Received: 14 February 2024 | Revised: 23 April 2024 | Accepted: 23 May 2024

DOI: 10.1111/aogs.14887

SYSTEMATIC REVIEW

The natural evolution of untreated deep endometriosis and the effect of hormonal suppression: A systematic literature review and meta-analysis

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Funding information
Italian Ministry of Health, Current research 2024 IRCCS Ca' Granda Ospedale Maggiore Policlinico Milano

Abstract

Introduction: Peritoneal infiltrating and fibrotic endometriosis, also known as deep endometriosis, is the most severe manifestation of the disease that can cause severe complications including bowel and ureteral stenosis. The natural history of these lesions and the possible effect of hormonal treatments on their progression are undefined. Therefore, we conducted a systematic review and meta-analysis to investigate whether and how frequently deep endometriosis progresses over time without or with ovarian suppression. This could inform management decisions in asymptomatic and mildly symptomatic patients.

Material and Methods: For this pre-registered systematic review (CRD42023463518), the PubMed and Embase databases were screened, and studies published between 2000 and 2023 that serially evaluated the size of deep endometriotic lesions without or with hormonal treatment were selected. Data on the progression, stability, or regression of deep endometriotic lesions were recorded as absolute frequencies or mean volume variations. Estimates of the overall percentage of progression and corresponding 95% confidence intervals were calculated using a random-effect model. When studies reported lesion progression as pre- and post-treatment volume means, the delta of the two-volume means was calculated and analyzed using the inverse variance method.

Results: A total of 29 studies were identified, of which 19 studies with 285 untreated and 730 treated patients were ultimately selected for meta-analysis. The overall estimate of the percentage of lesion progression in untreated individuals was 21.4% (95% CI, 6.8–40.8%; $I^2 = 90.5\%$), whereas it was 12.4% during various hormonal treatments (95% CI, 9.0–16.1%; $I^2 = 0\%$). Based on the overall meta-analysis estimates, the odds ratio of progression in treated versus untreated patients was 0.52 (95% CI, 0.41–0.66). During hormonal suppression, the mean volume of deep endometriotic lesions

Abbreviations: CI, confidence interval; COC, combined oral contraceptive; DIE, deep infiltrating endometriosis; SD, standard deviation.

decreased significantly by 0.87 cm^3 (95% CI, 0.19–1.56 cm^3; I^2 = 0%), representing −28.5% of the baseline volume.

Conclusions: Untreated deep endometriotic lesions progressed in about one in five patients. Medical therapy reduced but did not eliminate this risk. Given the organ function failure potentially caused by these lesions, the decision whether to use hormonal treatments in asymptomatic or mildly symptomatic women should always be shared, carefully weighing the potential benefits and harms of the two alternatives after extensive counseling.

KEYWORDS
deep endometriosis, hormonal therapy, meta-analysis, natural history, progression, systematic review

1 | INTRODUCTION

Endometriosis is a benign disease characterized by ectopic endometrial tissue growth, with an estimated prevalence of around 5%–10% in the general female population.[1–3] Endometriosis is often associated with infertility and pelvic pain symptoms that interfere with daily activities and affect health-related quality of life. In particular, peritoneal infiltrating and fibrotic endometriosis,[4] commonly known as "deep infiltrating endometriosis" (DIE), is more likely to involve multiple pelvic structures and organs and is considered the most severe form of the disease.[5]

Treatment options in highly symptomatic patients include hormone therapy and/or surgery. According to the current ESHRE guideline[6] and expert opinion,[7] surgical excision of DIE should be considered in individuals without bowel sub-occlusion or obstructive uropathy and not seeking a conception after the failure of first-line hormonal therapies. However, what to suggest in asymptomatic or mildly symptomatic individuals is unclear, and some authors include expectant management among alternative options because they observed lesion progression in a limited proportion of cases only.[8]

On the one hand, estrogen-progestogen combinations and progestogen monotherapies may be associated with unpleasant side effects such as irregular bleeding, bloating, weight gain, depression, and decreased libido.[9] This might tip the balance toward avoiding hormonal treatments when severe pain symptoms are not an issue. On the other hand, the potential serious complications of uncontrolled lesion progression, such as bowel occlusion and ureteral stenosis, should be carefully considered before deciding to abstain from medical suppression. Therefore, in these clinical circumstances, the trade-offs between potential benefits and potential harms associated with the above alternatives should be ideally quantified, which is currently difficult given the sparse data on untreated DIE and the effect of hormonal therapies on lesion progression over time. This would be important to provide complete and reliable counseling and to inform shared personalized treatments. Therefore, from both a pathogenetic and clinical point of view, we considered it relevant to perform a systematic review and meta-analysis of the literature to better define the trajectory of this type of lesion.

Key message

In a meta-analysis of literature data, the overall estimate of the percentage of deep endometriotic lesion progression over time in untreated individuals was 21.4% (95% CI, 6.8%–40.8%; I^2 = 90.5%), whereas it was 12.4% (95% CI, 9.0%–16.1%; I^2 = 0%) during various hormonal treatments.

2 | MATERIAL AND METHODS

2.1 | Search strategy and inclusion criteria

This systematic review was registered with PROSPERO and accepted for inclusion in October 2023 (Registration ID Number CRD42023463518). We searched the PubMed and Embase databases for eligible studies from 1st January 2000 to 12th September 2023, using the following terms: "endometriosis" in different pelvic sites, combined with "natural history" or "medical treatment" or "progression" or "regression." The search terms and the algorithm used are described in detail in the Data S1. We also manually checked the reference lists of the selected publications and used PubMed's 'similar articles' and 'cited by' functions to retrieve additional studies that were not identified by the electronic search. As published de-identified data were used, this study was exempt from ethical approval. The present systematic review and meta-analysis were conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[10]

2.2 | Study selection

Two reviewers (V.B. and D.A.) independently screened the publications by reviewing titles, abstracts, and keywords for the presence of DIE and their lesion size. The selected relevant full-text articles were then retrieved to assess eligibility. Discrepancies were resolved by discussion.

We included randomized controlled trials, cohort and case–control studies, and clinical series that evaluated and defined the number of patients showing progression, stability, regression, or volume variation over time of DIE lesions without therapy or during medical therapy. Case reports were excluded.

Studies that only assessed clinical response or patient satisfaction were excluded, as were studies that described exclusively patients who were pregnant, postmenopausal, or underwent surgery during follow-up.

