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- 2 Recurrence in Deep Infiltrating Endometriosis: A Systematic Review of the
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- 14 Running head: Recurrence of deep infiltrating endometriosis
- Disclosure statement: The authors declare that they have no conflicts of interest and
- 16 nothing to disclose.
- 250 word unstructured abstract, 5000 words limit 60 references
- Precis: Recurrence and related risk factors after surgery for deep infiltrating endometriosis
- were analyzed following a literature review, finding that younger age and higher body
- 20 mass index were predictors of recurrence.

### **ABSTRACT**

Deep infiltrative endometriosis (DIE) is an enigmatic disease that typically impacts
the rectovaginal septum, uterosacral ligaments, pararectal space, and vesicouterine fold
but can involve the rectum, sigma, ileum, ureters, diaphragm, and other less common
sites. Surgery is the treatment of choice as medical management alone commonly fails in
controlling the symptoms, although recurrence is very high following surgical treatment.
The goal of the current study was to review recurrence rates and identify risk factors
related to recurrence following surgery for DIE. The review involved searching the
Cochrane Library, PubMed, and Google Scholar for relevant articles in accordance with
the study's inclusion criteria; 45 studies were considered suitable. The results showed a
wide heterogenity regarding DIE recurrence, owing to inconsistent recurrence definitions
and follow-up length. Younger age and high body mass index were found to be risk factors
for DIE recurrence. Lack of complete surgical excision was another independent risk factor
for recurrence of disease. In conclusion, there is a need for prospective studies and a
more homogeneous standard for surgical treatment of DIE.

38 Keywords: DIE, Laparoscopy, Recurrence, Surgery, Risk factors.

#### Introduction

Endometriosis is a chronic gynecological condition that affects women primarily during the reproductive years causing infertility and pelvic pain, although there are rare reported postmenopausal cases [1]. Essentially, three types of lesions are reported: ovarian endometriosis, superficial peritoneal endometriosis, and deep infiltrating endometriosis (DIE) [2].

Deep infiltrating endometriosis is defined as an invasion greater than 5 mm of the peritoneal surface by endometriotic lesions, most commonly located at the rectovaginal septum, uterosacral ligaments, pararectal space, and vesicouterine fold [3]. These lesions differ from other peritoneal surface lesions, owing to histopathologic features and a strong pelvic pain correlation [4]. Deep infiltrating endometriosis can also infiltrate the rectum, sigma, ileum, bladder, and even the diaphragm and upper abdomen [3]. Gastrointestinal involvement of endometriosis in the rectosigmoid, small bowel (distal ileum), cecum, and appendix is the most common extragenital location [3,5].

Surgery is the treatment of choice for DIE management as medical treatment alone fails to control symptoms; there is evidence that indicates that surgery reduces pain associated with endometriosis in all stages of the disease [6]. After excisional surgery, recurrence of DIE varies between 2% and 43% depending on the length of follow-up [5,7-14]. The cause of this statistical fluctuation is unclear [7] but may depend on the definition of recurrence, sample size, and study group. The aim of this review is to evaluate the recurrence rate and risks factors of recurrence following surgery for DIE with the goal of reducing relapses.

#### **Materials and Methods**

We conducted a review of literature electronically using PubMed, Cochrane Central Register of Controlled Trials, and Google Scholar to find studies on recurrence and risk factors for recurrence of DIE published between January 2000 and June 2017. The MESH terms "deep endometriosis", "deep infiltrating endometriosis", "bowel endometriosis", "colorectal endometriosis", "rectovaginal endometriosis", "bladder endometriosis", "ureteral endometriosis", and "diaphragmatic endometriosis" were combined with "recurrence", "relapse", and "risk factors". Reference lists from the relevant publications were searched for additional studies on the subject. The studies were screened by title and abstract, and if after the reading of full text they met the inclusion criteria, they were selected by two authors.

Inclusion criteria encompassed articles in the English language with the primary topic being DIE and clearly reported recurrence rates and/or risk factors of relapse after surgery. Exclusion criteria were case reports, those papers not providing a clear differentiation between superficial endometriosis and DIE, and studies evaluating specifically the effect of hormone therapy on the recurrence rate of DIE.

