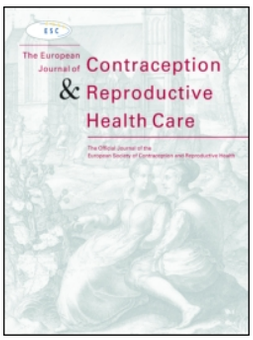

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REVIEW

Recurrent endometriosis: a battle against an unknown enemy

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ABSTRACT

Recurrence of endometriosis after conservative surgery is not an uncommon finding. There is no uniformity, however, on what the term 'recurrence' means. Recurrence is variously defined in the literature as the relapse of pain, clinical or instrumental detection of an endometriotic lesion, repeat rise in CA 125 levels, or evidence of recurrence found during repeat surgery. Consequently, the reported recurrence rate varies widely (0–89%) in the different series, depending on its definition and the type of study performed. As endometriosis recurrence seems to be an indeterminate enemy, we set out to examine exactly what we were fighting in our everyday battle. In this narrative review, we aimed to seek an answer to questions related to endometriosis recurrence, some of which are often asked by our patients.

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KEYWORDS
Dysmenorrhoea; endometrioma; endometriosis recurrence; laparoscopy; pelvic pain

Introduction

Endometriosis recurrence, once described as a rare event [1], is nowadays considered a real challenge [2,3]. Recurrence after surgery may be either due to development of *de novo* lesions or to *in situ* growth of residual foci [4]. To date, surgery is considered the treatment of choice for symptomatic endometriosis, especially after the failure of medical therapy [5,6], but, since it is cytoreductive rather than curative [7], postoperative medical treatment is recommended to limit the growth of residual endometriotic cells [8].

The mean recurrence rate of endometriosis is estimated to be around 20% (range 0–89.6%) at 2 years of follow-up [4,9,10] and up to 50% (15.1–56%) at 5 years [11,12]. The enormous variability in recurrence rate found in the literature may depend on different factors according to the definition of the term 'recurrence'; the type of endometriotic lesion; the stage of disease; the surgeon's skill and surgical technique used; and the type, dose and duration of postoperative medical treatment. There is no uniformity about what the term 'recurrence of endometriosis' means and there is also great ambiguity about the related terminology used.

As endometriosis recurrence seems to be an indeterminate enemy, we sought to examine what exactly we were fighting in our everyday battle. In our study, we aimed to find answers to questions related to endometriosis recurrence, some of which are frequently asked by our patients. We reviewed the recent literature in order to find the different definitions of endometriosis recurrence and to try to clarify which is the best to adopt. As the incidence of endometriosis recurrence depends on certain factors, we analysed the possible confounding factors that may influence reported rates of recurrence.

Methods

To perform this narrative review we searched the MEDLINE database for articles on endometriosis recurrence using the Medical Subject Heading (MeSH) terms 'endometriosis' AND 'recurrence'. Results were limited to English-language articles reporting results from human studies published after 1990 and with available full text. Using this strategy we identified 392 articles. Initial screening of the title and abstract was performed by three authors (VEB, MM and RC), after which appropriate studies to include in the review were selected by reading and discussing the full text version of the articles. Other potentially relevant studies were identified from the references of each selected study. Randomised controlled trials (RCTs) and prospective and retrospective studies were included. Eighty studies were included in the discussion and analysis of the concept of recurrence (Figure 1).

Results

What is recurrent endometriosis? The dilemma of non-uniformity

Recurrence has been variously defined in the literature as the recurrence of pain, as clinical or instrumental detection of an endometriotic lesion (anatomical relapse), or as a repeat rise of the marker CA 125 after surgery. For some authors the recurrence of endometriosis is based only on surgical findings during repeat surgery. As a consequence,

