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**Risk of appendiceal endometriosis among women with deep-infiltrating endometriosis**

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**Keywords:** Appendiceal endometriosis; Appendix; Deep-infiltrating endometriosis; Endometriosis

**Synopsis:** Women with deep-infiltrating endometriosis have an increased risk of appendiceal endometriosis. Coincidental appendectomy should be considered during complete endometriosis excision for these women.

#### **Abstract**

**Objective:** To determine whether deep-infiltrating endometriosis (DE) carries an increased risk of appendiceal endometriosis (AppE) as compared with superficial endometriosis or no endometriosis.

**Methods:** In a retrospective study, data were obtained by chart review of an internal database for women who underwent incidental appendectomy during benign gynecologic surgery between July 2009 and February 2014 at a tertiary referral center in the USA. Univariate, bivariate, and regression analyses were performed. The primary exposure was surgically documented endometriosis (DE, superficial, or no endometriosis). The primary outcome was AppE.

**Results:** Endometriosis was diagnosed for 151 (38.2%) of 395 women; 82 (54.3%) had DE. The prevalence of AppE was 13.2% (52/395) overall; 8 (11.6%) of 69 women with superficial endometriosis and 32 (39.0%) of 82 with DE were affected. Frequency of AppE was increased among women with DE, abnormal appendix appearance, and surgical indication (all  $P < 0.001$ ). Women with DE had a 5.9-fold

(95% confidence interval [CI] 2.9–11.9) higher risk of AppE compared with women without endometriosis, controlling for appendiceal appearance and surgical indication, and a 2.7-fold (95% CI 1.2–6.2) higher risk of AppE compared with those with superficial endometriosis.

**Conclusion:** Women with DE have increased risk of AppE. Coincidental appendectomy should form part of complete endometriosis excision for these patients.

## 1 INTRODUCTION

Endometriosis—the presence of endometrial glands or stroma in an ectopic location [1]—is characterized as superficial peritoneal implants or deep infiltrating [2]. Deep-infiltrating endometriosis (DE) extends at least 5 mm below the peritoneum; common areas affected by this form of the disease include the uterosacral ligaments, adnexae, colon, and appendix [3]. Complete surgical excision of DE lesions improves painful functional symptoms, irrespective of the disease location [4].

Although the prevalence of appendiceal endometriosis (AppE) in the general population is estimated to be 0.4%–1% [5,6], its prevalence among patients with endometriosis is 4%–22% [7,8]. Appendectomy has a special role in the care of a patient with chronic pelvic pain, both from a therapeutic perspective [9,10] and to simplify any future differential diagnosis should the patient subsequently present emergently with acute exacerbation of pain symptoms. Coincidental appendectomy does not confer a significant increase in operative time, morbidity, or mortality [7,11,12]. The American College of Obstetrics and Gynecology recommends consideration of the risks and benefits associated with elective coincidental

appendectomy, depending on patient age and clinical circumstance [13]. However, there is no current consensus about which patients have a higher risk of appendiceal pathology and might benefit from coincidental appendectomy.

The primary aim of the present study was therefore to determine whether patients with DE have an increased risk of AppE as compared with those without endometriosis or with only superficial endometriosis. A secondary aim was to identify the prevalence of AppE and its associated characteristics among women undergoing benign gynecologic surgery.

## **2 MATERIALS AND METHODS**

In a retrospective study, data were assessed from patients who underwent appendectomy during surgery for benign gynecologic conditions performed by members of the division of Minimally Invasive Gynecologic Surgery at University of North Carolina Hospitals, NC, USA, between July 1, 2009, and February 28, 2014. The study women were identified from an internally maintained surgical database on the basis of the procedures that had been coded (e.g. laparoscopic appendectomy). Women with a history of appendectomy or who did not undergo coincidental appendectomy were excluded. The study was reviewed by the institutional review board of the University of North Carolina at Chapel Hill and was determined to be exempt from formal approval.

Endometriosis was confirmed by histologic evidence of endometrial glands and stroma present in excised tissue, and was considered deeply infiltrating if it penetrated more than 5 mm beyond the peritoneum or affected other organs or

ligaments (e.g. uterosacral nodule or intestinal involvement) [3]. Women with infiltration less than 5 mm were categorized as having superficial endometriosis. Demographic information, surgical details, perioperative and postoperative complications, and pathology reports were abstracted from the electronic medical record by four researchers (JKM, MTS, EGJ, and KAH) and stored in a de-identified, electronic database for analysis.