A meta-analysis was not performed as the data were widely heterogeneous and incomplete, with inconsistent definitions of DIE recurrence, inconsistent types of surgery, and other varying analyzed risk factors of relapse.

#### **Conclusions**

#### Recurrence Rate of DIE: Overall Consideration

One thousand five hundred and twenty-six publications were identified. After duplicates were removed and studies were screened for inclusion and exclusion criteria, 38 articles were suitable for review [5,8-44].

The reported risk of recurrence after surgery for DIE varies greatly among studies, but overall does so owing to the definition of recurrence and length of follow-up. In particular, the recurrence rate of DIE has been reported in less than 50% of studies as shown by Meuleman et al [10]. The majority of studies report a short- or mid-term follow up of 2 to 4 years, with a tendency of an increased recurrence rate in studies with a longer follow up [10-12]. According to Guo [7], Doussett et al [8], and Vignali et al [9] the recurrence rate in women with DIE varies between 2% and 43.5% and is higher when the symptom recurrence noted is pain rather than surgical findings as the definition of relapse [13-14]. In addition to these differing factors, the majority of randomized controlled or retrospective studies [45,46] do not focus on DIE recurrence but use a matched rate for superficial endometriosis and DIE as per the revised American Fertility Society classification [47].

The articles summarized in the current review evaluate DIE recurrence rate and recurrence risks factors following DIE surgery and are summarized in Table 1 [5,8-44].

# Recurrence and Risk Factors of Relapse of DIE, Bowel Endometriosis, Colorectal Endometriosis, Rectovaginal Endometriosis

From an accurate evaluation of the literature, 3 risk factors for recurrence of DIE involving the bowel were found to be modifiable and nonmodifiable factors, such as age, weight, and type of surgery.

Younger age at primary surgery for DIE excision is recognized by several authors as a risk factor for recurrence of DIE [9,13]. It is well known that the incidence of laparoscopically confirmed endometriosis decreases with increasing age [48]. Busacca et al reported that women ≥ 34 years have a decrease of recurrence compared with woman ≤

33 years [11]. Similar results are reported in a retrospective study by Nirgianakis et al, in which women < 31 years independently predicted DIE recurrence [15].

Body mass index (BMI) is another independent risk factor for disease recurrence [15,16]. Obese women have a significantly higher rate (p = .002) of recurrence compared with those with normal BMI [16]. In the study of Nirgianakis et al, BMI  $\geq$  23 kg/m<sup>2</sup> was associated with higher recurrence risk (p < .001) [15].

Several authors have concluded that pregnancy after surgery seems to reduce recurrence of DIE [11,13]. Donnez and Squifflet, in 2010, reported that the recurrence rate of pelvic pain was significantly lower in women who became pregnant after surgery for DIE [17].

Incomplete excision during surgery for DIE seems to be an independent risk factor for recurrence of symptoms [9,18,49]. A retrospective study of Vignali et al [9] showed that reoperation for DIE was predicted only by incomplete excision during the first operation (odds ratio 21.9; 95% confidence interval 3.2-146.5; p < .001).

Concerning the type of surgical treatment for DIE, two approaches are being practiced: radical bowel surgery and conservative bowel surgery [17,19-25,49-53]. Radical rectal surgery includes colorectal resection by complete excision of the rectal segment affected by the disease [19,51]. Conservative techniques may be performed by the practice of rectal shaving in which the rectum is not opened [17,20] or by full excision in which only the endometriosis nodule along with the surrounding rectal wall is removed [21,52].

As the causes for recurrence are still not completely clear, there are conflicting opinions regarding the role of clear bowel resection margins and disease recurrence. We found only four reports that focused on the correlation between the histopathological margins, collected from the resected tissue, and the risk of recurrence of DIE or symptoms

of DIE [15,22-24]. Nirgianakis et al [15] found 38.5% positive bowel resection margins in women with disease recurrence compared with 13.2% positive bowel resection in women without recurrence during a median follow up period of 53 months (range, 12–120; p < .05). Other authors failed to demonstrate a correlation between positive bowel resection margins and higher risk of recurrence [22-24].

There is a possible explanation for these conflicting results. Bowel occult microscopic endometriosis (BOME) is detected in visually normal peritoneum with an estimated prevalence up to 19% [15,23,24]. Despite these data, BOME seems to have no impact on either pelvic or digestive symptoms or on recurrence of DIE after surgery [22-24].