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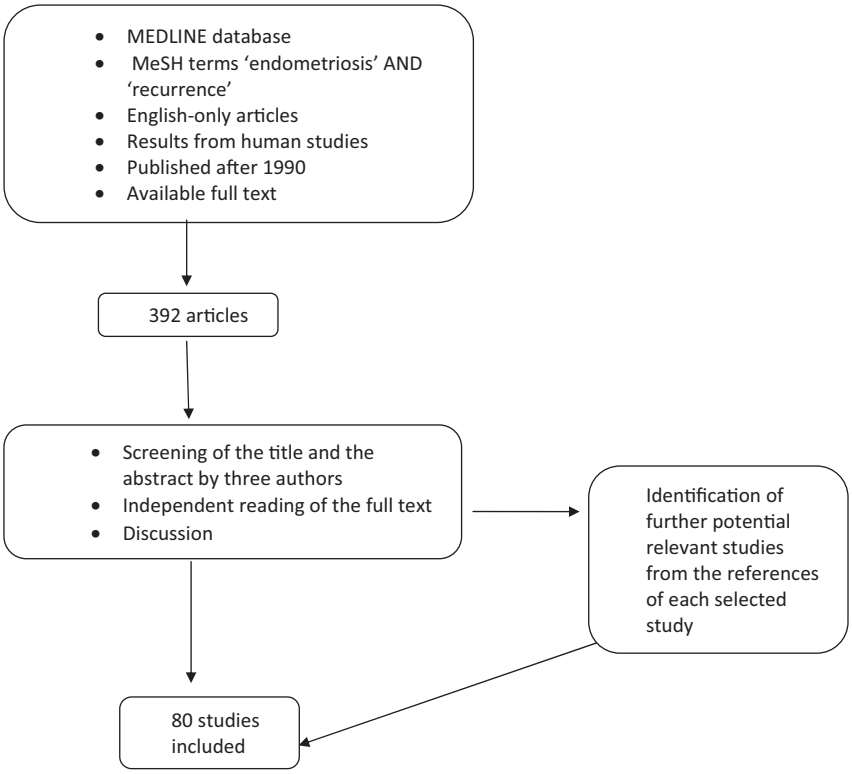

Figure 1. Flow chart.

the incidence of endometriosis recurrence varies depending on how it is defined. Table 1 shows the wide variability in the literature of endometriosis recurrence rate after first surgery, depending on the type of definition adopted.

Recurrence of pain

Pain includes dysmenorrhoea, dyspareunia or pelvic pain, with or without clinical signs or instrumental evidence, equal or greater in severity to that experienced before surgery [12,13]. Pain is self-reported by the patient, scoring $\geq$5 on a 10 mm visual analogue scale (VAS) [14–16] or similar [17].

Many studies consider recurrence as the reappearance of pain [10–13,15–30]. This definition of recurrence, however, has some limitations due to the subjectivity of the evaluation. The VAS scoring system is a valid tool but it is not an objective measurement since it is based on self-evaluation by the patient, which can vary according to personal and psychological factors. Some studies used postal questionnaires to evaluate pain [1,18], which would seem to be less accurate than evaluation made during follow-up. Moreover, in the study of Abbott et al. [18], 23% of patients did not respond to the questionnaire; non-responding women are often those who are unsatisfied with the postoperative outcome, owing to pain recurrence [31].

As regards the type of pain, dysmenorrhoea is the more widely reported symptom in the literature [16,18,28,29]. Many studies, however, do not specify the kind of pelvic pain; but, when specified, dyspareunia and chronic pelvic pain are reported with a lower recurrence rate [16]. Other symptoms, such as dyschezia, are rarely considered. Deep infiltrating endometriosis is strongly associated with pelvic pain and dyspareunia. Nevertheless, in the literature, it is reported to have a lower rate of pain recurrence [32,33] in comparison with peritoneal and ovarian endometriosis. Conversely, Busacca et al. [13] found a high recurrence rate of deep infiltrating endometriosis (30% at 4 years of follow-up).

Clinical findings

Some studies consider recurrence on the basis of a pelvic examination suggestive of endometriosis, with typical findings of pelvic fibrotic areas or tender nodules [11–13,30,34–36]. Vignali et al. [30] defined the recurrence of deep infiltrating endometriosis as either the relapse of pain or the presence of clinical findings. Depending on the adopted definition, in their retrospective analysis of 115 patients, pain recurrence was 20.5% at 3 years, but recurrence of deep infiltrating endometriosis was only 9% if defined through clinical findings.

The main problem with this definition is related to the subjectivity of the clinician and to the potential intra- or inter-examiner variability. Another limitation is due to the non-specificity of the clinical findings. For example, a pelvic nodulation may be the expression of either endometriosis recurrence or fibrosis due to previous surgery. On the other hand, a fibrotic nodule may represent endometriotic disease suppressed by medical therapy. The clinical definition would be meaningful only if supported by confirmation of the suspicious findings through direct intraoperative visualisation of the lesions or through correlation with histopathological reports, which are not available when treating recurrence with a non-surgical approach. The definition of recurrence based on clinical findings may therefore lead to an overestimation of its true incidence.