The primary exposure was intraoperative diagnosis of DE, superficial endometriosis, or no endometriosis; the primary outcome was AppE. Data were analyzed by STATA version 13 (StataCorp, College Station, TX, USA) using mean  $\pm$  SD for continuous variables and number (percentage) for categorical variables. Association of factors with the outcome AppE was examined by using a two-sample *t* test for continuous variables and Pearson  $\chi^2$  test for categorical variables.

A modified Poisson regression analysis was used [14] to estimate risk ratios for AppE by type of endometriosis (DE, superficial, or none), adjusting for potential confounders. Covariates that did not alter the association between type of endometriosis and AppE were excluded from the final model, which included the covariates of appendix appearance and surgical indication. Age, body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters), race, parity, and a history of chronic pelvic pain were not considered to be confounders and therefore were not included in the final model. The adjusted risk ratio (RR) and 95% confidence interval (CI) were estimated from the final model.  $P < 0.05$  was considered statistically significant.

### 3 RESULTS

During the study period, there were 395 cases of coincidental appendectomy among women undergoing benign gynecologic surgery. Overall, the study population was young, white, and overweight (Table 1). The most common indications for surgery were pelvic pain and fibroids (Table 1). Most women underwent total laparoscopic hysterectomy with or without bilateral salpingo-oophorectomy; this was the most common procedure for women without endometriosis, and for women with DE (Table 1). The most common procedure for women with superficial endometriosis was laparoscopic excision of endometriosis.

Most surgeries were performed laparoscopically (389/395, 98.5%); there were only three unplanned conversions to laparotomy to complete the primary procedure. The median operative time was 122 minutes (range 5–519), and the median estimated blood loss was 25 mL (range 0–1200). The surgery that lasted 519 minutes involved a bowel resection for intestinal endometriosis, whereas that with an estimated blood loss of 1200 mL was a robotic myomectomy that was converted to laparotomy. Overall, there were two complications directly related to appendectomy (monopolar electrosurgery injury of the terminal ileum and bipolar injury to the sigmoid mesentery), both addressed by over-sewing the area laparoscopically. Neither patient experienced further sequelae.

Overall, endometriosis was identified in 151 (38.2%) women during surgery, of whom 82 (54.3%) had DE. All women with an ovarian endometrioma had concurrent DE and were therefore categorized as having DE. Women with DE were older than those with superficial endometriosis ( $P<0.001$ ) (Table 1). Women with DE and those

with superficial endometriosis had a lower BMI than those without disease ( $P=0.040$  and  $P=0.008$ , respectively) (Table 1). Additionally, more women with DE and superficial endometriosis were nulliparous (both  $P<0.001$ ) and had chronic pelvic pain ( $P=0.028$  and  $P<0.001$ , respectively) as compared with women without disease (Table 1).

At the time of gynecologic surgery, AppE was identified in 52 (13.2%) of the 395 cases of coincidental appendectomy (Figure 1). AppE was present in 12 (4.9%) of 244 women without endometriosis, 8 (11.6%) of 69 women with superficial endometriosis, and 32 (39.0%) of 82 women with DE (Figure 2). Among the women with AppE, the most prevalent primary surgical indication was endometriosis (Table 2). No significant difference was noted in age, BMI, parity, and chronic pelvic pain between those with and those without AppE (Table 2).

Women with DE had significantly higher risk of AppE than did those without endometriosis (Table 3). When comparing with superficial endometriosis, the risk was also increased (RR 2.7, 95% CI 1.2–6.2).

Most appendices were normal in appearance (243/395, 61.5%). Frequency of AppE was higher among women with appendices with an abnormal appearance (35/152, 23.0%) than among other women with normal-appearing appendices (17/243, 7.0%;  $P<0.001$ ). The prevalence of AppE in a normal-appearing appendix was higher for women with superficial endometriosis (3/44, 6.8%) and DE (5/27, 18.5%) than for those without endometriosis (9/172, 5.2%;  $P=0.042$ ). Appendiceal pathology of any type was found for 247 (62.5%) of the 395 women (Table 4).

