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Review Article

Dienogest and the Risk of Endometriosis Recurrence Following Surgery: A Systematic Review and Meta-analysis

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ABSTRACT **Study Objective:** To determine whether dienogest therapy after endometriosis surgery reduces the risk of endometriosis recurrence compared with expectant management.

Data Sources: Ovid MEDLINE, Ovid EMBASE, PubMed, Cochrane Central Register of Controlled Trials, Web of Science, LILACS, clinicaltrials.gov, and International Standard Randomized Controlled Trial Number Registry were searched from inception to March 2019 for observational and randomized controlled trials.

Methods of Study Selection: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed. Medical Subject Heading terms and keywords such as "dienogest," "endometriosis," and "recurrence" were used to identify relevant studies.

Tabulation, Integration, and Results: The search yielded 328 studies, 10 of which were eligible for inclusion, representing 1184 patients treated with dienogest and 846 expectantly managed controls. Among these studies, 9 looked exclusively at endometrioma recurrence, whereas 1 used reappearance of symptoms as evidence of disease recurrence. Data on both incidence of and time to recurrence of endometriosis were extracted.

The incidence rate of endometriosis recurrence in patients treated with dienogest was 2 per 100 women over a mean follow-up of 29 months (95% confidence interval [CI], 1.43−3.11) versus 29 per 100 women managed expectantly over a mean follow-up of 36 months (95% CI, 25.66−31.74). The likelihood of recurrence was significantly reduced with postoperative dienogest (log odds −1.96, CI, −2.53 to −1.38, p <.001).

Conclusion: Patients receiving dienogest after conservative surgery for endometriosis had significantly lower risk of postoperative disease recurrence than those who were expectantly managed. Journal of Minimally Invasive Gynecology (2020) 27, 1503−1510. © 2020 AAGL. All rights reserved.

Keywords: Dienogest; Endometrioma; Endometriosis; Recurrence; Surgery

Dienogest is a unique fourth generation synthetic progestogen and has been approved for the treatment of endometriosis and as a part of combined hormonal contraception (CHC) across Europe and North America [1−3]. Studies have demonstrated its high specificity for progesterone receptors; strong antiproliferative effects on endometriosis implants; and antiandrogenic, antiangiogenic, and anti-inflammatory properties [4−6].

Given its high tolerability and effectiveness, dienogest has become an important option for medical management

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of endometriosis in many parts of the world [7]. Until recently, dienogest has been the only available oral, disease-specific agent in the treatment of endometriosis [8]. Effective methods of suppressing postoperative recurrence is needed to ensure sustained benefit from surgery because endometriosis recurrence rates after excisional treatment are high, ranging up to 50% to 60% [9]. Besides dienogest, a spectrum of medical therapies have been investigated in the literature for prevention of recurrence including the CHC, the levonorgestrel intrauterine contraceptive device, and gonadotropin-releasing hormone (GnRH) analog therapy, with varying degrees of success [10−13]. In clinical practice, the choice of medication is dependent on myriad factors including patient, clinician, and disease characteristics. A Cochrane review published in 2004 (updated in 2011) evaluating the evidence for postoperative hormonal suppression for endometriosis showed no evidence of decreased disease recurrence; however, data were limited to 3 trials (148 patients), none of which examined the use of dienogest [14]. Despite this seeming lack of evidence, guidelines and expert opinion continue to recommend the use of postoperative suppression for secondary prevention [15,16]. Given this knowledge gap, we undertook a systematic review and meta-analysis to evaluate the efficacy of postoperative dienogest for the prevention of endometriosis recurrence.

Materials and Methods

Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to conduct a systematic review of the literature (refer to Supplemental File 1 for PRISMA checklist). The following electronic databases were searched from inception to March 27, 2019 using a comprehensive search strategy developed by an information specialist (see Supplemental Appendix S1 for complete search strategy): (1) Ovid MEDLINE, (2) Ovid EMBASE, (3) PubMed (non-MEDLINE records only), (4) Evidence-Based Medicine Reviews—Cochrane Central Register of Controlled Trials, (5) Web of Science, and (6) LILACS. We also searched the World Health Organization International Clinical Trials Registry Platform and International Standard Randomised Controlled Trial Number Registry for all registered clinical trials and randomized controlled trials (RCTs). Additional studies were hand-searched from references of relevant studies. All references were managed and screened in EndNote and Covidence, respectively. Institutional review board approval was not required for the completion of this study. Given the nature of this study, no direct patient engagement was involved. Authors were contacted, if necessary, for missing outcome data.

Funding

Financial support was provided by a hospital grant. Apart from the authors, there was no external involvement in the study design; collection, analysis, or interpretation of data; writing of the report; or the decision to submit the article for publication.