Anatomical relapse

The recurrence of ovarian endometrioma is defined in most studies as the presence on transvaginal ultrasound of a

Table 1. Differences in definitions and recurrence rates after first-line surgery for endometriosis.

Outcome and study Pain recurrence	Type of study	No. of patients	Surgical treatment	Definition of recurrence	Follow-up (months)	Recurrence rate (%)
Vercellini et al. [26]	Multicentre prospective RCT	134 (expectant management arm)	LPS/LPT	Total symptom score (dysmenorrhoea, deep dyspareunia, non-menstrual pain) VRS $\geq$4	12 24	21.4 36.5
Porpora et al. [16]	Prospective observational	166	LPS	Dysmenorrhoea Deep dyspareunia Chronic pelvic pain VAS $\geq$5	36	15.6 6.0 4.6
Taylor and Williams [25]	Prospective	39	LPS	Persistent chronic pelvic pain or dyspareunia	18	37.0
Busacca et al. [13]	Observational	1106	LPS/LPT	Recurrence of pelvic pain (dysmenorrhoea, dyspareunia or pelvic pain), with severity worse or the same as before surgery	48	Ovarian 24.6 Peritoneal 17.8 Deep 30.6 Ovarian and peritoneal 23.7
Liu et al. [44]	Retrospective	710	LPT/LPS	Dysmenorrhoea occurring at least 3 months after surgery, with severity worse or the same as before surgery	12 24 36	9.6 11.8 33.8
Vercellini et al. [29]	Retrospective	729	LPS	Dysmenorrhoea Non-menstrual pelvic pain Deep dyspareunia VAS + VRS	36	24.0 14.0 7.0
Coccia et al. [15]	Retrospective	401	LPS	Chronic pelvic pain VAS >5	72	38.4
Fedele et al. [11]	Retrospective	359 (A) 301 primary surgery (B) 54 repeat surgery for recurrent endometrioma	LPS	Recurrence or persistence of at least one pain symptom (dysmenorrhoea, pelvic pain, dysmenorrhoea with radiation to the rectum, deep dyspareunia, dyschezia) of moderate or severe intensity (10 point ranked ordinal scale)	35.4 ± 27.6	(A) 20.5 (B) 17.4
Vignali et al. [30]	Retrospective	115	LPS/LPT	Recurrence or persistence of at least one symptom of pain that was moderate to severe (evaluated through a multidimensional scale for the social impact of pain symptoms and an analogue linear scale for the subjective aspects of pain)	36 60	20.5 43.5
Fedele et al. [34]	Retrospective	83	LPS/LPT	Dysmenorrhoea Pelvic pain Dyspareunia VAS	36	25.3 19.3 25.3
Tandoi et al. [12]	Retrospective	57	LPS/LPT	Pelvic pain (dysmenorrhoea, dyspareunia, dyschezia, chronic pelvic pain), with severity worse or the same as before surgery, self-reported VAS $\geq$5	60	56.0
Fedele et al. [19]	Retrospective	47	LPS/LPT	Recurrence of $\geq$1 symptom or urinary complaints (urgency, frequency and pain at micturition) of moderate-to-severe intensity attributable to bladder endometriosis recurrence	36	17.5

(*continued*)

Table 1. Continued.