Regarding type of surgery, there is some evidence to support the idea that conservative bowel surgery can lead to a higher risk of recurrence [10]. A large meta-analysis pooled more than 1,600 patients from 49 retrospective studies. Seventy one percent of patients underwent colorectal resection; 10% full excision and 17% treated with superficial surgery [10]. Overall, the proven endometriosis recurrence rate appeared to be significantly lower in the resection-anastomosis group (2.5%; 20/812) compared with the conservative group (5.7%; 49/865).

Afors et al [25] compared symptoms and need for reintervention retrospectively, after segmental resection, discoid resection, or shaving technique in 106 patients who underwent surgery for bowel endometriosis. The data showed higher rate of reintervention for recurrence in the shaving group compared with discoid or segmental resection (27.6%, 13.3%, and 6.6%, respectively). Similar results were reported by Roman et al in 2016 who found the recurrence rate after conservative surgery to be 8.6% versus 0% for patients who underwent colorectal resection, in a mean follow-up period of 80 months [20].

bowel or discoid resection, after a medium follow-up of 30 months with no significant
difference in recurrence between radical bowel surgery and conservative surgery (13.8%
vs. 11.5%) [21].

#### Recurrence and Risk Factors of Relapse for Urinary Tract Endometriosis

Urinary tract endometriosis is a form of DIE affecting 0.3% to 12% of all women suffering from endometriosis [53]. The recurrence rate of ureteral endometriosis ranges between 0 to 12% [27,28,54,55].

There are poor data regarding risk factors associated with a higher recurrence rate after ureterolysis or ureterocystoneostomy. Uccella et al showed that younger age (32.4 vs. 37.6 years) at the time of ureterolysis (P=.004) and hydronephrosis grade  $\geq$  2 (p = .02) were associated with recurrence of symptoms after long-term follow-up (52 months) [28].

Radical surgery seems to lower recurrence of DIE in patients with ureteral endometriosis [30,31,55]. A recent review comparing ureterolysis with ureterocystoneostomy showed a recurrence rate or reoperation for DIE persistence of 3.9% in the conservative management group and 0% in the ureteral reimplantation group [55].

Only Fedele et al [32] have evaluated the risk factor for recurrence of bladder endometriosis and found the extent of surgical excision to be impactful. When the resection included both the bladder lesion and 0.5 to 1 cm deep portion of the adjacent myometrium, recurrence was less frequent compared with the removal of the bladder lesion only (7% versus 37% for symptom recurrence) [32].

### Recurrence and Risk Factors of Relapse for Diaphragmatic and Thoracic

#### **Endometriosis**

Recurrence of thoracic endometriosis lesions or catamenial pneumothorax after surgery were noted in 12 studies [33-44].

The rate of pneumothorax recurrence was widely heterogeneous varying between 0% and 40% [33,35,37,39]. According to Korom et al [34], the mean time to recurrence is 24 months after diaphragm removal with or without pleurodesis and 61 months after pleurodesis. These results appear to not be associated with the extent of the procedure but rather with the presence of diaphragmatic defects on the increased rate of recurrence [38].

According to Ceccaroni et al [37], laparoscopy is another possible approach for the treatment of diaphragmatic endometriosis and gives the opportunity to adequately investigate the diaphragmatic surfaces with or without completely mobilizing the liver.

#### **Discussion**

The challenge in evaluating the literature stemmed from the inconsistent definitions of DIE recurrence depending on author determination, varying clinical examination [13,17,26] and histological variation in proving endometriosis recurrence [12,15,16,25].

Recurrence is higher if the follow-up is longer [7,11]. Two risk factors were identified as risk factors for recurrence: an elevated BMI [15,16] and a younger age at primary surgery [9,11,13,15], although a universal cut-off age was not noted.

Moreover, we believe that another risk linked to younger age could be the rejection of postoperative hormonal therapy owing to the wish for pregnancy.

The higher risk of recurrence for obese or overweight women is probably owing to the presence of more adipose tissue and consequently higher output of estrogen produced by the aromatase activity in those tissues [16].