Study Selection

Included studies were limited to retrospective and prospective observational studies (cohort, case-control, and case series) and RCTs of premenopausal women undergoing conservative surgery (retaining at least 1 ovary) for endometriosis. Postoperatively, participants required at least 6 months of daily dienogest therapy, with a follow-up of at least 6-month duration. Studies with no comparator group were included because this would provide information regarding the background risk of recurrence in patients treated with dienogest. Only full-text published articles in English were considered for inclusion. Studies were excluded if the medical treatment was initiated remote from surgery (>6 weeks), if the surgery was only diagnostic, if the surgery involved cyst aspiration/sclerosis only, or if any experimental chemical treatment (e.g., interferon α-2b) was involved.

Two authors (A.Z. and D.E.) independently reviewed titles and abstracts for the initial screening and subsequently performed full-text reviews to identify eligible studies for the final inclusion. Any conflicts were resolved by a third reviewer (A.M.). All screening and risk of bias analysis were performed using the online platform Covidence, available at www.covidence.org. The study protocol was submitted to PROSPERO for registration (identification number: CRD42019140767) and executed following PRISMA guidelines for systematic reviews.

Outcome Measures

The primary outcome was to determine the rate of endometriosis recurrence, defined as (1) radiographic evidence of endometriosis (endometrioma on ultrasound [US] or magnetic resonance image [MRI], plaques, deep disease, or other suggestive findings on MRI), (2) symptom recurrence in patients after conservative endometriosis surgery treated with dienogest, or (3) findings from second-look laparoscopy and to compare this rate with controls, if available. Acceptable definitions of symptom recurrence included patient-reported recurrence of pelvic pain (dysmenorrhea, dyspareunia, or noncyclic pelvic pain), increase in pain on standardized measures (e.g., visual analog scale), or decrease in quality of life using standardized tools (e.g., Short Form 36). Patients who were managed expectantly, not offered hormonal therapy, or treated with placebo were considered as controls. Our secondary outcome was to determine the odds of recurrence in patients treated with dienogest compared with controls who received no postoperative hormonal suppression. Outcomes were assessed at a minimum of 6 months postoperatively, however when long-term data were available (≥12 months), data were preferentially extracted at the 12-month mark.

Data Extraction

Two independent reviewers (A.Z. and D.E.) completed data extraction using pretested, customized worksheets. Any conflicts in the data extraction were resolved with the help of a third reviewer (A.M.).

Risk of Bias

Risk of bias was assessed using the Cochrane risk of bias tool for RCTs [17]. A modified Newcastle-Ottawa Scale was used for observational studies and assisted in assigning the study quality as poor, fair, or good on the basis of the Agency of Healthcare Research and Quality standards [18,19]. The risk of bias was once again evaluated independently by 2 authors (A.Z. and D.E.), with discrepancies resolved by a third author (A.M.).

Statistical Analysis

Extracted data were analyzed with the help of a statistician, using commercially available SAS software (version 6.1; SAS Enterprise Guide, Cary, NC). Data were analyzed to produce an overall recurrence rate, with a corresponding 95% confidence interval (CI). Statistical heterogeneity was assessed using I^2. With available comparator data, the odds of recurrence compared with control was assessed and reported as log odds with a significant p-value set at <.05.

Results

Study Selection and Characteristics

Our initial electronic database search yielded 328 studies, of which 13 were duplicates. After the title and abstract screening, 18 were assessed for full-text review (Fig. 1), and 8 were excluded for the following reasons: outcome of

Fig. 1

PRISMA flow chart for study identification and inclusion/exclusion. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