2.3 | Data extraction

We extracted the following data from each report: first author's last name, year of publication, country in which the research was conducted, study design, sample size (number of untreated or treated patients at baseline and number at the end of follow-up), age of participants, type of medication used, length and modality of follow-up, anatomic site of DIE lesions, and definition of lesion progression. In addition, the volume of DIE lesions before and during treatment together with standard deviation (SD) or standard error (SE), and the percentage of patients without or with hormone therapy who had progression, stability, or regression of DIE lesions at the end of follow-up were collected. Data were extracted by V.B. and checked for accuracy by F.G. Disagreements were resolved by discussion.

Two main groups of patients with DIE lesions were separately analyzed in this study. One group consisted of individuals who were not using pharmacological therapies, whereas the other group included patients who were using hormonal treatments (combined oral contraceptives (COCs), progestin monotherapies, danazol, GnRH agonists, aromatase inhibitors, vaginal ring, levonorgestrel-releasing intrauterine device). Individual patient data were provided by Abrao and co-workers upon request.[11]

2.4 | Quality assessment and risk of bias

We assessed the quality of the included studies and their potential risk of bias using the risk of bias in non-randomized studies of interventions (ROBINS-I) tool[12] and version 2 of the Cochrane Risk-of-Bias Tool (RoB2) for randomized trials.[13] The assessment was performed independently by two reviewers (V.B. and F.C.). Any disagreement in the assessment of the quality of evidence was discussed with a third reviewer (S.C.) to reach a consensus. These data were collected and reported in the Tables S1 and S2.

2.5 | Data synthesis and meta-analysis

For the quantitative synthesis, the analysis was performed using Metaprop, a command implemented in Stata to compute meta-analysis of proportions,[14] when the article reported the number of patients who had disease progression or regression. A Freeman Tukey arcsine square root transformation was applied to the data before pooling for meta-analysis.[15] Estimates of overall proportions of progression and corresponding 95% confidence intervals (CIs) were calculated by using a random-effect model. The heterogeneity I^2 value was also reported to assess heterogeneity among studies.

To compare the percentage of progression between treated and untreated patients, we compute the OR, and relative 95% confidence intervals, by using the overall estimates of the percentage of progression of the two meta-analyses mentioned above.

When the studies expressed lesion progression as a change in the mean volume of lesions at baseline and after treatment, the delta of the means of the two volumes was calculated and analyzed using the inverse variance method random-effect model meta-analysis. To calculate the percentage of volume reduction, we also performed a meta-analysis of the mean lesion volume at baseline. Statistical analysis was performed using rBiostatistics.com—Cloud Graphical User Interface for R Statistics and eLearning Platform.[16]

Sensitivity analysis was performed when appropriate.

3 | RESULTS

3.1 | Study selection

The flowchart of the study screening process is shown in Figure 1. A total of 29 reports were ultimately selected for this review and included in the qualitative synthesis, of which 19 studies were analyzed also in the quantitative synthesis. The characteristics of the selected studies are detailed in Table 1. Sample size, length of follow-up, definition of disease progression, and hormonal therapy varied widely among the studies. Absolute numbers and percentages of patients with DIE progression, stability, and regression over time were extrapolated from nine studies.[8,11,17–23] The mean change in DIE lesion volume before and after treatment was analyzed using data from the remaining 10 studies.[24–33]

3.2 | Quality of evidence

Based on the ROBINS-I tool, we identified two studies with low risk of bias,[8,24] nine with moderate risk of bias,[11,17,18,21,25,28,30–32] and seven with serious risk of bias.[19,20,22,23,26,29,33] Moreover, the only randomized controlled trial included in the meta-analysis that was analyzed using RoB2 was found to have a moderate risk of bias.[27]

3.3 | Meta-analysis

3.3.1 | The natural course of untreated DIE

Four studies reported data on the natural course of DIE lesions in a total of 285 participants.[8,11,19,23] Three studies included both untreated and pharmacologically treated patients,[11,19,23] whereas one