#### 4 DISCUSSION

AppE was found to be fairly common in the present patient population (prevalence 13.2%), and most cases of AppE occurred among women with DE. AppE was not associated with any specific patient characteristics. The risk of AppE was higher among women with endometriosis, and AppE was found even among those with a normal appendix appearance. Furthermore, women with DE had a 5.9-fold higher risk of AppE than did women without endometriosis. Thus, surgical excision should be considered for women with endometriosis, and specifically for those with DE, irrespective of the appearance of the appendix.

The prevalence of AppE was higher than has been previously reported, although most cases occurred in women with DE. The study practice is at an academic tertiary referral center, which could account for the greater degree of pathology noted in the cohort. The reported range of AppE is 0.4%–1% [5,6], increasing to up to 22% among women with endometriosis [7]. The present study specifically examined the comparative risk among patients without endometriosis, those with superficial disease, and those with DE.

Although endometriosis has been associated with decreased parity [15] and chronic pelvic pain [16], these factors were not linked with AppE in the present bivariate analyses. For women with symptoms of pelvic pain, visible endometriosis observed during surgery should be treated [17] and, in the setting of pelvic endometriosis, appendectomy has been advocated for those with a visibly abnormal appendix [18]. In the present study, women with DE had an increased risk of AppE as compared with women without endometriosis. The risk of recurrence and subsequent

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reoperation varies by age [19]; however, the present findings suggest that women of any age with DE might benefit from appendectomy at the time of excision of endometriosis, given the increased risk of AppE observed. Although the greatest benefit from coincidental appendectomy is conferred on women younger than 35 years, women who are undergoing extensive pelvic surgery and/or who are at high risk of postoperative adhesions might also benefit from this procedure, even if they are older [13]. Irrespective of age, women with DE who are undergoing surgical excision have increased surgical complexity and adhesive disease, supporting a procedure of coincidental appendectomy.

As mentioned above, the risk of AppE was higher for women with endometriosis, and some of those with a normal appendix appearance had the disorder. Abnormal histopathology in a grossly normal appendix has been previously reported [11]. For patients with endometriosis, especially those with DE, complete excision of disease is generally advocated by surgeons with significant experience of treating these patients [20]. Surgical excision of endometriosis is recommended for definitive diagnosis and reduction of pain associated with the disease [21,22]. Incomplete or conservative excision of disease results in an increased risk of future surgical intervention [19]. Given the higher risk of AppE among women with DE, appendectomy should be offered if complete excision of endometriosis is the surgical objective, irrespective of the appearance of the appendix. Women with superficial endometriosis also have an increased risk of AppE, and a preoperative discussion of coincidental appendectomy in this setting would be appropriate.

The present study has some limitations. First, not all women undergoing gynecologic surgery during the study period desired appendectomy; thus, it was not possible to describe the overall prevalence of AppE in the gynecologic surgery population. However, a review of the patient characteristics of women undergoing truly coincidental appendectomy (i.e. for an indication other than pelvic pain or endometriosis) revealed them to be similar to those of the general surgical population. Additionally, very few of the women with pelvic pain or endometriosis as their surgical indication declined concurrent appendectomy; thus, evaluation of appendiceal pathology in this group is likely to be representative. Second, because the study institution is a referral center, many patients return to their referring providers after surgery; as such, it is not possible to prospectively study a cohort of patients to determine whether coincidental appendectomy prevents future surgical intervention for endometriosis or pelvic pain. For patients with DE, however, pain symptoms associated with endometriosis are known to correlate with the anatomic location of DE [23], and complete excision of DE does improve these symptoms [4]. The patients in the present cohort had the benefit that the need for emergency surgery for acute appendicitis was prevented; however, as a referral practice, it was not possible to determine how many of the patients who declined coincidental appendectomy went on to develop acute appendicitis.

In conclusion, the prevalence of AppE might be higher than previously reported, particularly among women with DE. The risk of AppE was 5.9 times higher for women with DE than for women without endometriosis, and the disorder occurred even in the absence of a grossly abnormal appendix. Women undergoing extensive pelvic surgery for endometriosis can be offered coincidental appendectomy,

particularly because complete surgical excision of endometriosis is advocated for women with DE. The present findings demonstrate that this is a relatively safe procedure to perform and could confer the additional benefit of minimizing the risk of reoperation for endometriosis, although future prospective research is needed to confirm this benefit.