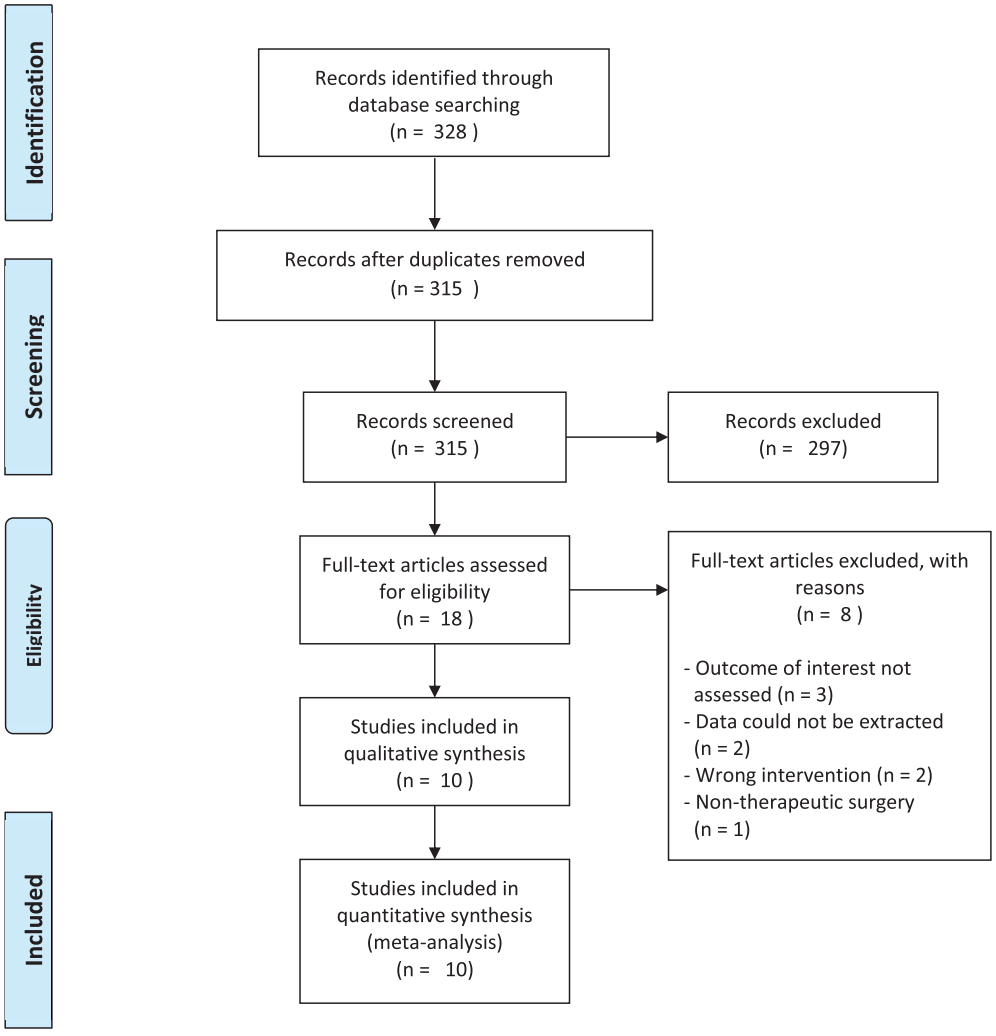


Table 1

Study characteristics

Study	Design	Surgery	Intervention (n)	Control (n)	Mean F/U (months)	Definition of recurrence
Adachi et al, 2016 [20]	Retrospective cohort	Cystectomy	40	41	20	Presence of ≥2-cm −oma on US
Chandra et al, 2018 [26]	Retrospective cohort	Cystectomy, EE	182	N/A	30	Presence of ≥2-cm −oma on US
Koshiba et al, 2018 [21]	Retrospective cohort	Cystectomy, excision	27	83	38	Presence of ≥2-cm −oma on US
Lee et al, 2016 [27]	Retrospective cohort	Cystectomy, EE	36	N/A	6	Recurrence of pain symptoms
Lee et al, 2018 [28]	Retrospective cohort	EE	514	N/A	18	New −oma on US
Ota et al, 2015 [22]	Retrospective cohort	Cystectomy, EE	151	416	59	Lesion previously diagnosed as −oma on MRI, with ≥ size
Ouchi et al, 2014 [23]	Retrospective cohort	Cystectomy	7	160	38	Presence of ≥2-cm −oma on US
Park et al, 2016 [29]	Retrospective cohort	Cystectomy, EE	114	N/A	17	Presence of ≥2-cm −oma on US
Takaesu et al, 2016 [24]	Prospective cohort	Cystectomy, EE	54	79	24	MRI findings suggesting recurrence
Yamanaka et al, 2017 [25]	Retrospective cohort	Cystectomy, EE	59	67	35	Presence of persistent cyst ≥1.5 cm on US or MRI

EE = excision of endometriosis; F/U = follow-up; MRI = magnetic resonance imaging; N/A = not applicable; −oma = endometrioma; US = ultrasound.

interest not assessed [3], data could not be extracted [2], intervention did not meet criteria [2], and heterogeneous study population [1].

Ten studies were eligible for inclusion, comprising 9 retrospective cohort studies and 1 prospective cohort study. No studies involved patients undergoing hysterectomy. All studies were conducted in Japan [20−25] and Korea [26−29]. A total of 2030 patients were included (1184 treated with dienogest and 846 controls). Six studies had both an intervention and a control arm. In these 6 comparative studies, 338 patients treated with dienogest were compared with 846 controls. Treatment duration varied widely among the studies, from 6 months to 79 months. The follow-up period and the assessment of outcomes ranged from 6 months [27] for 1 study to 59 months [22] for another, with the remaining 8 studies reporting follow-up periods ranging from 12 months to 43 months. The mean follow-up period for all studies and the subset of studies with a comparator arm was 28.5 months and 35.7, respectively. Study characteristics are presented in Table 1 with the individual study definitions of recurrence included.