Outcome and study	Type of study	No. of patients	Surgical treatment	Definition of recurrence	Follow-up (months)	Recurrence rate (%)
Pain recurrence						
Ultrasound recurrence						
Parazzini et al. [36]	Prospective cohort multicentre study	311	LPS	Diagnosis of ovarian endometrioma	24	9.0
Busacca et al. [39]	Prospective	366	LPS/LPT	Diagnosis of ovarian endometrioma (homogeneous contents of low echogenicity, with echoes present in different positions), with confirmation of the suspected mass on repeat US in the early follicular phase	27.7 ± 17.9	7.1
Porpora et al. [16]	Prospective observational	166	LPS	Diagnosis of ovarian endometrioma	36	9.6
Busacca et al. [13]	Observational	1106	LPS/LPT	Diagnosis of ovarian endometrioma	48	Ovarian 24.6 peritoneal 17.8 Deep 30.6 ovarian and peritoneal 23.7
Ghezzi et al. [40]	Observational cross-sectional	121	LPS	Diagnosis of ovarian endometrioma (round-shaped cysts with thick walls, regular margins, diameter ≥4 cm, and homogeneous low echogenicity of fluid) during proliferative phase of menstrual cycle	33	17.3
Vercellini et al. [29]	Retrospective	729	LPS	Evidence of ovarian endometrioma (round-shaped cystic mass, with thick walls, regular margins, homogeneous low echogenic fluid content with scattered internal echoes and without papillary proliferations)	36	12.0
Liu et al. [44]	Retrospective	710	LPT/LPS	Presence of ovarian cysts >3 cm in diameter, with a typical aspect detected for two consecutive menstrual cycles	12 24 36	7.8 17.7 32.3
Coccia et al. [15]	Retrospective	401	LPS	Ovarian endometrioma >2 cm or deep endometriosis implants	72	18.4
Fedele et al. [11]	Retrospective	359 (A) 301 primary surgery (B) 54 repeat surgery for recurrent endometrioma	LPS	Presence of a homogeneous hypoechogenic cyst, persistent on a repeat scan in the early follicular phase	35.4 ± 27.6	(A) 18.9 (B) 15.1
Kikuchi et al. [42]	Retrospective	315	LPS	Diagnosis of ovarian endometrioma (diffuse, hypoechoic area ≥2 cm)	21.4 ± 16.8	15.9
Koga et al. [43]	Retrospective	224	LPS	Diagnosis of ovarian endometrioma (typical cyst >2 cm persisting after several menstrual cycles), within 2 years after surgery	24	30.4
D'Hooghe et al. [35]	Retrospective	67 (39 IVF; 11 IVF + IUI; 17 IUI)	LPS/LPT	Presence of an endometriotic cyst at US confirmed by cytology of cyst fluid aspirated under US guidance	21	IVF 7.0 IVF + IUI 43.0 IUI 84.0
Tandoi et al. [12]	Retrospective	57	LPS/LPT	Diagnosis of ovarian or pelvic endometriosis	60	56.0
Fedele et al. [19]	Retrospective	47	LPS/LPT	Endometriotic nodule involving vesical base at TV US	36	10.9
Clinical findings suggestive of recurrence						
Busacca et al. [13]	Observational	1106	LPS/LPT	Pelvic masses, pelvic tenderness or nodulations	48	Ovarian 24.6 Peritoneal 17.8 Deep 30.6 Ovarian and peritoneal 23.7

(*continued*)

Table 1. Continued.

Outcome and study	Type of study	No. of patients	Surgical treatment	Definition of recurrence	Follow-up (months)	Recurrence rate (%)
Pain recurrence						
Ghezzi et al. [20]	Prospective collaborative cohort study	33	LPS	Symptoms, pelvic examination, TV US and renal US with clinical findings suggestive of ureteral recurrence	16	12.1
Taylor and Williams [25]	Prospective	39	LPS	Localised tenderness	18	37.0
Tandoi et al. [12]	Retrospective	57	LPS/LPT	Pelvic masses, pelvic tenderness, nodulation	60	56.0
Fedele et al. [19]	Retrospective	47	LPS/LPT	Pelvic examination suggestive of bladder endometriosis recurrence	36	10.9
Clinical findings suggestive of recurrence and US recurrence						
Vignali et al. [30]	Retrospective	115	LPS/LPT	Presence of fibrotic areas or tender nodularities affecting the pouch of Douglas or the uterosacral ligaments and diagnosis of ovarian endometrioma	36 60	9.0 28.0
Fedele et al. [34]	Retrospective	83	LPS/LPT	Evidence of deep endometriosis recurrence at clinical examination or at transrectal US	36	34.2
Surgically confirmed recurrence						
Taylor and Williams [25]	Prospective	39	LPS	Repeat surgery with visualisation of the lesion and histological confirmation	18	37.0
Vercellini et al. [29]	Retrospective	729	LPS	Repeat surgery with visualisation of the lesion and histological confirmation	36	12.0
D'Hooghe et al. [35]	Retrospective	67 (39 IVF; 11 IVF + IUI; 17 IUI)	LPS/LPT	Presence of clinical and/or biopsy-proven endometriosis at laparoscopy	21	IVF 7.0 IVF + IUI 43.0 IUI 84.0
Need for medical or surgical treatment for recurrence						
Fedele et al. [11]	Retrospective	359 (A) 301 primary surgery (B) 54 repeat surgery for recurrent endometrioma	LPS	Retreatment rate for recurrent cyst in the same ovary	35.4 ± 27.6	(A) 19.4 (B) 17.3
Fedele et al. [34]	Retrospective	83	LPS/LPT	New surgical intervention and/or GnRH agonist treatment due to recurrent deep endometriosis	36	27.0
CA 125 increase						
Parazzini et al. [36]	Prospective cohort multicentre study	311	LPS	CA 125 increase	24	9.0
Busacca et al. [13]	Observational	1106	LPS/LPT	CA 125 significant increase (>2 times normal value)	48	Ovarian 24.6 Peritoneal 17.8 Deep 30.6 Ovarian and peritoneal 23.7