### **Author contributions**

JKM, MTS, EGJ, and KAH contributed to conception, study design, and acquisition of data. JKM, KLM, and JG performed data analysis and data interpretation. All authors contributed to drafting and critical revision of the manuscript.

### **Conflicts of interest**

The work reported in the manuscript has not received any financial support or funding. JKM reports a paid consultancy for Teleflex Medical. MTS is a paid consultant for Teleflex Medical, Intuitive Surgical, Applied Medical, and Olympus. The other authors have no conflicts of interest.

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#### Figure legends

**Figure 1** Appendiceal endometriosis in the setting of deep infiltrating endometriosis. Shown is an image from a 37-year-old woman with cyclic pelvic pain, known endometrioma, and surgical diagnosis of deep infiltrating endometriosis. Final pathology confirmed appendiceal endometriosis. The appendix can be seen on the bottom right; a 5-cm left ovarian endometrioma can be seen on the left.

**Figure 2** Prevalence of AppE. Abbreviation: AppE, appendiceal endometriosis.

**Table 1** Baseline characteristics.<sup>a</sup>

Characteristic	Overall (n=395)	Women with deep-infiltrating endometriosis (n=82)	Women with superficial endometriosis (n=69)	Women without endometriosis (n=244)
Age, y	36.3 ± 9.4	37.4 ± 6.5	31.7 ± 7.5	37.4 ± 10.3
Body mass index <sup>b</sup>	29.9 ± 8.8	28.6 ± 7.2	27.7 ± 8.3	30.9 ± 9.3
Race				
White	244 (61.8)	45 (54.9)	51 (73.9)	148 (60.7)
Black	108 (27.3)	22 (26.8)	12 (17.4)	74 (30.3)
Hispanic	16 (4.1)	5 (6.1)	1 (1.4)	10 (4.1)
Other	27 (6.8)	10 (12.2)	5 (7.2)	12 (4.9)
Chronic pelvic pain	201 (50.9)	47 (57.3)	48 (69.6)	106 (43.4)
Nulliparous	182 (46.1)	49 (59.8)	45 (65.2)	88 (36.1)
Prior abdominal surgery	275 (69.6)	57 (69.5)	52 (75.4)	166 (68.0)
Current smoker	79 (20)	17 (20.7)	14 (20.3)	48 (19.7)
Surgical indication				
Pelvic pain	172 (43.5)	13 (15.9)	48 (69.6)	111 (45.5)
Fibroids	95 (24.1)	20 (24.4)	6 (8.7)	69 (28.3)
Pelvic mass	43 (10.9)	7 (8.5)	2 (2.9)	34 (13.9)
Endometriosis	47 (11.9)	38 (46.3)	8 (11.6)	1 (0.4)
Abnormal bleeding	28 (7.1)	4 (4.9)	3 (4.3)	21 (8.6)
Other	10 (2.5)	0	2 (2.9)	8 (3.3)
Primary procedure				
Total laparoscopic hysterectomy ± bilateral salpingo-oophorectomy	232 (58.7)	44 (53.7)	21 (30.4)	167 (68.4)
Laparoscopic excision of endometriosis	58 (14.7)	23 (28.1)	31 (44.9)	4 (1.6)
Laparoscopic adnexal surgery	40 (10.1)	4 (4.9)	4 (5.8)	32 (13.1)
Operative laparoscopy	23 (5.8)	0	1 (1.4)	23 (9.4)
Laparoscopic myomectomy <sup>c</sup>	23 (5.8)	6 (7.3)	7 (10.1)	11 (4.5)
Abdominal myomectomy	7 (1.8)	4 (4.9)	0	1 (0.4)
Other <sup>d</sup>	12 (3.0)	1 (1.2)	5 (7.2)	6 (2.5)

<sup>a</sup> Values are given as mean ± SD or number (percentage).

<sup>b</sup> Calculated as weight in kilograms divided by the square of height in meters.