The risk of bias and quality were assessed using the modified Newcastle-Ottawa Scale for all studies and deemed poor, fair, or good on the basis of the Agency of Healthcare Research and Quality standards (Table 2). Overall, 4 studies were found to be good, 4 were fair, and 2 were poor. Most of the studies evaluated as being of poor quality had issues related to selection bias, in which it was unclear how patients were assigned to the intervention arm. In the studies considered to be at a high risk of bias in

Table 2

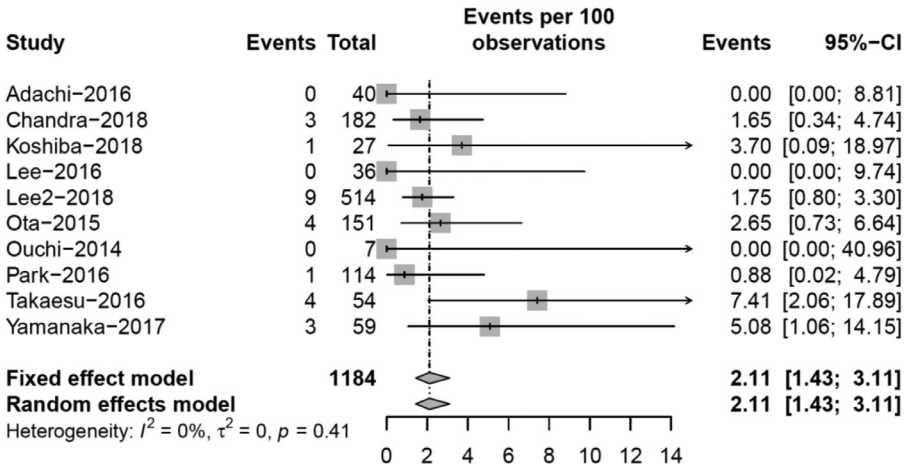
Risk of bias

Study	Study selection	Comparability	Outcomes	Overall
Adachi et al, 2016 [20]	Low	Low	Low	Good
Chandra et al, 2018 [26]	High	N/A	Low	Fair
Koshiba et al, 2018 [21]	High	High	Low	Poor
Lee et al, 2016 [27]	Low	N/A	High	Poor
Lee et al, 2018 [28]	High	N/A	Low	Fair
Ota et al, 2015 [22]	Low	Low	Low	Good
Ouchi et al, 2014 [23]	Low	Low	Low	Good
Park et al, 2016 [29]	High	N/A	Low	Fair
Takaesu et al, 2016 [24]	Low	Low	Low	Good
Yamanaka et al, 2017 [25]	Low	High	Low	Fair
Total	4 High	2 High	1 High	4 Good
	6 Low	4 Low	9 Low	4 Fair
		4 N/A		2 Poor

N/A = not applicable.

Fig. 2

Incidence rate of endometriosis recurrence−dienogest. CI = confidence interval.



comparability, the 2 groups were typically found to be significantly different in baseline characteristics; often patients with more extensive endometriosis (i.e., endometriomas or deeply infiltrating endometriosis [DIE]) were more likely to receive postoperative suppression than patients with milder disease. All studies ranked low for risk of bias in relation to outcome reporting, with 1 exception [27].

Primary Outcome

Among the 10 studies included, 9 defined recurrence radiologically as recurrent ovarian endometrioma, and 1 relied on patient-reported recurrence of symptoms as evidence of relapsing endometriosis. Of these 9 studies, 5 used similar criteria by US (presence of a ≥2-cm endometrioma), 1 study left the criteria unspecified (US finding of an endometrioma), and 2 studies used either US or MRI findings of persistent cystic lesion on the ovary. Overall, the incidence rate of endometriosis recurrence in patients receiving postoperative suppression with dienogest was 2 recurrences per 100 treated women over a mean duration of 28.5 months (2.11 events/100 women; 95% CI, 1.43−3.11, 10 studies, 1184 patients, $I^2 = 0\%$ fixed effects model). Additional analysis showed patients on dienogest had 0.89 recurrences per 1000 woman-months (95% CI, 0.60−1.31, 10 studies, 1184 patients, $I^2 = 26\%$ fixed effects model). The subgroup analysis of the 9 studies examining endometrioma recurrence showed similar results (2.18/100 women; 95% CI, 1.48−3.20, 9 studies, 1148 patients, $I^2 = 0\%$ fixed effects model). In the control group, the incidence rate of endometriosis recurrence was significantly higher, at 29 recurrences per 100 women over a mean duration of 35.7 months (28.61 events/100 women; 95% CI, 25.66−31.74, 6 studies, 846 patients, $I^2 = 83\%$ fixed effects model). Women without hormonal suppression had 5.46 recurrences per 1000 woman-months (95% CI, 4.81−6.19, 6 studies, 846 patients, $I^2 = 84\%$ fixed effects model).