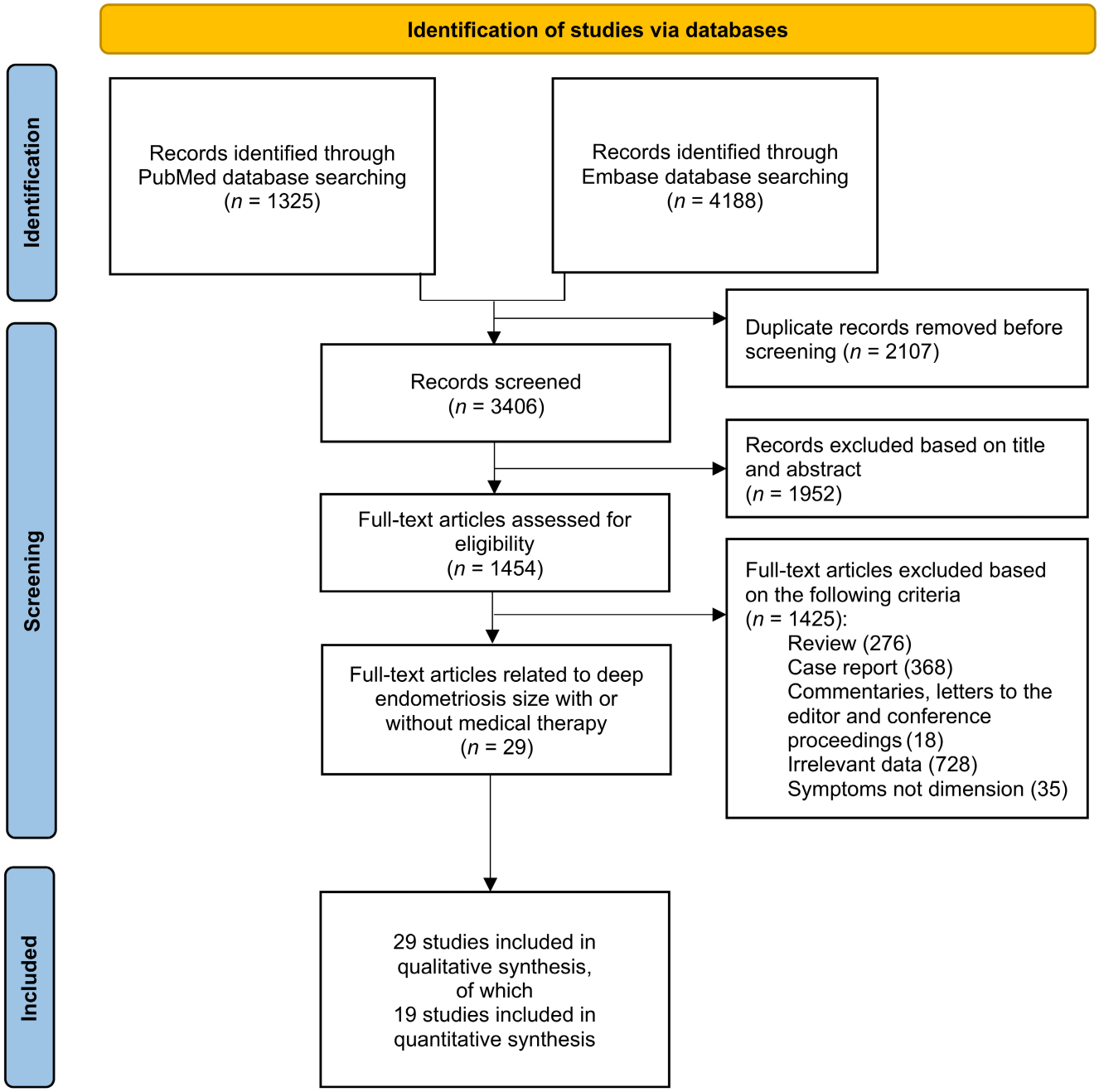

FIGURE 1 Study selection flowchart for systematic review and meta-analysis on deep infiltrating endometriosis lesion size variation without and with hormone therapy.

study[8] included untreated women only. The absolute numbers and percentages of progression, stability, and regression of DIE lesions in untreated patients are shown in Table 2.

For the quantitative synthesis, two groups were considered: patients with disease progression versus patients with stability or regression in lesion size. The overall estimate of the percentage of lesion progression in untreated individuals is 21.4% (95% CI, 6.8%–40.8%; $I^2 = 90.5\%$) (Figure 2).

As shown in Table 2, the most divergent data are those of Fedele et al. where only 4% of patients showed disease progression, while the remaining 94% remained stable.[19] These data may be partially biased by the fact that of the total of 64 untreated women in whom disease progression was assessed, 16 women became spontaneously pregnant, four women entered menopause, and eight women underwent pelvic surgery. In addition, the population of women studied by Fedele et al. consisted of asymptomatic patients.[19] Conversely, Netter et al. and Knez et al. included patients with the highest percentage of lesion progression over time (38.5% and 37%, respectively[8,23]) (Table 2). However, only Netter et al. assessed untreated patients with symptomatic DIE, whereas Knez et al. included both asymptomatic and mildly symptomatic women, but with very limited follow-up compared to the other three studies (Table 2).[8,23]

3.3.2 | The course of medically treated DIE

A total of 18 studies with 730 participants were selected for the meta-analysis. Absolute numbers and percentages of progression, stability, or regression of DIE lesions over time were extracted from eight studies, including a total of 383 patients (Table 3). The change in the mean volume of deep endometriotic lesions before and after treatment was analyzed in the remaining 10 studies, including 347 treated patients.[34–43] Patients were dichotomized in this analysis also, that is, participants with disease progression versus participants with stability or regression in lesion size.

The pooled estimate of lesion progression during hormonal treatment in the eight studies considered was 12.4% (95% CI, 9.0%–16.1%) (Figure 3). This estimate refers to the overall effect of the different types of hormonal medications used (Table 1).

Except for the group of Hefler et al. and Netter et al. (Table 3 and Figure 3),[21,23] data on the progression of DIE are homogeneous between the studies ($I^2 = 0\%$). The only study showing an equal percentage of progression, stability, and regression is that of Hefler et al. in which nine patients with rectovaginal endometriosis were treated with vaginal anastrozole alone (0.25 mg/day) for 6 months.[21] Volume at baseline and the end of follow-up was unchanged after treatment. At sensitivity analysis after excluding the study by Hefler et al.,[21] the overall estimate of the percentage of lesion progression was 12.2% (95% CI, 8.8–16.0%; $I^2 = 0\%$). Netter et al. observed that the mean amenorrhea time during treatment with COCs or GnRH agonists was significantly shorter in women with progression of rectosigmoid nodule than in those with stability or regression (7.5 months, 8.5 months, and 21 months, respectively; $p < 0.001$).[23] Lesion progression was observed in 34% of patients without persistent amenorrhea but in none of those with persistent amenorrhea. In addition, lesion progression was detected in 39% of untreated patients. In the study by Morotti et al., disease progression was more common in patients with more invasive DIE, as three of the seven patients with lesion growth over time had rectal infiltration reaching the muscularis mucosae.[22]

In 347 patients, the lesion volume was assessed at baseline and the end of follow-up after an average of 11.4 months of medical treatment. These studies used different types of hormones alone or in combination (Table 1). In all studies, lesion volume decreased after treatment, with no heterogeneity between studies ($I^2 = 0\%$). The overall estimated decrease was 0.87 cm^3 (95% CI, 0.19–1.56 cm^3), which is statistically significant ($p = 0.01$) (Figure 4), representing −28.5% of the baseline volume (data not shown). The mean ± SD DIE lesion volume ranged from 2.3 ± 0.9 to 12.8 ± 10.4 cm^3 at baseline and from 1.2 ± 0.8 to 4.8 ± 3.9 cm^3 at the end of follow-up (Table 4). At sensitivity analysis after excluding the study by Ferrari et al., in which particularly large lesions were considered, the meta-analysis result remained substantially similar (0.86 cm^3; 95% CI, 0.17–1.55 cm^3).[25]

All the studies showed a statistically significant reduction in volume over time, except two studies that demonstrated lesion stability during treatment with dienogest[29,33] in participants who had not benefited from prior therapy with another progestin.