<sup>c</sup> Denotes laparoscopic or robotic-assisted laparoscopy.

<sup>d</sup> Laparoscopic trachelectomy (n=5), laparoscopic uterine suspension (n=3), laparoscopic presacral neurectomy (n=2), and laparoscopic cuff revision (n=2).

**Table 2** Unadjusted associations between patient characteristics and appendiceal endometriosis.<sup>a</sup>

Characteristic	Total no. of women	Women with appendiceal endometriosis	Women without appendiceal endometriosis	P value <sup>b</sup>
Age, y	395	36.9 ± 8.1	36.2 ± 9.6	0.642
Body mass index <sup>c</sup>	395	29.5 ± 9.1	29.9 ± 8.8	0.724
Race				0.078
White	244	30 (12.3)	214 (87.7)	
Black	108	11 (10.2)	97 (89.8)	
Hispanic	16	4 (25.0)	12 (75.0)	
Other	27	7 (25.9)	20 (74.1)	
Parity				0.132
Nulliparous	182	29 (15.9)	153 (84.1)	
Parous	213	23 (10.8)	190 (89.2)	
Chronic pelvic pain				0.647
Yes	201	28 (13.9)	173 (86.1)	
No	194	24 (12.4)	170 (87.6)	
Endometriosis				<0.001
None	244	12 (4.9)	232 (95.1)	
Superficial	69	8 (11.6)	61 (88.4)	
Deep-infiltrating	82	32 (39.0)	50 (61.0)	
Abnormal appearance of appendix				<0.001
Yes	152	35 (23.0)	117 (77.0)	
No	243	17 (7.0)	226 (93.0)	
Surgical indication				<0.001
Pelvic pain	172	14 (8.1)	158 (91.9)	
Fibroids	95	9 (9.5)	86 (90.5)	
Endometriosis	47	18 (38.3)	29 (61.7)	
Pelvic mass	43	6 (14.0)	37 (86.0)	
Abnormal bleeding	28	3 (10.7)	25 (89.3)	
Other	10	2 (20.0)	8 (80.0)	

<sup>a</sup> Values are given as mean ± SD or number (percentage), unless indicated otherwise.

<sup>b</sup> Based on Pearson  $\chi^2$  test for categorical variables and *t* test for continuous variables.

<sup>c</sup> Calculated as weight in kilograms divided by the square of height in meters.

**Table 3** Risk of appendiceal endometriosis by type of endometriosis.

Type of endometriosis	Unadjusted risk ratio (95% confidence interval)	Adjusted risk ratio (95% confidence interval) <sup>a</sup>
Superficial	2.4 (1.0–5.5)	2.1 (0.9–5.1)
Deep-infiltrating	7.9 (4.3–14.7)	5.9 (2.9–11.9)
None	Ref.	Ref.

<sup>a</sup> Based on a modified Poisson regression model, adjusted for abnormal appendix appearance and surgical indication.

**Table 4** Appendiceal pathology.<sup>a</sup>

Primary pathologic finding <sup>b</sup>	Overall (n=395)	Women with deep-infiltrating endometriosis (n=82)	Women with superficial endometriosis (n=69)	Women without endometriosis (n=244)
Normal	148 (37.5)	23 (28.0)	24 (34.8)	101 (41.4)
Benign variants <sup>c</sup>	159 (40.3)	24 (29.3)	33 (47.8)	102 (41.8)
Endometriosis	46 (11.6)	30 (36.6)	7 (10.1)	9 (3.7)
Inflammation <sup>d</sup>	21 (5.3)	3 (3.7)	2 (2.9)	16 (6.6)
Fecalith	18 (4.6)	2 (2.4)	3 (4.3)	13 (5.3)
Tumor <sup>e</sup>	3 (0.8)	0	0	3 (1.2)

<sup>a</sup> Values are given as number (percentage).

<sup>b</sup> Some specimens had more than one pathologic diagnosis (e.g. adhesions and endometriosis).

<sup>c</sup> Included lymphoid hyperplasia, melanosis coli, mucous cyst polyp, adhesions, fibrous obliteration, or neuroma.

<sup>d</sup> Included acute and chronic appendicitis, and serositis.

<sup>e</sup> Included neuroendocrine tumors or carcinoid tumors.