GnRH: gonadotropin-releasing hormone; IUI: intrauterine insemination; IVF: *in vitro* fertilisation; LPS: laparoscopy; LPT: laparotomy; TV: transvaginal; US: ultrasound; VRS: verbal rating scale.

round, homogeneous, low echogenic cyst with thin internal trabeculations, with or without internal septa and no or poor vascularisation of the capsule [37]. The definition of recurrence as demonstrated by ultrasound evidence of endometrioma is widely used throughout the literature [11–13,15,16,21,29,30,34–36,38–46]. In many studies, the cyst must be at least 2 cm in diameter to fulfil the ultrasound criteria for endometrioma recurrence [15,40,42–44,46] and must persist over time (for at least two consecutive menstrual cycles) to be distinguished from a functional cyst [39,43,44,46]. For Seracchioli et al. [45], the cut-off for diagnosing recurrence was 1.5 cm, but other authors did not specify a cut-off diameter [21].

The potential problem with this definition is that patients with asymptomatic recurrence also risk being surgically treated. To avoid this problem, many authors added pain to the ultrasound criteria in order to define recurrence [11–13,15,16, 21,29,30,34,36,41,44]. Moreover, throughout the literature, the rate of recurrence defined by objective criteria such as ultrasound examination is lower than when symptom recurrence alone is considered [4].

Significant increase in CA 125

A significant increase in CA 125 is defined as twice the normal value in women with elevated CA 125 before first surgery and negative CA 125 after surgery [13]. CA 125 is a non-specific serum biomarker that may be increased in the presence of malignancies or chronic disease, including advanced endometriosis. The sensitivity of CA 125 levels for the diagnosis of minimal and mild endometriosis seems, however, less useful [47,48].

Chen et al. [47] demonstrated the value of CA 125 as a good predictor of endometriosis recurrence in patients with advanced endometriosis and initially elevated CA 125 levels. Busacca et al. [13] used the rise in CA 125, alone or in association with pain recurrence, clinical diagnosis or relapse defined by ultrasound examination, as a criterion for recurrence. The non-specificity of this definition may explain the high rates or recurrence observed in their study. In the multicentre study of Parazzini et al. [36], the overall recurrence rate was assessed on clinical and ultrasound examination and according to CA 125 elevation, revealing a 4.6% and a 9% recurrence rate, respectively, at 1 and 2 years of follow-up.

Second-look surgery

Some studies consider as recurrence only a relapse verified by surgery [9,18,49]. For Saleh and Tulandi [49], the rate of recurrence was expressed as the rate of repeat surgery required for recurrent endometriomas larger than 3 cm. As highlighted by Tandoi et al. [12], using surgery as the only criterion to define recurrence may be an expression of the surgeon's attitude to treat recurrence with surgery rather than a reflection of the real rate of recurrence. This definition tends to underestimate the recurrence rate, since only patients undergoing surgery are considered to have relapsed.

Possible confounding factors in recurrence rates

Endometriosis recurrence rates vary widely in the literature, ranging from 0% [9] to 89.6% [10]. Several factors may explain this huge difference. Recurrence is defined variously in the literature and as a consequence the incidence of endometriosis largely differs, as previously explained. Other factors, however, can influence the rate of recurrence, such as the length of follow-up, the study design and the sample size, the type and stage of disease, the type of surgery and the postoperative medical treatment.

Duration of follow-up

The recurrence rate seems to increase with the duration of follow-up. Most studies report the 2-year recurrence rate, and some report the 5-year recurrence rate [1,11,12,30,50], but the long-term incidence has been poorly evaluated [15]. It has been observed that most recurrences occur 28–30 months after surgery, as a consequence of reimplantation and new growth of ectopic endometrial cells [4]. This is almost the same length of time that it takes an endometrioma to develop after menarche [44]. Consequently, we believe that 2 years after surgery might be the minimum follow-up period, and that results from studies investigating recurrence with a follow-up shorter than 1 year should not be generalised.