Two different treatments were compared in three studies.[26,30,32] Leone Roberti Maggiore et al. and Scala et al. assessed the effect of a progestin (desogestrel and NETA, respectively) versus an estrogen-progestin combination (vaginal ring and 91-day extended cycle OC, respectively) and observed a significant and similar reduction in lesion volume with both therapeutic regimens.[30,32] Ferrero et al. compared two combination treatments (letrozole plus NETA vs. letrozole plus triptorelin). At 6-month follow-up, regression in nodule volume was observed in both groups, but the reduction was significantly greater in the letrozole plus triptorelin group ($p < 0.001$).[27]

3.4 | Systematic review

3.4.1 | Qualitative analysis

Twenty-nine studies were selected. All 29 were included in the qualitative analysis, 19 of which were also eligible for the meta-analysis. Ten studies were excluded from the meta-analysis, because they did not report the absolute number of patients showing progression, stability, or regression of DIE lesions, nor the SD of the mean lesion volume change, but exclusively unidimensional (i.e., length/diameter) or bidimensional (i.e., area) parameter variation over time at transvaginal ultrasound (TVUS).[34–43] All of these studies included treated women, except one in which lesion progression was also assessed in a group of untreated subjects.[40]

Fedele et al. evaluated the dimensions of rectovaginal lesions in 13 patients receiving monthly intramuscular leuprolide acetate depot therapy for 12 months. Overall, a slight reduction in lesion size was observed starting from the third month of treatment. The difference was significant after 12 months of therapy (1.9 mL at baseline and 1.7 mL at 12 months; $p = 0.001$),[44] but the size returned to the baseline volume within 6 months after drug discontinuation.[36]

The same group[37] assessed the evolution of rectovaginal endometriotic lesions in 11 women who used the levonorgestrel-releasing intrauterine device for 12 months. At 6-month transrectal ultrasound, a significant reduction in nodule volume was observed ($p < 0.05$), with a further significant reduction at 12-month evaluation (from 1.6 to 1.2 mL; $p < 0.01$).[37,44]

Fedele et al. studied nodule changes also in 10 women with bladder endometriosis, five of whom were treated with a GnRH agonist and the other five with a COC used continuously. At cystoscopic evaluation after 6 months of therapy, bladder lesions regressed almost completely only in patients treated with the GnRH agonist.[38]

Harada et al. evaluated the course of rectosigmoid ($n = 4$) and bladder ($n = 1$) DIE during dienogest therapy. A reduction in lesion size was observed in all patients after 10–11 months of treatment.[39]

Mabrouk et al. observed a significant increase in the diameter of endometriotic nodules in the Douglas pouch over about 6 months in 31 untreated patients (from 23.1 ± 11.1 to 30.9 ± 19.1 mm; $p = 0.007$), but no significant change in lesions in 75 patients who used a COC (dienogest plus ethinyl estradiol) cyclically before undergoing surgery.[40] Similarly, Mariani et al. found no significant reduction in

TABLE 1 Main characteristics of the selected studies evaluating deep endometriotic lesion size variation without or with hormonal treatment (literature data, 2000–2023).

Author	Year	Country	Study design	No of patients	Age (mean ± SD)	Treated/ untreated
Abrao et al.[11]	2021	Brazil	Retrospective (cohort)	164	39.6 ± 6.2	Treated
						Untreated
Angioni et al.[24]	2015	Italy	Prospective series of cases	6	34.2 ± 4.7[c]	Treated
Andres et al.[34]	2019	Brazil	Retrospective (cohort)	238	40.5 ± 5.1	Treated
Barra et al.[17]	2020	Italy	Retrospective analysis of prospectively collected data	83	32.8 ± 5.0	Treated
Carrillo Torres et al.[35]	2023	Spain	Prospective observational (cohort)	64	38.5 ± 4.8	Treated
Egekvist et al.[18]	2019	Denmark	Prospective observational (cohort)	98	38.6 ± 5.8	Treated
Fedele et al.[36]	2000	Italy	Prospective observational (cohort)	15	29.4 ± 3.7	Treated
Fedele et al.[37]	2001	Italy	Prospective observational (cohort)	11	29.1 ± 5.9	Treated
Fedele et al.[19]	2004	Italy	Prospective observational (cohort)	88	31.6 ± 3.2	Treated
						Untread
Fedele et al.[38]	2008	Italy	Prospective comparative clinical trial	10	N.R.	Treated
Ferrari et al.[25]	2012	Italy	Prospective observational (cohort)	26	30.0 ± 4.1	Treated
Ferrero et al.[26]	2011	Italy	Prospective observational pilot study	15	37.9 ± 3.6	Treated
Ferrero et al.[27]	2011	Italy	RCT	35	35.0 ± 3.6 (T) 35.2 ± 4.0 (N)	Treated
Ferrero et al.[20]	2013	Italy	Prospective non-randomized, self-controlled clinical trial	92	34 ± 4.9	Treated
Ferrero et al.[28]	2020	Italy	Retrospective analysis of prospectively collected data	43	32.8 ± 6.1	Treated
Harada et al.[39]	2011	Japan	Retrospective case series	5	43 ± 4.4[c]	Treated
Hefler et al.[21]	2005	Austria	Prospective observational	10	31.2 ± 4.3	Treated
Knez et al.[8]	2023	England	Retrospective (cohort)	135	40 (26–53)[d]	Untreated
Leonardo-Pinto et al.[29]	2017	Brazil	Prospective observational (cohort)	30	36.1 ± 6.2	Treated
Leone Roberti Maggiore et al.[30]	2014	Italy	Patient preference study	143	34.7 ± 3.3 (D) 33.8 ± 4.8 (SN)	Treated
Mabrouk et al.[40]	2011	Egypt	Prospective observational (cohort)	106	34.5 ± 5.1	Treated
					34.5 ± 5.4	Untreated
Mariani et al.[41]	2021	Italy	Retrospective (cohort)	39	34.9 ± 1.8	Treated
Morotti et al.[22]	2017	Italy	Retrospective analysis of prospectively collected data	103	30.5 ± 3.5	Treated
Nagashima et al.[42]	2022	Japan	Retrospective observational	17	36.7 ± 6.7	Treated

