5.96)	0.6	-	-
Constipation	1.93 (1.03-3.62)	0.04	1.27 (0.62-2.59)	0.5
Diarrhea	1.50 (0.53-4.26)	0.4	-	-
Pain in RIF	4.95 (1.44-17.01)	0.01	3.60 (0.86-15.07)	0.08
ENDOMETRIOTIC ANATOMICAL FINDINGS				
Adenomyosis	2.22 (1.26- 3.90)	0.006	2.48 (1.32-4.68)	0.005

Peritoneal involvement	1.59 (0.81-3.13)	0.2	-	-
Bladder	2.95 (1.62-5.37)	<0.001	2.05 (1.05-3.99)	0.04
PPE	5.29 (2.79-10.03)	<0.001	5.79 (2.82-11.90)	<0.001
Left LPE	2.18 (1.23-3.86)	0.007	2.11 (1.10-4.02)	0.02
Right LPE	1.86 (1.02-3.41)	0.04	1.13 (0.54-2.34)	0.08
Ileocecal region	30.01 (6.53-137.88)	<0.001	12.51 (2.07-75.75)	0.02
Left endometrioma	0.32 (.15-.68)	0.003	0.46 (0.19-1.11)	0.08
Right endometrioma: - none - <5 cm - ≥5 cm	2.82 (1.59-4.99) 1 1.47 (.62-3.49) 3.99 (2.17-7.35)	<0.001 0.4 <0.001	8.03 (4.08-15.80) 1 3.25 (1.22-8.69) 13.90 (6.63-29.15)	<0.001 0.02 <0.001
Maximum diameter of the main DIE lesion (cm)*	1.13 (0.67-1.92)	0.7	-	-

* Continuous variables: OR per one-unit increase.

Severe pain symptoms had numeric rating scale score □ 7.

Abbreviations: OR: odds ratio; aOR: adjusted odds ratio; CI: confidence intervals; BMI: body mass index; CPP: chronic pelvic pain; RIF: right iliac fossa; LPE: lateral pelvic endometriosis; PPE: posterior pelvic endometriosis; DIE: deep infiltrating endometriosis

Table 3. Appendiceal Endometriosis in patients submitted to surgery for endometriosis

Author	Year	Study design	Surgical strategy	AE cases	Number of appendectomies	Total patients	Prevalence (%) AE
Mabrouk M et al. (present study)	2019	R	S	50	51	1,935	2.6
Gimonet et al. (4)	2016	R	S	5	5	96	5.2
Padovesi Mota IL et al. (16)	2015	R	S	4	6	108	3.7
Abrao M et al. (2)	2010	R	S	26	26	737	3.5
Roman JD (17)	2010	R	NS	7	13	194	3.6
Wie HJ et al. (18)	2008	R	I	14	106	106	13.2
Gustofson R et al. (5)	2006	P	S	4	6	97	4.1
Berker B et al. (15)	2005	R	S	51	231	231	22.1
Douglas C	2004	R	NS	2	NS	379	0.5

& Rotimi O (19)							
Harper AJ & Soules MR (7)	2002	NS	I	3	NS	200	1.5
Harris RS et al. (20)	2001	P	S	12	52	337	3.6
Prystowsky JB et al. (21)	1988	NS	I	17	NS	1,573	1.1
Weed JC & Holland JB (22)	1977	R	I	4	NS	142	2.8
Tedeschi LG &Masand GP (23)	1971	NS	NS	4	NS	720	0.6
Burns FJ (24)	1967	NS	NS	10	NS	360	2.8
Macafee CH & Greer HL (25)	1960	R	NS	5	NS	803	0.6
Kratzer GL &Salvati EP (26)	1955	NS	NS	1	NS	255	0.4

Henriksen E (27)	1955	NS	NS	17	NS	1,000	1.7
Total [a]				236	496	9,273	2.5
Total [b]				186	445	7,338	2.5

Abbreviations: NS = not stated; AE = appendiceal endometriosis; S = selective; I = incidental; R = retrospective; P= prospective; [a]= including our findings; [b]= without our findings

Table 4. Appendiceal Endometriosis in women undergoing surgery for overall benign gynecologic or non-gynecologic conditions

Author	Year	Study design	Surgical strategy	AE cases	Number of appendectomies	Total patients	Prevalence (%) AE
Moulder J et al. (14)	2017	R	I	52	395	395	13.2
Jocko JA et al. (6)	2013	R	S	26	71	71	36.6
Lee H et al (28)	2011	R	I	16	172	356	4.5
Shavell VI et al. (29)	2011	R	NS	1	22	22	4.5
Song JY et al. (30)	2009	R	I	17	772	772	2.2
O'hanlan KA et al. (31)	2007	R	I	8	257	257	3.1
AgarwalaN & Liu CY (32)	2003	R	NS	14	317	317	4.4
Onders RP &Mittendorf EA (33)	2003	P	NS	2	NS	61	3.3
Lyons TL et al. (34)	2001	R	NS	18	154	190	9.5

AlSalilli M &Vilos GA (35)	1995	P	NS	8	100	483	1.7
Pittaway DE (36)	1983	R	I	13	500	500	2.6
Nielsen M et al. (37)	1983	NS	NS	22	10,000	10,000	0.2
LangmanJ et al. (38)	1981	NS	NS	6	NS	3,578	0.2
Williams TJ & Pratt JH (39)	1977	R	NS	19	NS	968	2.0
Total				222	12,760	17,970	1.2

Abbreviations: NS = not stated; AE = appendiceal endometriosis; S = selective; I = incidental; R = retrospective; P= prospective