Moreover, the longer the observation period, the higher the number of patients lost to follow-up. Most of the studies do not report the number of patients lost to follow-up and the reason for the loss. To this end, it would be useful to favour the intention-to-treat model, because it fits better with reality. Loss to follow-up and non-compliance with therapy occur in everyday life, especially in chronic pathologies such as endometriosis, in which there may be dissatisfaction with therapy, both because of the persistence of symptoms and the high rate of side effects due to surgical or medical treatment.

Type of study

Variability in the incidence of endometriosis recurrence also depends on the study design and the sample size. RCTs included only a limited number of patients and most did not use power analysis to determine sample size [9,10,17,21,23,24,26–28,38,45,51]. On the other hand, most published studies are retrospective and some investigators enrolled a significant number of patients [13,29,44]; however, the limitation in this case is due to the type of study design itself. In an analysis of the relationship between the reported 2-year recurrence rate and the sample size of 23 studies, Guo [4] noted that smaller studies tended to report higher recurrence rates. For case–control studies, a possible bias could be linked to the choice of control group; in multicentre studies, it is important to include patients from comparable areas who have been exposed to similar risk factors and are attending centres with comparable diagnostic, clinical and surgical experience.

Differences in reported recurrence rates may also be due to the studied groups and the main endpoint of the study. The recurrence rate is, in fact, extrapolated from a variety of studies with different aims: some studies compare different surgical procedures [9,27,38,41,49], while others compare different postoperative therapies [10,23,45], evaluate whether no therapy is better than postoperative therapy [17,21,26,28,43,46,52], or consider the need for fertility treatment [35]. Another bias may be caused by the

inclusion or exclusion of patients with potential, but uncertain, risk factors such as previous ovarian stimulation [16].

Type of endometriosis

With regard to the anatomical location of endometriosis, the recurrence rate seems to be higher in patients treated for ovarian endometrioma (12–30% at 2–5 years) [11,36,42–44] or superficial peritoneal endometriosis (4.1% at 1 year and 6.7% at 2 years) [36], since conservative treatment is performed at these sites. Furthermore, for some authors, the presence of bilateral endometriomas increases the risk of recurrence [41]; in other series the number of ovarian endometriotic cysts does not influence the recurrence rate [16,39]. The size of the cysts is sometimes considered a predictor of endometriosis recurrence [43,49] and the need for repeat surgery [39,49]. Considering disease stage, there is agreement across the literature on the fact that recurrence is more frequent in patients with advanced disease [1,16,18,30,36,39] or with a more severe form of endometriosis [12,15,30,42].

Type of surgery

Discrepancy in the incidence of endometriosis recurrence may depend also on the surgeon's experience, the kind of surgical procedure performed and the extent of radicality. Previous surgery for endometriosis and the extent of surgical excision have been considered by some authors as predictors of recurrence [16,19,39], probably reflecting more severe disease. The recurrence of clinical findings of disease and the need for repeat surgery seem to be more frequently observed in women with incomplete excision during first surgery [25,35], better defined as persistence of the disease; moreover, some authors noted that the recurrence of deep infiltrating endometriosis often occurred in the same areas treated during first surgery [25,30,35]. Consequently, radicality of surgery, defined as ablation of all visibly suspicious disease lesions, may be associated with a lower rate of recurrence [13]. As stated by Koninckx et al. [33], however: 'The evidence that endometriosis surgery needs to be 100% complete is lacking.' As endometriosis is a benign disease occurring in young women, surgery has to be as complete as possible but also 'organ-sparing'. For other investigators, surgical radicality in severe cases of deep infiltrating endometriosis is mandatory and needs to include visceral resection, using a 'nerve-sparing' approach for reducing organ dysfunction [53]. For ovarian surgery, it has been demonstrated that the skill of the surgeon inversely correlates with the healthy ovarian tissue accidentally removed [54]. In addition, when recurrence occurs, surgery may be needed, causing potential further damage to ovarian reserve. Thus, it has been observed that the risk of recurrence is higher in women with a more intact residual ovarian reserve after surgery [36,55] and lower in women with severely compromised ovaries [55].

For endometrioma treatment, comparing ovarian cystectomy versus ablation of the cyst wall with bipolar coagulation and CO_2 laser or plasma energy vaporisation [56], a significantly lower repeat surgery rate for recurrent endometriomas was found after excision of endometriomas compared with ablation of the cyst wall [38,49–51].