Treatment	No of patients at FU	Length of FU (months)	Modality of FU	Definition of progression	Anatomical site of lesion
Oral progestogen, COC, GnRH-a[a]	87	47.6 ± 33.3[b]	TV-US + bowel preparation	Length and circumference	Rectosigma
-	73				
DNG	6	12	Cystoscopy (+biopsy)	Volume	Bladder
Oral progestogen, COC, medroxyprogesterone injections, LNG-IUD, GnRH-a[a]	238	6	TV-US	Diameter and compromised circumference (%)	Rectosigma
DNG	34	36	TV-US + rectal water contrast	Diameter and volume	Rectosigma
DNG/EE	53	24	TV-US	Mean of both maximum diameters	-Rectosigma -Torus -USL
LNG-IUD, COC, oral progestogen[a]	80	12	TV-US	Length	Rectosigma
Leuprolide acetate	13	12	TV/TR-US	Volume	Rectovaginal
LNG-IUD	11	12	TV/TR-US + MRI	Volume	Rectovaginal
EE/desogestrel	24	65.2 ± 26.6[b]	TR-US	Volume	Rectovaginal
-	64				
GnRH-a, COC[a]	10	6	Cystoscopy (+biopsy)	N.R.	Bladder
EE/gestodene	26	12	TR-US	Volume	Colorectal nodules
LNG-IUD + vaginal danazol	14	6	TV-US + water contrast	Volume	Rectovaginal
Letrozole + NETA (N), letrozole + triptorelin (T)	26 10 (T) 16 (N)	6	TV-US	Volume	Rectovaginal
NETA, triptorelin, letrozole + NETA, desogestrel, EE/desogestrel	83	12	TV-US	Volume	Rectovaginal nodules
Etonogestrel releasing implant	40	24	TV-US	Volume	Rectovaginal
DNG	5	11	TV-US	Area	-Rectosigma -Bladder
Vaginal anastrozole	9	6	MRI, TR-US & rectoscopy	Volume	Rectovaginal
-	135	666 (181–2984) days[d]	TV-US	No of nodules and/or size	Anterior and posterior compartment
DNG	30	12	TV-US + bowel preparation	Volume	-Rectosigma -Posterior fornix
Desogestrel (D), vaginal ring (SN)	125 54 (D) 71 (SN)	12	TV-US	Volume	Rectovaginal
EE/drospirenone	75	5.8 ± 3.7[b]	TV-US	Mean nodule diameter	Douglas pouch
-	31				
Estradiol valerate/ nomegestrol acetate	26	6	TV-US	Mean diameter	-USL -Sigmoid colon and rectum -Rectovaginal -Bladder
NETA	59	60	MRI + rectal water TV-US or mCT enema	Volume	Rectovaginal
DNG	15	48	TV-US	Long and short axis	Bladder

(Continues)

TABLE 1 (Continued)

Author	Year	Country	Study design	No of patients	Age (mean ± SD)	Treated/ untreated
Netter et al.[23]	2019	France	Case–control observational retrospective	43	33.1 ± 5.5	Treated Untreated
Piacenti et al.[43]	2021	Italy	Prospective observational (cohort)	100	32.1 ± 1.1 (A) 30.7 ± 1.2 (B)	Treated
Razzi et al.[31]	2007	Italy	Prospective observational	21	32.6 (28–37)[d]	Treated
Scala et al.[32]	2018	Italy	Patient preference prospective study	52	32.5 ± 5.3 (A) 33.1 ± 4.4 (B)	Treated
Yela et al.[33]	2015	Brazil	Prospective observational (cohort)	16	36 ± 6.2	Treated

Abbreviations: COC, combined oral contraceptives; DNG, dienogest; EE, ethinyl estradiol; FU, follow-up; GnRH-a: Gonadotropin-Releasing Hormone analogues; LNG-IUD, Levonorgestrel-IntraUterine Device; MRI, magnetic resonance imaging; NETA, norethindrone acetate; NR, not reported; RCT, randomized controlled trial; SD, standard deviation; TR-US, TransRectal UltraSound; TV-US, TransVaginal UltraSound; USL, uterosacral ligaments.

[a]Not specified type of hormone therapy.

[b]Mean and standard deviation.

[c]Calculated from data extracted from the article.

[d]Median (range).

TABLE 2 Absolute numbers and percentages of women with progression, stability, and regression of untreated deep infiltrating endometriosis.

Author, Year	Length of follow-up (months ± SD)	Modality of follow-up	Definition of progression	Progression No (%)	Stability No (%)	Regression No (%)
Fedele et al. 2004[19]	65.2 ± 26.6	TR-US	Volume	4 (6%)[a]	60 (94%)[a]	0
Netter et al. 2019[23]	38.3 ± 22.1	MRI	Increase of ≥20% in length or thickness	5 (38.5%)	8 (61.5%)	0
Abrao et al. 2021[11]	47.6 ± 33.3	TV-US with bowel preparation	Mean increase in length and circumference	11 (15.1%)	29 (39.7%)	33 (45.2%)
Knez et al. 2023[8]	666 (181–2984)[b]	TV-US	Increase in No of nodules and/or change in mean size of nodule (>2.6 mm)	50 (37%)	68 (50%)	17 (13%)

Abbreviations: MRI, magnetic resonance imaging; SD, standard deviation; TR-US, TransRectal UltraSound; TV-US, TransVaginal UltraSound.

[a]This group could also include women undergoing surgery, and those who have become pregnant or have entered menopause.

[b]Median (range) in days.

the diameter of DIE at 6-month follow-up (from 18.2 to 16.9 mm; $p = 0.12$) in 39 patients with various DIE lesions using a COC (estradiol valerate plus nomegestrol acetate) cyclically or continuously depending on patient preference.[41]

Andres et al. conducted a retrospective cohort study on 238 persons with rectosigmoid endometriosis treated with various medications for 6 months and observed lesion progression at TVUS in 26 (11%) of them. Absolute numerical variations of lesion dimensions were not reported. Individuals who did not respond to medical treatment had significantly larger rectosigmoid lesions at baseline (3.1 ± 2.2 vs 2.1 ± 1.9 cm; $p = 0.008$), and one patient experienced bowel sub-occlusion during therapy.[34]

In the comparative study by Piacenti et al., dienogest 2 mg/day significantly reduced DIE lesion size after 6-month treatment (from 16.0 ± 5.2 to 8.7 ± 2.8 mm, $p = 0.014$), whereas a COC (levonorgestrel/ethinyl estradiol), used continuously for the same period, did not.[43] According to Nagashima et al. the effect of dienogest 2 mg/day on DIE lesions was already evident after 3 months of use, and it was maintained for up to 48 months of treatment. Absolute numerical variations of lesion dimensions were not reported.[42]

More recently, Carrillo et al. evaluated 53 patients with various types of DIE lesions treated with a COC (dienogest plus ethinyl estradiol) used according to an extended cycle schedule (120 active pills/4 placebo pills) for 24 months. The mean diameter

