Efficacy of Dienogest for Prevention of Endometriosis Recurrence: A Systematic Review and Meta-Analysis

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Abstract

Aim of Study: To evaluate the efficacy of postoperative dienogest for prevention of endometriosis recurrence.

Methods: Several databases were used to search for recent studies (i.e., published in 2016-2020). The search keywords included: “dienogest,” and “endometr*,” Patients who were not treated with dienogest were considered controls. Reviews, comments, animal trials, case reports, abstracts, single-arm studies, low-quality studies, and non-English articles were excluded. The primary outcome of interest was to determine the odds of recurrence in patients who received dienogest compared to controls who were managed expectantly, or offered a substitute hormonal therapy. Secondary outcomes included pain improvement and side effects of received treatment.

Results: Included studies comprised three retrospective cohort studies, and two prospective cohort studies. These studies included 608 patients; 216 were managed in the Dienogest Group, while 392 were managed in the Control Group (163 received hormonal suppression, and 228 received no treatment). Overall, the recurrence rate of endometriosis in patients receiving Dienogest was 8/216, i.e., 3.7 events per 100 treated women over a mean duration of 28.5 months, and 1.3 recurrences per 1000 woman-months. On the other hand, the recurrence rate of endometriosis in the Control Group was 69/392 recurrences over a mean duration of 29.3 months, i.e., 17.6 per 100 women (6.0 recurrences per 1000 women-months). Difference in recurrence rates between study groups was statisticallysignificant (X^2=24.3, p<0.001). Reported recurrence rates were significantly less among patients in the Dienogest Group than those in the Control Group, with a pooled estimate of RR = 0.239, and 95% CI: 0.119-0.488. Generally, patients in the Dienogest Group experienced less pain and less side effects than those in the control group.

Conclusions: Endometriosis patients who receive dienogest following conservative surgery have a significantly lower rate of recurrence, better pain control, and less side effects than their control counterparts.

Key Words: Endometriosis, Dienogest, Goserelin, Systematic Review, Meta-Analysis,

Introduction

Endometriosis is a chronic, estrogen-dependent disease that affects 10-15% of women in their reproductive age (1). It is characterized by the presence of endometrial-like tissues outside the uterine cavity that induce chronic inflammation, ovarian cyst formation, and fibrosis (2). Dysmenorrhea and chronic non-menstrual pelvic pain are the most prevalent symptoms. A common pathogenic mechanism shared by all forms of endometriosis is the impact of estradiol (3).

The licensed pharmaceutical agents for treatment of endometriosis are still limited (4). For medical treatment of endometriosis associated pain is based on suppression of estrogen production and induction of amenorrhea (5), and treatments are often accompanied by clinically relevant side effects (6).

Dienogest is a unique 4th generation synthetic progestogen, which has been approved as a treatment for endometriosis and as part of combined hormonal contraception (7). Studies have demonstrated its high specificity for progesterone receptors, strong anti-proliferative effects on endometriosis implants, as well as anti-androgenic, anti-angiogenic, and anti-inflammatory properties (8).

Dienogest has high tolerability and effectiveness. Therefore, it has become an important choice for management of endometriosis (9). Until recently, dienogest has been the only available oral, disease-specific agent in the treatment of endometriosis (10).

Several medications, besides dienogest have been investigated for prevention of recurrence of endometriosis, e.g., the combined hormonal contraception, levonorgesterel intra-uterine contraceptive device, and GnRH-a therapy, with varying degrees of success (11-12). However, the choice of medication is dependent upon many factors including patient, clinician, and disease characteristics.

A systematic review evaluating the evidence for post-operative hormonal suppression for endometriosis revealed no evidence of decreased disease recurrence; however, data were limited, and none examined the use of dienogest (13). Nevertheless, guidelines and expert opinion continue to recommend the use of post-operative suppression for secondary prevention (14).

Therefore, the present systematic review and meta-analysis was undertaken to evaluate the efficacy of postoperative dienogest for prevention of endometriosis recurrence.

Materials and Methods

Search Strategy

The PubMed, Medline, and EMBASE databases were used to search for recent studies (i.e., published between 2016-2020). The search keywords included: “dienogest,” and “endometr*,” Types of included studies were retrospective, prospective studies and randomized controlled trials that compared dienogest treatment (G1, study group) with other treatments (G2, Control Groups) in patients with endometriosis following surgery.