The subgroup analysis performed on only good quality studies yielded similar findings (3.17 events/100 women; 95% CI, 1.60−6.22, 4 studies, 252 patients, $I^2 = 0\%$ fixed effects model vs 28.45 events/100 women; 95% CI, 25.22 −31.92, 4 studies, 696 patients, $I^2 = 89\%$ fixed effects model). Sensitivity analysis with random effects modeling did not change the outcome results. These results are presented in Figs. 2 and 3.

Secondary Outcome

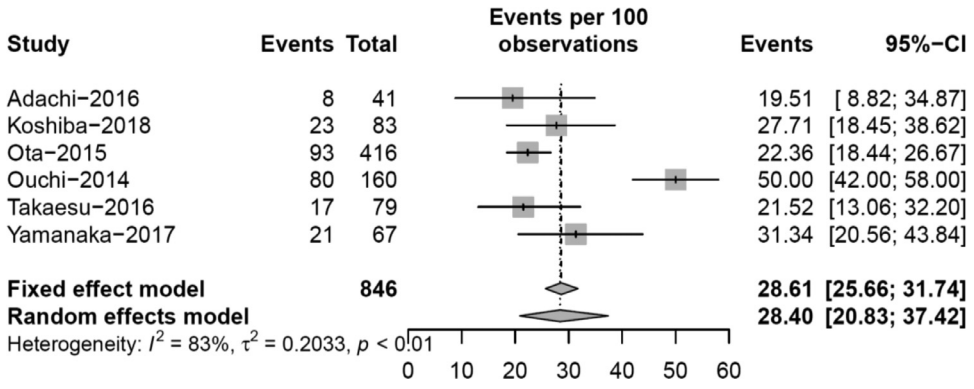
Six studies had a control arm for comparison, all of which used the same definition of recurrence (i.e., recurrent endometrioma on imaging). Compared with controls, patients receiving dienogest therapy were less likely to have a recurrence of endometriosis (log odds −1.96; 95% CI, −2.53 to −1.38, p <.001; 6 studies, 1184 patients). These findings were consistent after the subgroup analysis of only good quality studies (log odds −1.99; 95% CI, −2.70 to −1.27, p <.001; 4 studies, 948 patients). See Fig. 4 for forest plot.

Discussion

In this systematic review and meta-analysis of 10 studies (9 retrospective cohort and 1 prospective cohort) comprising 2030 patients, we found a low rate of endometriosis recurrence with postoperative dienogest therapy at 2 events per 100 women over a mean follow-up period of 28.5 months. The eligible studies for this review overwhelmingly defined recurrence radiologically, as a recurrent ovarian endometrioma (9 of 10 studies). In addition, the odds of recurrence in patients receiving dienogest were significantly

Fig. 3

Incidence rate of endometriosis recurrence−control. CI = confidence interval.



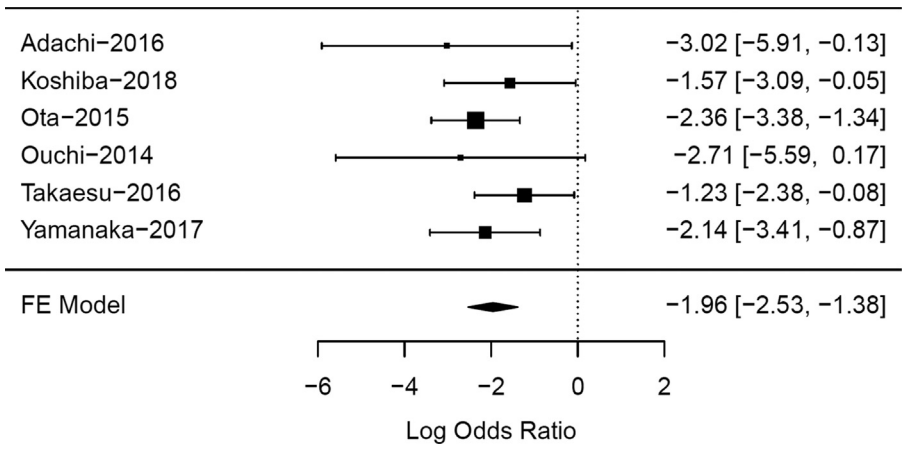
lower than those receiving no postoperative treatment. These findings support the use of dienogest after conservative surgery for endometriosis in the management of women who do not intend to conceive immediately.