Treatment	No of patients at FU	Length of FU (months)	Modality of FU	Definition of progression	Anatomical site of lesion
COC, GnRH-a[a]	7	38.3 ± 22.1[b]	MRI	Length and thickness	Rectosigma
-	13				
DNG (A), levonorgestrel/EE (B)	86 43 (A) 43 (B)	6	TV-US	N.R.	N.R.
Vaginal danazol	21	12	TV/TR-US	Volume	Rectovaginal
NETA (A), LNG/EE (B)	43 18 (A) 25 (B)	12	TV-US	Volume	-Rectovaginal - Colorectal - USL - Vaginal
DNG	16	6	TV-US	Volume	-Intestinal -Rectovaginal -Bladder

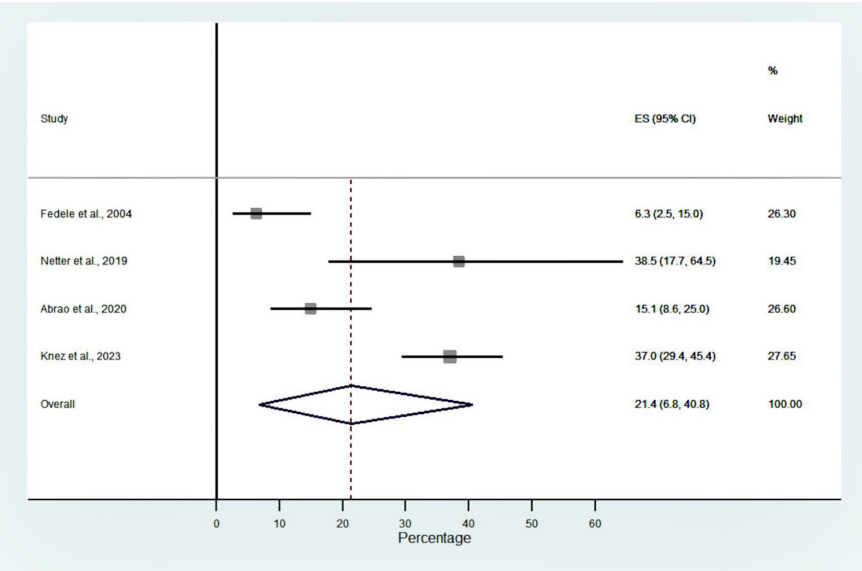

FIGURE 2 Overall estimated percentage of deep infiltrating endometriosis progression without therapy.

of all lesions decreased during treatment, but the variation was statistically significant for uterosacral nodules only (20.9 ± 8.8 vs. 13.1 ± 4.5 mm; $p < 0.004$).[35]

Finally, Keckstein et al. investigated the relationship between the duration of hormone treatment and the risk of DIE progression. Thirty-eight women with a single rectal endometriotic nodule, 15 of whom received hormone therapy for varying lengths of time, were followed for an average of 7.2 years. A significant negative correlation was observed between lesion length and thickness at the end of treatment, and the time spent on hormone therapy. Untreated lesions tended to grow until the fourth decade of life, after which stabilization of dimensions was recorded.[45] This article was published in December 2023 after the conclusion of our systematic literature search, and it is here described for completeness only. However, because we were unable to extract quantitative information for treated and untreated participants, we did not deem it opportune to run a new search with the aim of including this report in the meta-analyses.

4 | DISCUSSION

This systematic literature review included the few available studies on the natural course of untreated DIE lesions. In addition, the

TABLE 3 Absolute numbers and percentages of women with progression, stability, and regression of medically treated deep infiltrating endometriosis.

Author, Year	Length of follow-up (months ± SD)	Modality of follow-up	Definition of progression	Progression No (%)	Stability No (%)	Regression No (%)
Fedele et al., 2004[19]	65.2 ± 26.6	TR-US	Volume	2 (8.3%)	22 (91.6%)	0
Hefler et al., 2005[21]	6	MRI, TR-US and rectoscopy	Volume	3 (33.3%)	3 (33.3%)	3 (33.3%)
Ferrero et al., 2013[20]	12	TV-US with bowel preparation	Volume (±5%)	11 (13.3%)	4 (4.8%)[a]	68 (81.9%)
Morotti et al., 2017[22]	60	MRI + rectal water TV-US or mCT enema	Volume[b]	7 (11.9%)	19 (32.2%)	33 (55.9%)
Netter et al., 2019[23]	38.3 ± 22.1	MRI	Increase of ≥20% in length or thickness	0	5 (71.4%)	2 (28.6%)
Egekvist et al., 2019[18]	12	TV-US	two dimension	9 (11.25%)	59 (73.75%)[a]	12 (15%)
Barra et al., 2020[17]	36	TV-US with rectal water contrast	Diameter and volume (±10%)	4 (11.8%)	12 (35.3%)	18 (52.9%)
Abrao et al., 2021[11]	47.6 ± 33.3	TV-US with bowel preparation	Increase in No of nodules and/or change in mean size of nodule (>2.6 mm)	16 (18.4%)	25 (28.7%)	46 (52.9%)

Abbreviations: mCT, multidetector computerized tomography; MRI, magnetic resonance imaging; SD, standard deviation; TR-US, TransRectal UltraSound; TV-US, TransVaginal UltraSound.

[a]Number obtained indirectly by subtracting from the total the patients with progression and those with regression.

[b]RECIST criteria: defined partial response (PR) at least a 30% decrease in the sum of the longest diameters (LD) of target lesions, taking as reference the baseline sum LD. Stable disease (SD) indicated neither sufficient shrinkage to qualify for PR nor sufficient increase for progressive disease (PD). PD was defined as at least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started.

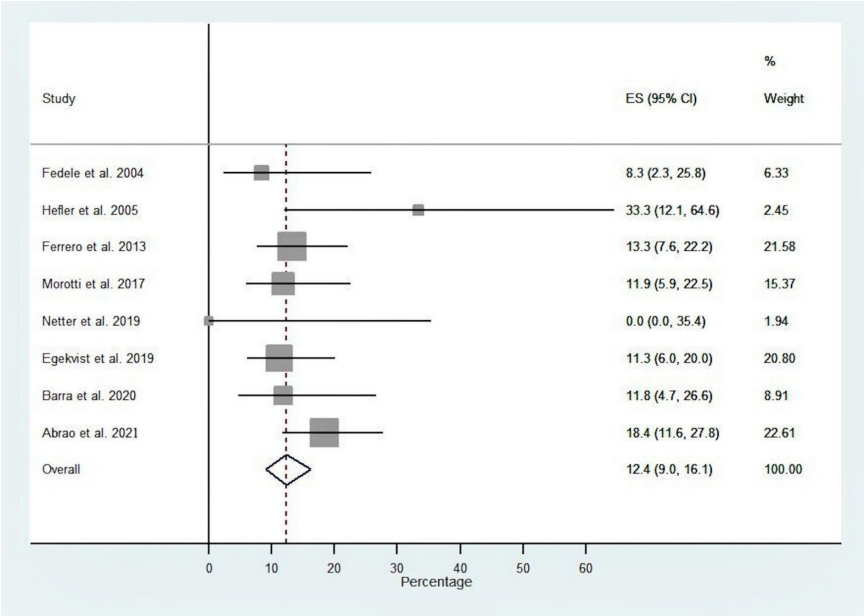

FIGURE 3 Overall estimated percentage of deep infiltrating endometriosis progression with hormonal therapy.

response to medical treatment was assessed in terms of progression percentage and lesion dimension change, both quantitatively and qualitatively.