The researchers started by reading the titles and abstracts of retrieved articles, then reviewing the full text of relevant articles. Studies were included if they met the following inclusion criteria: Full text, English language, patients are premenopausal women undergoing surgery for endometriosis, one group is treated with dienogest, and at least one group who received other treatments, regardless of dosage, duration of treatment, and adverse effects. All included patients should have been followed up for at least 12 months postoperatively.

Patients who were not treated with dienogest were considered controls. On the other hand, reviews, comments, animal trials, case reports, abstracts, single-arm studies, low-quality studies, and non-English articles were excluded.

The primary outcome of interest in this systematic review and meta-analysis was to determine the odds of recurrence in patients who received dienogest compared to controls who were managed expectantly, or offered a substitute hormonal therapy. Recurrence was defined by three studies (15-17) as the ultrasound detection of an ovarian endometrioma measuring greater than 2 cm in diameter in the treated ovary; by one study (18) as an endometrioma that was larger than 20 mm in diameter on transvaginal ultrasonography and persisted for more than 2 months; and by one study (19) as the presence of a persistent ovarian cyst with a minimum diameter of > 15 mm based on non-invasive imaging (e.g., ultrasound and MRI),

On the other hand, secondary outcomes included pain improvement and side effects of received treatment.

The guidelines for the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) were followed to conduct this systematic review of the literature. Given the nature of the present study, with no involvement of direct patient engagement, an Institutional Review Board approval was not a necessary prerequisite for the completion of this study.

Two researchers (HA and MO) independently reviewed articles’ titles and abstracts for initial screening, and then conducted full text reviews to identify studies for inclusion. Any conflicts were resolved by a third reviewer (ME).

Extracted data were analyzed with 95% confidence interval using the Statistical Package for Social Sciences (IBM, SPSS, version 25). Relative risk of recurrence was calculated and reported in addition to 95% confidence interval.