For deep infiltrating rectal/rectosigmoid endometriosis (DIER), defined as endometriosis that involves at least the muscular layer of the rectal wall [31], the possible surgical approaches are segmental bowel resection or nodule excision, either without opening the rectum (shaving) or by removing the nodule with the surrounding rectal wall (discoid excision or full-thickness nodulectomy) [31,57]. Theoretically, segmental colorectal resection for DIER is a more complete surgery because of segmental excision of the palpable nodule together with other possible endometriotic foci, but a higher rate of postoperative complications is reported to be associated with this type of surgery [31,58]. Discoid resection is feasible for selected patients, in particular for DIER nodules <3 cm in diameter and with bowel stenosis $\leq 60\%$ [57]. Considering bowel endometriosis as multifocal disease, some authors reported that shaving and disc excision did not guarantee complete removal of all microscopic endometriotic lesions, which can be responsible for the relapse of pelvic pain or for digestive symptoms (diarrhoea, tenesmus, dyschezia) after surgery [59].

Positive bowel resection margins were found to be significantly associated with endometriosis recurrence after laparoscopic segmental bowel resection for bowel endometriosis [60]. However, a complete resection of microscopic endometriosis seems unfeasible [59,61,62] and other studies showed no correlation between histopathological margins and treatment outcomes [63,64]. Positive resection margins after bowel resection may thus be considered predictors of endometriosis recurrence but should not lead the surgeon to more aggressive surgery with the aim to completely remove possible residual microscopic lesions.

Only a few comparative studies on recurrence rate using the different surgical techniques for DIER are available [57,65]. In the case–control study of Fanfani et al. [57], no significant difference in endometriosis recurrence rate was observed between patients who underwent discoid excision or sigmoid resection at 30 months (13.8% vs. 11.5%, respectively); in the study of Roman et al. [65], no nodule recurrence was observed in the discoid excision and colorectal resection groups and no significant difference was reported between pelvic pain relapse depending on the type of surgery performed for DIER.

Comparing the different surgical approaches, most studies agree that the probability of recurrence is similar with either laparoscopy or laparotomy [12]; however, a minimally invasive approach is associated with a shorter hospital stay and a reduced rate of postoperative morbidity, as well as with better visibility and thus assessment of the abdominal cavity.

Postoperative medical treatment

Since endometriosis is a chronic disease, secondary prevention with medical treatment after surgery is needed. The purpose of medical therapy is to induce a hypoestrogenic state in order to avoid the regrowth of endometriotic foci. Many types and doses of drugs have been proposed and evaluated. The type and the timing of postoperative medical treatment greatly determine the inconsistency in the rate of recurrence.

Available guidelines recommend prescribing combined oral contraceptives (COCs) as secondary prevention [6].

Many authors consider COCs to be effective in preventing endometriosis-associated pain recurrence and/or anatomical relapse [23,45,46,52,66]. In other studies, postoperative COCs did not significantly decrease endometriosis recurrence [21,43]. The discrepancy between these results may be explained by the different durations of administration. Short-term therapy (<1 year) was administered in the studies that did not find a protective role of COCs in preventing recurrence, whereas long-term therapy (1–2 years) was used in the studies that found COCs to be effective in preventing endometriosis recurrence. This suggests that, in order to effectively reduce endometriosis recurrence, COCs require long-term administration, ideally until the woman wants to get pregnant or until the menopause, rather than just for a few months of therapy. Short-term postoperative COC administration is highly unlikely to prevent endometriosis recurrence, since it would neither eradicate possible residual lesions nor prevent the establishment of new lesions when the treatment stops. COCs can be used cyclically [21,46,52] or in a continuous regimen. Some studies have evaluated both [23,45]; other studies did not specify the adopted regimen [43]. Recent evidence suggests that continuous COC administration after surgery may be preferable because of lower recurrence rates of dysmenorrhoea [3].

In patients with a recurrence of endometrioma after second-line surgery for recurrent disease, early dienogest therapy may be an alternative option to avoid multiple surgeries [67]. A Cochrane review of three RCTs suggests that there is limited but consistent evidence showing that postoperative use of the levonorgestrel-releasing intrauterine system (LNG-IUS) reduces the recurrence of pain [68].

Risk factors for recurrence

Several risk factors to predict postsurgical recurrence have been evaluated in the literature. Risk factors may be classified as patient disease-related and surgery-associated [69].