Among the 10 studies, 4 in this review were classified as good quality, and all except 1 were retrospective in design. Although the findings were consistent across these, large-scale prospective data are needed to rigorously validate these findings and quantify the attributable benefit of postoperative dienogest. Furthermore, recurrence in all but 1 study was defined radiologically, with the appearance of an ovarian endometrioma. This narrow definition may result in an underreporting of recurrent disease presenting subtly with patients' symptoms or lesions undetectable by imaging or alternatively may inflate a truly lower risk of recurrence for other forms of endometriosis such as deep nodules. A more inclusive definition of recurrence should incorporate not only radiologic end points but also patient symptoms (dysmenorrhea, dyspareunia, and pelvic pain), physical examination findings, and surgical findings when available. One study relied on patient-reported symptoms as a measure of recurrence; however, the use of medication in 1 arm and the absence of a placebo in the control arm allowed for the placebo effect to contribute to the perceived efficacy of the active treatment. This highlights the importance of placebo-controlled RCTs when evaluating complex parameters such as pain.

The strengths of this study included the systematic nature of the literature review, which elicited clinically relevant outcomes with long-term follow-up. The broad inclusion criteria enabled us to synthesize important outcome data from different trials, and the heterogeneity of the analysis was low [17]. However, these data must be interpreted in the context of the study design. Nearly all studies included were retrospective in nature; this potentially introduces selection bias because patients with more extensive endometriosis may have preferentially received suppressive therapy and been more encouraged to comply with long-term treatment. In addition, there was likely potential for publication bias, with reluctance toward publishing studies

Fig. 4

Log odds of endometriosis recurrence for dienogest compared with controls. FE = fixed effects.



in which postoperative suppression failed to show significant reduction in recurrence. Understanding which patients are likely to benefit the most from postoperative suppression is an important question to address, ideally in the context of a randomized trial. Furthermore, there was significant heterogeneity within and between studies in the specific pathology (DIE vs endometrioma) as well as the stage of disease, if reported at all. Finally, all the studies included in this review originated from East Asia, which may limit the generalizability of the findings considering the ethnic-related differences in endometriosis phenotype [30].

Furthermore, although the outcomes of interest presented here are informative in regards to the recommended management of postoperative endometriosis, they provide little guidance in patient tolerability, predictors of responsiveness to treatment, and efficacy compared with alternative regimens (such as other progestogens and GnRH agonist and antagonist therapy).

Complete excision of all visible endometriosis results in the most substantial and long-lasting improvement in patients' symptoms, however such an optimal debulking cannot always be attained owing to a challenging location of the lesion or extensive infiltration [31,32]. Incomplete surgery may cause misclassification of disease persistence as possible recurrence. Furthermore, microscopic disease may be present but not recognized intraoperatively. Residual disease provides a focus for future recurrence, which may proliferate unchecked in the absence of medical suppression. Indeed, studies have shown that recurrence of DIE often occurs in the same site of a previous resection [9]. In addition, recurrent endometriomas occur significantly more frequently on the previously operated side compared with a previously unaffected side (80.6% previously treated ovary vs 11.3% previously unaffected ovary vs 8.1% both ovaries) [9]. Taken together, these data underlie the importance of complete removal of all endometriotic lesions, when possible.

Given the chronic nature of the disease and high rates of postoperative recurrence, patients need safe, long-term maintenance options for endometriosis. Although the Cochrane review did not demonstrate significant benefit to postoperative treatment, numerous RCTs and observational cohort studies on other medical options, such as CHC, the levonorgestrel intrauterine systems, and GnRH agonists, have shown benefit in reducing recurrence and pain symptoms, giving clinicians and patients options to tailor the suppressive therapy to individual needs [24,33−35]. When patients opt for suppression with agents such as the levonorgestrel intrauterine systems or CHC, they not only benefit from the suppressive effects of these medications on endometriosis but also from reliable contraception, which may be appealing for many patients within this demographic. The choice of hormonal suppression may also depend on economic factors such as drug cost, which has unique and nuanced implications in different healthcare systems. Regarding long-term experience with dienogest, there are limited data, with most of the published research extending to 15 months of treatment [36]. Two large-scale postapproval studies are currently underway, evaluating the safety and tolerability of dienogest over extended periods of time, ranging from 2 to 6 years [37,38]. Findings from these studies will help guide patient counseling and clinical decision making. The concern of bone mineral density changes with prolonged use of dienogest has been evaluated in several trials [39−41]. Although a decrease in bone mineral density has been observed with treatment up to 52 weeks, partial recovery follows cessation of use, and the clinical significance of these changes remains uncertain.