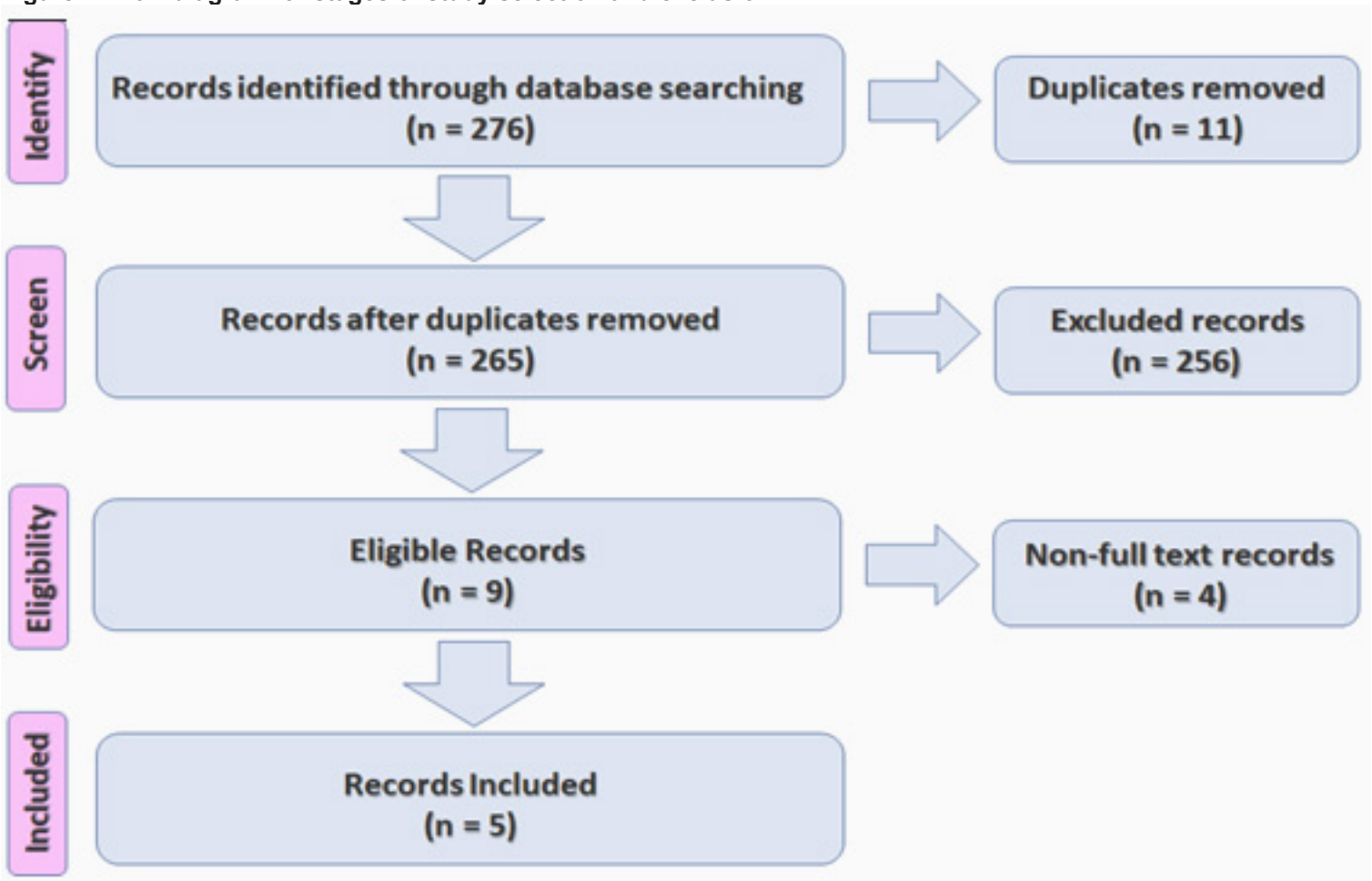
Results

Study Selection and Characteristics
The initial database search yielded 276 studies. However, after exclusion of duplicates, title and abstract screening, and applying the inclusion criteria, five studies, which had both intervention and control arms, were assessed for full text review (Figure 1). The exclusions were based on: the outcome of interest (i.e., recurrence) was not assessed, data could not be extracted, intervention did not meet the study criteria, or heterogeneous study population. Study characteristics and main results are summarized and presented in Table (1).

Included studies comprised three retrospective cohort studies, and two prospective cohort studies, but no controlled trials were included. These studies included 608 patients; 216 were managed in the Dienogest Group, while 392 were managed in the Control Group (163 received hormonal suppression, and 228 received no treatment).

Follow-up period and assessment of outcomes ranged from 12 months (17) to 60 months (18). The mean follow-up period was 28.5 months.

Figure 1: Flow diagram for stages of study selection and exclusion



Primary outcome
Overall, the recurrence rate of endometriosis in patients receiving Dienogest was 8/216, i.e., 3.7 events per 100 treated women over a mean duration of 28.5 months, and 1.3 recurrences per 1000 woman-months. On the other hand, the recurrence rate of endometriosis in the Control Group was 69/392 recurrences over a mean duration of 29.3 months, i.e., 17.6 per 100 women (6.0 recurrences per 1000 women-months). Difference in recurrence rates between study groups was statistically significant (X^2=24.3, p<0.001).

Within the Control Group, women who received hormonal suppression (n=163) had 28 recurrences (i.e., 17.2 events per 100 women, and 5.7 recurrences per 1000 woman-months), while those who received no treatment (n=229) had 41 recurrences (i.e., 17.9 events per 100 women, and 5.7 recurrences per 1000 woman-months). Difference in recurrence rates between these two groups was not statistically significant (X^2 =0.03, p=0.852).

Figure 2: Forest Plot for recurrence rates among patients in the Dienogest and Control Groups

Study	Dienogest(n/N)	Control (n/N)	RR	95% CI
Adachi et al., 2016	0/40	8/41	0.072	0.004-1.206
Takaesu et al., 2016	4/55	25/134	0.431	0.157-1.187
Yamanaka et al., 2017	3/59	21/67	0.203	0.063-0.650
Koshiba et al., 2018	1/27	15/115	0.310	0.043-2.248
Ozaki et al., 2020	0/35	0/35	1.000	0.020-49.042

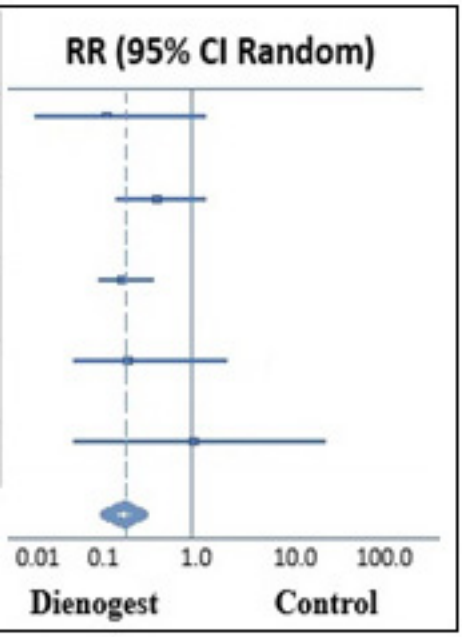


Figure (2) shows reported recurrence rates were significantly less among patients in the Dienogest Group than those in the Control Group, with a pooled estimate of RR = 0.239, and 95% CI: 0.119-0.488.