In addition, although the recurrence of superficial peritoneal endometriosis could be different than that of DIE, Taylor and Williams [56] reported that recurrence is more likely to be related to the cluster of disease from the original area of involvement and reflects that incomplete excision at the initial surgery is an important risk factor for recurrence.

There is some evidence that positive bowel surgical resection margins are associated with a higher risk of recurrence [15], although several authors were unable to demonstrate a clear correlation [22-24]. Available data concerning the microscopic satellite lesions near the resection margins could explain the inconsistent results regarding positive resection margins and risk of recurrence [22-24].

Darwish and Roman in their recent paper [50] compared the evolution of oncologic conservative surgery in the oncologic field to that of radical DIE nerve-sparing or fertility-sparing surgery. Actually there are no available data to recommend a conservative approach for bowel endometriosis. The debate concerning the best surgical approach in the treatment of DIE of the bowel is far from over, warranting the need for prospective follow-up studies with large sample sizes and clear definitions of DIE recurrence to compare the recurrence rate of different surgical approaches.

Concerning the recurrence of urinary tract endometriosis, in particular for ureteral endometriosis, the more significant risk factor seems to be the extent of disease excision from the ureter [55]. Despite the approach to spare the ureter whenever possible, ureteral endometriosis might be an intrinsic lesion [57] that cannot be treated with ureterolysis [31]. As it is impossible to differentiate intrinsic and extrinsic ureteral endometriosis preoperatively, several studies note that the indication for ureterocystoneostomy should be moderate/severe hydronephrosis owing to ureteral stenosis [31,58]. The conservative approach may be used as the initial treatment option in most patients with ureteral

endometriosis, but for some patients with suspect of ureteral intrinsic lesion, and in case of failure of ureterolysis, ureteral resection and reanastomosis/reimplantation may be best.

The relation between the recurrence rate of bladder endometriosis and the depth of surgical resection of the adjacent myometrium was postulated by Donnez et al in 2000, owing to the hypothesis that bladder endometriosis is an adenomyotic nodule arising from the myometrium and spreading to the bladder [59]. In the case of bladder endometriosis, the option of radical surgery to reduce DIE recurrence should be balanced with the risk of myometrial lesions, especially for women who wish to preserve fertility.

The varying data concerning recurrence of diaphragmatic endometriosis may stem from the small sample size, follow-up period varying between 3 to 52 months [33,37], the surgical techniques (pleurodesis or surgical resection), as well as postoperative hormonal treatment.

Standardized reporting of surgical treatment for deep endometriosis, as suggested in the CORDES statement [60], may prevent bias in data collection, as much possible. The deep endometriosis surgical sheet (DESS), proposed by Vanhie et al [60], could be a useful tool for physicians to use the same surgical language and similar rigorous protocols to compare results of different studies of DIE.

#### Conclusion

Younger age and increased BMI appear to be risk factors for DIE recurrence.

Prospective, large studies are warranted to establish the definitions of DIE as well as recurrence, attempt various surgical approaches, with long-term follow-up to determine the most effective medical and surgical treatment of DIE. Considering that DIE is a benign disease, very often responsive to medical treatment, correct timing for the first surgery and the radical nature of that surgery implies a progression of standardized essential key steps

- in the management of the disease to reduce recurrence and reoperations as well as
- 262 anatomic damage while preserving fertility.

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### Table 1 Recurrence rate as reported by various published studies