The potential limitations of the present overview are mainly related to the paucity and heterogeneity of the published data. In particular, only four articles were identified on untreated DIE, with different study designs, methods and lengths of follow-up, and definitions of lesion progression. This may have contributed to the overall high heterogeneity that was observed in this analysis. Due to the characteristics of the available data, the analysis regarding the effect of hormone therapy on DIE was divided into two parts, the first one expressing the effect as a progression percentage, and the second one as a quantitative modification of DIE volume. Regarding the calculated ORs, it must be considered that the two meta-analyses included different studies, and the one comprising untreated patients showed a significantly high heterogeneity. This could imply a potential bias that could alter the value of the OR.

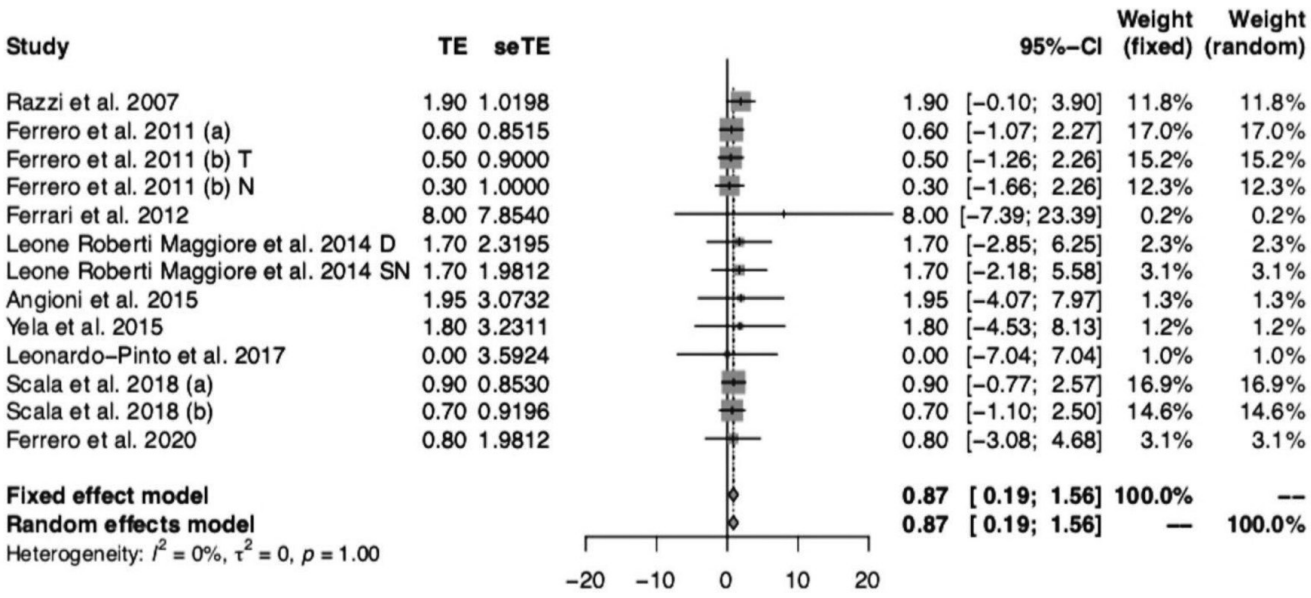

FIGURE 4 Effect of hormonal therapy on deep infiltrating endometriotic lesion volume. T, letrozole + triptorelin; N, letrozole + NETA; D, desogestrel; SN, vaginal ring; a: NETA; b: 91-day extended cycle OC.

TABLE 4 Change in the mean volume of deep infiltrating endometriotic lesions treated with hormonal therapy.

Author, Year	Length of follow-up (months ± SD)	Modality of follow-up	Definition of progression	Pre-treatment volume	Post-treatment volume
Razzi et al. 2007[31]	12	TV-US and TR-US	Volume	3.1 ± 1.2	1.2 ± 0.8
Ferrero et al. 2011[26]	6	Rectal examination + water contrast TV-US	Volume	2.3 ± 0.9	1.7 ± 0.8
Ferrero et al. 2011[27]	6	US using virtual organ computer-aided analysis	Volume	Gr T: 3.2 ± 0.9 Gr N: 3.4 ± 1.0	Gr T: 2.7 ± 0.9[a] Gr N: 3.1 ± 1.0[a]
Ferrari et al. 2012[25]	12	TR-US	Volume	12.8 ± 10.4	4.8 ± 3.9
Leone Roberti Maggiore et al. 2014[30]	12	TV-US	Volume	Gr D: 5.4 ± 2.6 Gr SN: 5.5 ± 2.3	Gr D: 3.7 ± 2.0 Gr SN: 3.8 ± 1.6
Angioni et al. 2015[24]	12	Cystoscopy (+biopsy)	Volume	5.4 ± 3.6[a]	3.6 ± 2.3[a]
Yela et al. 2015[33]	6	TV-US	Volume	3.4 ± 4.2	1.6 ± 1.8
Leonardo-Pinto et al. 2017[29]	12	TV-US with bowel preparation	Volume	2.18 ± 2.99	2.21 ± 4.06
Scala et al. 2018[32]	12	TV-US	Volume	Gr A: 2.7 ± 0.9 Gr B: 2.6 ± 1.0	Gr A: 1.8 ± 0.8 Gr B: 1.9 ± 0.8
Ferrero et al. 2020[28]	24	TV-US	Volume	4.1 ± 2.3	3.3 ± 1.6

Abbreviations: A, NETA; B, 91-day extended cycle OC; D, desogestrel; N, letrozole + NETA; SD, standard deviation; SN, vaginal ring; T, letrozole + triptorelin; TR-US, TransRectal UltraSound; TV-US, TransVaginal UltraSound.