Patient disease-related risk factors

A positive family history of endometriosis has been identified as an independent risk factor for endometrioma recurrence after surgery [70]. Moreover, the risk of endometrioma recurrence after surgery seems to be higher in younger women [60,71]. A retrospective study of women who underwent laparoscopic endometrioma cystectomy confirmed the data and found that age ≤35 years was a significant risk factor for recurrence [72]. In a multicentre retrospective cohort study of 105 surgically treated woman below 20 years of age, ultrasound-proven recurrence was observed in 6.4% of patients at 24 months of follow-up, 10% at 36 months of follow-up, 19.9% at 60 months of follow-up and 30.9% at 96 months of follow-up, and repeat surgery was required in 7% of patients, independently of cyst diameter, disease stage, unilateral or bilateral involvement and coexistence of deep endometriosis. The high rate of long-term recurrence in adolescents suggests that in younger women receiving surgery continuous follow-up is needed [73]. Furthermore, a body mass index ≥23 kg/m^2 was found to be significantly associated with endometriosis recurrence after laparoscopic segmental bowel resection [60].

Some authors found an increased risk of recurrence in women with previous use of drugs for ovarian stimulation [16]. Others, however, found no association between endometriosis recurrence and prior ovarian stimulation for *in vitro* fertilisation [35].

Other patient disease-related risk factors for recurrence of endometrioma after surgery are the presence at diagnosis of large endometrioma size and preoperative pain (non-cyclical pelvic pain and dysmenorrhoea) [74]. A high CA 125 level before surgery is also considered a risk factor for recurrence [74,75]. Moreover, the stage of disease, evaluated through the revised American Society for Reproductive Medicine score, significantly correlated with recurrence of endometrioma in a 2016 study of 352 patients [76]. In a study evaluating the histopathological specimens of endometriomas, the depth of penetration of endometrial tissue into the cyst wall was found to be an independent risk factor for recurrence [72].

Surgery-associated variables

The intraoperative finding of adhesion extension may be associated with recurrence of endometrioma [74]. Moreover, more radical surgery is associated with a lower rate of recurrence [13] but also with lower fertility. For bowel endometriosis, positive bowel resection margins are significantly associated with endometriosis recurrence after surgery [60].

Prevention of recurrence

Predicting a patient's risk of recurrence risk is very important for the future management of the disease, in order to correctly treat each woman, offer personalised management and follow-up in accordance with clinical status and prevent overtreatment of low-risk patients [72,74].

Early and long-term therapy after surgery for a first or second recurrence, with a gonadotropin-releasing hormone agonist followed by a COC or dienogest, may help in avoiding further recurrence and consequent repeat surgeries [67,77]. The LNG-IUS may also be considered as an alternative treatment for preventing endometriosis recurrence [68,75].

Recommendations for authors reporting endometriosis recurrence

Since no uniformity exists in discussing endometriosis recurrence, it is recommended that every author describe disease recurrence based on a standardised definition. It has been previously suggested by other authors that endometriosis recurrence should be clearly documented in every study as follows [78]:

- Symptom recurrence based on patient history, but no proof of recurrence by imaging and/or surgery.
- Endometriosis recurrence based on non-invasive imaging (e.g. ultrasound, magnetic resonance imaging) in patients with or without symptoms (pain, infertility).
- Surgical reintervention without recurrence of endometriosis: surgery without visual diagnosis of endometriosis

in patients with recurring symptoms who have either a normal pelvis or other abnormalities (e.g. adhesions).
- Recurrence of visible endometriosis without histological proof: during laparoscopy, endometriosis was visually observed but either not biopsied or biopsied without histologically proven endometriosis.
- Recurrence of histologically proven endometriosis: during laparoscopy, endometriosis was visually observed and confirmed histologically.

Conclusion

In our opinion, disease relapse should be individually judged on the basis of clinical and imaging findings. The patient's symptoms should be the first item to guide an expert decision, as in most cases medical therapy may be enough to heal symptoms if relapse is diagnosed early. Nevertheless, symptoms may be uneven in the presence of clear imaging evidence of harmful progressive disease (bowel stricture, ureteral stenosis, suspected ovarian cysts). In those cases, surgical treatment is the only option even in absence of patient complaints.

At present, there is no uniformity in the literature as regards the definition and incidence of recurrent endometriosis. Since there is great heterogeneity in the studies, there is an impelling need for the scientific community and endometriosis experts to formulate a standardised definition of endometriosis recurrence. Further RCTs with large sample sizes and a long follow-up ($\geq$2 years), documenting endometriosis recurrence according to a standardised method, are required to better investigate the recurrence of endometriosis.

Disclosure statement

No potential conflict of interest was reported by the authors.

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