Author and year of publication	Type of study and sample size	Type of endometriosis	Definition of recurrence	Recurrence, %	Length of follow up
Ruffo et al	Retrospective n = 900	Bowel	Symptom recurrence,	2.9%	1–120
2014 [5]		endometriosis	reintervention		months
Dousset at al 2010 [8]	Prospective n = 100	Bowel endometriosis	Reintervention	2%	63–93 months
Vignali et al 2005 [9]	Retrospective n = 150	DIE	Symptom recurrence, clinical findings, ultrasound	Symptom recurrence after 36 months: 20.5% Clinical recurrence after 36 months: 9% Symptom recurrence after 60 months: 43.5% Clinical recurrence after 60 months: 28%	10–60 months
Meuleman et al 2011 [10]	Retrospective n = 45	Bowel endometriosis	Reintervention	2.2% after 12 months follow-up 4.4% after 26 months of follow-up	12–36 months
Busacca et al 2006 [11]	Retrospective n = 1,106 Ovarian endometriosis n = 367 Peritoneal endometriosis n = 198 DIE n = 152 Peritoneal + ovarian endometriosis n = 320	Ovarian, peritoneal, DIE, ovarian + peritoneal endometriosis	Symptom recurrence, clinical findings, ultrasound, increase CA 125	DIE group after 48 months: 30.6% DIE group after 96 months: 43.3%	96 months
Meuleman et al 2014 [12]	Prospective n = 203	DIE with or without bowel endometriosis	Reintervention	After 12 months follow-up: 1% After 24 months follow-up: 7% After 36 months follow-up: 10%	12–36 months
Fedele et al 2004 [13]	Retrospective n = 83	DIE, bowel endometriosis	Clinical findings, ultrasound, reintervention	Pain recurrence: 28% Clinical recurrence: 34% Reintervention: 27%	36 months
Hanssens et al 2015 [14]	Retrospective n = 108 DIE group n = 49 Superficial endometriosis (SE) n = 59	DIE	Symptom recurrence, reintervention	DIE group symptom recurrence: 50% DIE group reintervention: 35.7% SE group symptom recurrence: 21.7% SE group reintervention: 19.6%	6–80 months

Nirgianakis et	Retrospective n = 81	Bowel	Reintervention	16%	12–120
al 2014 [15]		endometriosis			months
Nezhat et al	Retrospective n = 193	Bowel	Reintervention	10%	12–96
2011 [16]		endometriosis		00/	months
Donnez et al	Prospective n = 500	Bowel	Symptom recurrence	8%	24–76
2010 [17]	Detroopeding	endometriosis	Company was a company as	Computance recommends	months
Stepniewska et al 2010 [18]	Retrospective Segmental resection	Bowel endometriosis	Symptom recurrence, radiological evaluation,	Symptoms recurrence group A: 10%	48 months
ai 2010 [10]	(A) n = 60	DIE without bowel	ultrasound,	group B: 35%	
	DIE without bowel surgery	endometriosis	reintervention	group C: not specified	
	(B) n = 40	Chaomethodo	Temes vention	Radiologic recurrence	
	DIE (no bowel endometriosis)			group A: 7%	
	(C) n = 55			group B: 23%	
	,		62	group C: 5%	
				Reintervention	
				group A: 7%	
				group B: 15%	
			* O	group C: 0%	
Minelli et al	Retrospective n = 357	Bowel	Symptom recurrence,	8.4%	6–48
2009 [19]		endometriosis	radiological evaluation,		months
			ultrasound,		
Roman et al	Retrospective n = 71	Bowel	reintervention	Group I shaving: 8.6%	60–120
2016 [20]	Group I shaving n = 46	endometriosis	Reintervention	Group II bowel resection: 0%	months
2010 [20]	Group I shaving II – 40 Group II bowel resection n = 25	endometrosis		Group it bower resection. 0 %	monus
Fanfani et al	Prospective case-control study	Bowel	Symptom recurrence,	Discoid resection group: 13.8%	16–46
2010 [21]	Discoid resection (case) n = 48	endometriosis	radiological evaluation,	Segmental resection group: 11.5%	months
	Segmental resection (control) n		ultrasound	3 1 1 3 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	
	= 88	O			
Koh CE et al	Retrospective n = 91	Bowel	Reintervention	11%	12–116
2012 [22]		endometriosis			months
Mabrouk et al	Retrospective n = 47	Bowel	Symptom recurrence	19%	6–35
2012 [23]		endometriosis			months
Roman et al	Prospective n = 103	Bowel	Reintervention	Patients without BOME: 0%	12–36
2016 [24]	Women without BOME n = 88 Women with BOME n = 15	endometriosis		Patients with BOME: 6.6%*	months
Afors et al	Retrospective n = 92	Bowel	Symptom recurrence,	Group I shaving: 27.6%	24 months
2016 [25]	Group I shaving n = 47	endometriosis	reintervention	Group II discoid resection: 13.3%	