[a]Calculated from data extracted from the article.

In our opinion, the most important finding of our overview is that, in the meta-analysis, DIE progressed in more than one in five untreated patients. These results contrast with those of Fedele et al. in which progression of the disease was observed in only 6% of the patients. However, the higher 95% confidence limit of their point estimate is well included in the 95% CI of our pooled estimate.[19]

In addition, the recruitment of only asymptomatic patients may partially explain the similar disease progression percentage in treated and untreated women (Tables 2 and 3) observed in the studies by Fedele et al.[11] and Abrao et al.,[19] as this atypical participant subgroup may harbor less aggressive DIE lesions compared to the usually encountered population of highly symptomatic patients.

According to Koninckx et al., most DIE lesions are stable over time, with a minority of them regressing.[46,47] This is likely due to the presence of an abundant fibrotic component, which is a manifestation of a post-inflammatory scarring outcome that confers stability to the entire endometriotic lesion, regardless of location, overall dimension, and infiltrative characteristics.

However, the estimated overall percentage of progression, even if in a minority of cases, questions the clinical alternative of proposing a watchful waiting approach to these patients. Indeed, when large endometriotic nodules infiltrate the rectosigmoid junction or, more rarely, the cecum, bowel obstruction may occur acutely without necessarily preceding warning symptoms. In addition, when rectovaginal plaques tend to extend laterally, especially on the left side, renal function may be partially or completely lost due to the silent but progressive development of obstructive uropathy.

Therefore, we wonder whether the position of Knez et al. can be safely shared when they state that "*medical or surgical treatment with the sole objective of preventing the progression of the disease in the absence of significant clinical symptoms is unlikely to be beneficial*."[8] Although we agree that surgery in asymptomatic individuals may constitute overtreatment, whether this also applies to safe, generally well-tolerated, and inexpensive first-line medications seems debatable. With hormonal suppression, the pooled probability of lesion progression was not zero but was still significantly lower than with expectant management (from about one in five to about one in eight individuals). Whether the magnitude of this protective effect is worth using long-term endocrine treatments in the absence of symptoms should be an individual woman's decision after complete and well-balanced counseling. Some women may decide to take the full risk and undergo expectant management, whereas others may prefer to reduce the risk using pharmacologic suppression.

In this regard, it should be emphasized that lesion progression is not necessarily synonymous with severe complications and, therefore, a number needed to treat cannot be defined based on currently published data. In particular, the available evidence does not allow us to define the risk of bowel occlusion or obstructive uropathy in patients with DIE progression. No cases were reported in the untreated persons recruited in the four studies included in the quantitative synthesis,[8,11,19,23] but one case of sub-occlusion during hormonal suppression was described in one study included in the qualitative synthesis.[34] Of concern, lesion progression was not associated with the onset or worsening of symptoms.[48]

After pooling the effects of diverse hormonal medications on lesion volume reported in 10 studies, a mean reduction of 28.5% was observed. Although this variation is relevant from a pathogenic standpoint, the practical significance of this finding is uncertain. In asymptomatic women, the goal is to prevent a dimensional increase of lesions, and once this is achieved, whether lesions remain stable, or regress may be inconsequential.

Given the few available studies, the limited number of participants included, and the use of different drugs in the same study, separate effect estimates could not be defined for first- and second-line drugs. Unexpectedly, inconsistencies were detected between the quantitative and the qualitative syntheses, as no heterogeneity was identified in the former one only. Conversely, the reported effect varied between studies using different hormones. In particular, COCs did not induce lesion regression in three studies.[40,41,43] Thus, in patients with high-risk lesions, the use of progestin monotherapies or GnRH agonists plus add-back therapy seems opportune to avoid even a limited stimulation of ectopic endometrium, as previously proposed.[49,50]

5 | CONCLUSION

Despite the suboptimal quality of the evidence reported in most of the studies included in this systematic literature review, the hypothesis that the dimensions of untreated DIE lesions only rarely increase over time can be reasonably rejected. Overall, this type of lesion progressed in over one in five asymptomatic or mildly symptomatic women not using hormonal suppression. Whether this estimate can be generalized to untreated women with severe pain symptoms cannot be determined, as these patients are always treated medically or surgically. Indeed, it cannot be excluded that the absence of symptoms is an indicator of limited metabolic activity of such lesions. In the selected studies on the effect of medications on DIE evolution, only symptomatic women were recruited. Therefore, it could be hypothesized that DIE lesions are more aggressive when they cause symptoms. If this is true, the difference between untreated and treated patients in the proportion of lesions that progressed may have been underestimated.

Hormonal suppression reduces the risk of progression (around one in eight people) but does not abolish it. Choosing between long-term progestin treatment or expectant management in an asymptomatic woman should be an individually shared and customized decision made after detailed and unbiased information. In any case, serial clinical and ultrasound evaluations are mandatory, especially for the early detection of silent obstructive uropathy.

AUTHOR CONTRIBUTIONS

Paolo Vercellini and Veronica Bandini conceived the study and drafted the original version of the article. Francesca Chiaffarino contributed to the design of the study and data collection, statistical analysis and drafted part of the article, and revised the paper. Veronica Bandini, Deborah Ambruoso, and Francesca Giola undertook the searches and data extraction, and interpretation. Sonia Cipriani contributed to the statistical analysis and revised the paper.

ACKNOWLEDGMENTS

We are extremely grateful to Mauricio Abrao and coworkers for providing individual patient data from their study upon our request.[11] The authors thank Giorgia Di Stefano, *Biol. Sci*., for creating the graphical abstract.

FUNDING INFORMATION

The open access publication of this paper was funded by Italian Ministry of Health, Current Research IRCCS Ca′ Granda Ospedale Maggiore Policlinico di Milano.

CONFLICT OF INTEREST STATEMENT

Paolo Vercellini has received royalties from Wolters Kluwer for chapters on endometriosis management in the clinical decision support resource UpToDate; and maintains both a public and private gynecological practice. All other authors declare that they have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Bandini V, Giola F, Ambruoso D, Cipriani S, Chiaffarino F, Vercellini P. The natural evolution of untreated deep endometriosis and the effect of hormonal suppression: A systematic literature review and meta-analysis. *Acta Obstet Gynecol Scand*. 2024;00:1-14. doi:10.1111/aogs.14887