Conclusion

Patients who receive dienogest after conservative surgery for endometriosis have a low rate of disease recurrence and are less likely than their untreated counterparts to be diagnosed with recurrent endometriosis, particularly endometriomas. In view of these findings, future studies are needed to determine the feasibility of long-term therapy with dienogest, identify whether a particular subset of patients is more likely than others to benefit from suppression, and clarify the optimal postoperative medical regimen to minimize the risks of disease recurrence.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.jmig.2020.05.007.

References

1. Köhler G, Göretzlehner G, Amon I. Therapy of endometriosis with dienogest [in German]. *Zentralbl Gynakol*. 1987;109:795–801.
2. Government of Canada. Summary basis of decision - Visanne - Health Canada. Available at: https://hpr-rps.hres.ca/reg-content/summary-basis-decision-detailOne.php?linkID=SBD00306. Accessed August 17, 2019.
3. Dienogest for the treatment of endometriosis. *(Archived) LNDG, ed. London New Drugs Group*, 2019. London New Drugs Group (Archived); 2011.
4. Oettel M, Breitbarth H, Elger W, et al. The pharmacological profile of dienogest. *Eur J Contracept Reprod Health Care*. 1999;4:2–13.
5. Laganà AS, Vitale SG, Granese R, et al. Clinical dynamics of dienogest for the treatment of endometriosis: from bench to bedside. *Expert Opin Drug Metab Toxicol*. 2017;13:593−596.
6. Miyashita M, Koga K, Takamura M, et al. Dienogest reduces proliferation, aromatase expression and angiogenesis, and increases apoptosis in human endometriosis. *Gynecol Endocrinol*. 2014;30:644–648.
7. Schindler AE. Dienogest in long-term treatment of endometriosis. *Int J Womens Health*. 2011;3:175–184.
8. Lamb YN. Elagolix: first global approval [published correction appears in *Drugs* 2018;78:1855] *Drugs*. 2018;78:1501–1508.
9. Guo SW. Recurrence of endometriosis and its control. *Hum Reprod Update*. 2009;15:441–461.
10. Seracchioli R, Mabrouk M, Manuzzi L, et al. Post-operative use of oral contraceptive pills for prevention of anatomical relapse or