	Group II discoid resection n = 15 Group III segmental resection n = 30			Group III segmental resection: 6.6%	
Kavallaris et al 2011 [26]	Retrospective n = 55	Bowel endometriosis	Symptom recurrence	6.6%	94 months
Soriano et al 2011 [27]	Prospective n = 45 Ureterolysis n = 41 Ureterocystoneostomy n = 4	Ureteral endometriosis	Reintervention	Ureterolysis: 4.8% Ureterocystoneostomy: 0%	13–33 months
Uccella et al 2014 [28]	Retrospective (ureterolysis) n = 109 (follow up > 12 months only for 80 women)	Ureteral endometriosis	Reintervention	8.6%	15–109 months
Camanni et al 2009 [29]	Retrospective n = 80 Ureterolysis n = 76 Ureterocystoneostomy n = 4	Ureteral endometriosis	Reintervention	Ureterolysis: 2.6% Ureterocystoneostomy: 0%	7–24 months
Frenna et al 2007 [30]	Retrospective (ureterolysis) n = 54	Ureteral endometriosis	Clinical findings	7%	5–12 months
Mereu et al 2010 [31]	Prospective 56 Laparoscopic ureteroureterostomy n = 17 Ureterolysis n = 35 Ureterocystoneostomy n = 2 Nephrectomy n = 2	Ureteral endometriosis	Clinical findings, ultrasound, reintervention	Laparoscopic ureteroureterostomy: 0% Ureterolysis: 21.4% Ureterocystoneostomy: 0%	10–62 months
Fedele et al 2005 [32]	Retrospective n = 47 Base vesical lesion n = 33 Dome vesical lesion n = 14	Bladder endometriosis	Clinical findings, symptom recurrence, radiologic evaluation	Base lesion symptoms recurrence: 24.7% Base lesion clinical/instrumental recurrence: 15.5% Dome lesion symptoms recurrence: 0% Dome lesion clinical/instrumental recurrence: 0%	24–108 months
Ciriaco et al 2009 [33]	Retrospective n = 10	Diaphragmatic endometriosis	Symptom recurrence	40%	14–168 months

Korom et al 2004 [34]	Retrospective n = 3	Diaphragmatic endometriosis	Symptom recurrence	0%	13–22 months
Alifano et al 2007 [35]	Retrospective n = 114 Catamenial pneumothorax n = 28; Noncatamenial pneumothorax n = 86	Diaphragmatic endometriosis	Symptom recurrence	Catamenial pneumothorax: 32% Noncatamenial pneumothorax endometriosis-related: 27% Noncatamenial pneumothorax/not endometriosis-related: 5.3%	32.7 months
Attaran et al 2013 [36]	Retrospective n = 12	Diaphragmatic endometriosis	Symptom recurrence	8.3%	17–73 months
Ceccaroni et al 2013 [37]	Retrospective n = 46	Diaphragmatic endometriosis	Symptom recurrence, radiological evaluation	Not specified	84 months
Visouli et al 2012 [38]	Retrospective n = 5	Diaphragmatic endometriosis	Symptom recurrence, radiologic evaluation	Recurrence of pneumothorax: 20%	16-46 months
Haga et al 2014 [39]	Retrospective n = 92	Diaphragmatic endometriosis	Symptom recurrence	39.1%	25–63 months
Chiantera et al 2016 [40]	Retrospective n = 9	Diaphragmatic endometriosis	Symptom recurrence	0%	6 months
Nezhat C et al 2014 [41]	Retrospective n = 25	Diaphragmatic endometriosis	Symptom recurrence, radiologic evaluation	8%	3–18 months
Fukuoka et al 2015 [42]	Retrospective n = 150	Diaphragmatic endometriosis	Not specified	34%	8–48 months
Alifano M et al 2011 [43]	Retrospective n = 35	Diaphragmatic endometriosis	Symptom recurrence, radiologic evaluation	17.1%	1.5–138 months
Rousset- Jablonski et al 2011 [44]	Retrospective n = 156	Diaphragmatic endometriosis	Symptom recurrence, radiologic evaluation	25%	20–100 months

DIE = Deep infiltrating endometriosis; SE = Superficial endometriosis; BOME = Bowel occult microscopic endometriosis.

\*Relapse was reported in 9 cases in the peritoneum and/or ovaries, in 2 cases in the rectovaginal septum, and 1 case required a new bowel resection.