symptom-recurrence after conservative surgery for endometriosis. *Hum Reprod*. 2009;24:2729–2735.
11. Koga K, Takamura M, Fujii T, Osuga Y. Prevention of the recurrence of symptom and lesions after conservative surgery for endometriosis. *Fertil Steril*. 2015;104:793–801.
12. Busacca M, Somigliana E, Bianchi S, et al. Post-operative GnRH analogue treatment after conservative surgery for symptomatic endometriosis stage III−IV: a randomized controlled trial. *Hum Reprod*. 2001;16:2399–2402.
13. Hornstein MD, Hemmings R, Yuzpe AA, Heinrichs WL. Use of nafarelin versus placebo after reductive laparoscopic surgery for endometriosis. *Fertil Steril*. 1997;68:860–864.
14. Yap C, Furness S, Farquhar C. Pre and post-operative medical therapy for endometriosis surgery. *Cochrane Database Syst Rev*. 2004;2004: CD003678.
15. Kuznetsov L, Dworzynski K, Davies M, Overton C, Guideline Committee. Diagnosis and management of endometriosis: summary of NICE guidance [published correction appears in *BMJ* 2017;358: j4227] *BMJ*. 2017;358:j3935.
16. ETIC Endometriosis Treatment Italian Club. When more is not better: 10 'don'ts' in endometriosis management. An *ETIC** position statement. *Hum Reprod Open*. 2019;2019:hoz009.
17. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Chichester, United Kingdom: John Wiley & Sons; 2011.
18. Wells G, Shea B, O'connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed August 17, 2019.
19. Viswanathan M, Ansari MT, Berkman ND, et al. Assessing the risk of bias of individual studies in systematic reviews of health care interventions.. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. Rockville, MD: Agency for Healthcare Research and Quality (US); 2008.
20. Adachi K, Takahashi K, Nakamura K, et al. Postoperative administration of dienogest for suppressing recurrence of disease and relieving pain in subjects with ovarian endometriomas. *Gynecol Endocrinol*. 2016;32:646–649.
21. Koshiba A, Mori T, Okimura H, et al. Dienogest therapy during the early stages of recurrence of endometrioma might be an alternative therapeutic option to avoid repeat surgeries. *J Obstet Gynaecol Res*. 2018;44:1970–1976.
22. Ota Y, Andou M, Yanai S, et al. Long-term administration of dienogest reduces recurrence after excision of endometrioma. *J Endometr Pelvic Pain Disord*. 2015;7:63–67.
23. Ouchi N, Akira S, Mine K, Ichikawa M, Takeshita T. Recurrence of ovarian endometrioma after laparoscopic excision: risk factors and prevention. *J Obstet Gynaecol Res*. 2014;40:230–236.
24. Takaesu Y, Nishi H, Kojima J, et al. Dienogest compared with gonadotropin−releasing hormone agonist after conservative surgery for endometriosis. *J Obstet Gynaecol Res*. 2016;42:1152–1158.
25. Yamanaka A, Hada T, Matsumoto T, et al. Effect of dienogest on pain and ovarian endometrioma occurrence after laparoscopic resection of uterosacral ligaments with deep infiltrating endometriosis. *Eur J Obstet Gynecol Reprod Biol*. 2017;216:51–55.
26. Chandra A, Rho AM, Jeong K, et al. Clinical experience of long-term use of dienogest after surgery for ovarian endometrioma. *Obstet Gynecol Sci*. 2018;61:111–117.
27. Lee DY, Lee JY, Seo JW, Yoon BK, Choi D. Gonadotropin-releasing hormone agonist with add−back treatment is as effective and tolerable as dienogest in preventing pain recurrence after laparoscopic surgery for endometriosis. *Arch Gynecol Obstet*. 2016;294:1257–1263.
28. Lee SR, Yi KW, Song JY, et al. Efficacy and safety of long-term use of dienogest in women with ovarian Endometrioma. *Reprod Sci*. 2018;25:341–346.
29. Park SY, Kim SH, Chae HD, Kim CH, Kang BM. Efficacy and safety of dienogest in patients with endometriosis: a single-center observational study over 12 months. *Clin Exp Reprod Med*. 2016;43:215–220.
30. Williams C, Long AJ, Noga H, et al. East and South East Asian ethnicity and moderate-to-severe endometriosis. *J Minim Invasive Gynecol*. 2019;26:507–515.
31. Cao Q, Lu F, Feng WW, Ding JX, Hua KQ. Comparison of complete and incomplete excision of deep infiltrating endometriosis. *Int J Clin Exp Med*. 2015;8:21497–21506.
32. Chopin N, Vieira M, Borghese B, et al. Operative management of deeply infiltrating endometriosis: results on pelvic pain symptoms according to a surgical classification. *J Minim Invasive Gynecol*. 2005;12:106–112.
33. Cucinella G, Granese R, Calagna G, et al. Oral contraceptives in the prevention of endometrioma recurrence: does the different progestins used make a difference? *Arch Gynecol Obstet*. 2013;288: 821–827.
34. Vercellini P, Somigliana E, Daguati R, Vigano P, Meroni F, Crosignani PG. Postoperative oral contraceptive exposure and risk of endometrioma recurrence. *Am J Obstet Gynecol*. 2008;198:504.. e1 −504.e5−.
35. Vercellini P, Frontino G, De Giorgi O, Aimi G, Zaina B, Crosignani PG. Comparison of a levonorgestrel-releasing intrauterine device versus expectant management after conservative surgery for symptomatic endometriosis: a pilot study. *Fertil Steril*. 2003;80:305–309.
36. Murji A, Biberoğlu K, Leng J, et al. Use of dienogest in endometriosis: a narrative literature review and expert commentary. *Curr Med Res Opin*. 2020;36:895–907.
37. Heinemann K, Imthurn B, Marions L, Faustmann T. VIPOS: A large non-interventional study examining the safety of dienogest and other hormonal treatments for endometriosis in real-world clinical practice. In: *Poster presented at: The 4th Congress of the Society of Endometriosis and Uterine Disorders; April 25-28*, Florence, Italy; 2018. http://seud.org/wp-content/uploads/2018/06/213-Bittante.pdf Accessed August 17, 2019.
38. Techatraisak K, Hestiantoro A, Ruey S, et al. Effectiveness of dienogest in improving quality of life in Asian women with endometriosis (ENVISIOeN): interim results from a prospective cohort study under real-life clinical practice. *BMC Women's Health*. 2019;19:68.
39. Ebert AD, Dong L, Merz M, et al. Dienogest 2 mg daily in the treatment of adolescents with clinically suspected endometriosis: the VISanne study to assess safety in ADOlescents. *J Pediatr Adolesc Gynecol*. 2017;30:560–567.
40. Momoeda M, Harada T, Terakawa N, et al. Long−term use of dienogest for the treatment of endometriosis. *J Obstet Gynaecol Res*. 2009;35:1069–1076.
41. Seo JW, Lee DY, Yoon BK, Choi D. Effects of long-term postoperative dienogest use for treatment of endometriosis on bone mineral density. *Eur J Obstet Gynecol Reprod Biol*. 2017;212:9–12.