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Secondary outcomes

Regarding pain improvement, one study reported experiencing significantly less pain among patients in the Dienogest Group than those in the Control Group (16). Another study reported that pain was reduced in patients receiving Dienogest & Goserelin, while a third study reported reduced pain in patients receiving Dienogest (19). Moreover, side effects of received treatment were stated by one study (15), which reported less side effects among patients receiving dienogest than those receiving goserelin.

Discussion

Endometriosis is a chronic disease characterized by high rates of post-operative recurrence. Therefore, patients need safe, long-term maintenance options for its management (20).

The present systematic review and meta-analysis included five studies (three retrospective cohort, and two prospective cohort). It included 608 patients, of whom 216 were managed in the Dienogest Group, while 392 were managed in the Control Group (163 received hormonal suppression, and 228 received no treatment). The follow up period of studies included in the present systematic review ranged from 12 to 60 months, with an average of 28.5 months. The two groups had comparable average durations of follow up (29 months and 29.3 months).

By the end of the follow-up periods, it was shown that side effects of dienogest were less than those associated with hormonal suppression or goserelin, while experienced pain was less among patients in the Dienogest Group than those in the Control Group.

Our systematic review showed significantly lower endometriosis recurrence rates among patients in the Dienogest Group (8/216, i.e., 3.7 events per 100 treated women over a mean duration of 30.4 months, and 1.23 recurrences per 1000 woman-months) than those in the Control Group (8/216 and 69/392 respectively, p<0.001), while, recurrence rates within the Control Group (patients receiving hormonal suppression vs. those not receiving treatment) did not differ significantly (28/163 and 41/229, respectively). These findings support the use of dienogest for postoperative management of endometriosis.

Murji et al. (21) noted that there are limited data, as far as the long-term experience with dienogest treatment, with most studies extending to 15 months of treatment. Zakhari et al. (7) described two large-scale post-approval studies that are still underway, which are evaluating the safety and tolerability of dienogest for management of endometriosis over extended periods of time (i.e., up to 6 years) (22-23). Results of these two studies are expected to guide counselling and clinical decision making of patients with endometriosis.

Despite the finding in our systematic review, that women who received dienogest had significantly better outcome than those in the control group, medical options that were used by women in the control group, e.g., combined hormonal contraceptives (18), and gonadotrophin-releasing hormone agonist (i.e., goserelin) have also shown favorable effects, e.g., reducing recurrence and pain symptoms (15; 17). This offers both clinicians and patients the option to tailor prescribed suppressive therapy to individual needs (15; 24-25).

However, some studies raised concerns over bone mineral density changes associated with prolonged use of dienogest. Decreased bone mineral density has been reported with prolonged treatment (up to 52 weeks). However, partial recovery was observed to follow cessation of its use, but the clinical significance of these findings is still uncertain (26-28). Therefore, further long-term studies on the possible side effects associated with dienogest therapy are needed.

The strength features of our systematic review include the systematic nature of the literature review, which elicited clinically relevant outcomes with follow-up that ranged from 12 to 60 months. Moreover, the broad inclusion criteria enabled us to synthesize relevant outcome data from different studies.

However, it is to be noted that "recurrence" was defined radiologically by all included studies. However, Zakhari et al. (7) argued that this limited definition may give rise to lower sensitivity, with under-reporting of recurrence of endometriosis among patients' with lesions that are undetectable by imaging, or alternatively, it may give rise to lower specificity, by inflating a truly lower risk of recurrence for other clinical forms of endometriosis. They stressed that, beside radiological endpoints, the definition of recurrence must also include patient symptoms such as pain (e.g., dysmenorrhea, or pelvic pain), or clinical findings.

Moreover, the research design of studies included in our systematic review was mainly retrospective (three studies). This may raise the possibility of selection bias, since patients with more extensive endometriosis may have preferentially received suppressive therapy, and become more encouraged to comply with long-term treatment.

It is also to be noted that, one of the studies included in our systematic review (19) used dienogest medication in one arm and there was no alternative treatment in the control arm. This design allows for the possible placebo-effect to contribute to the perceived efficacy of dienogest administered to the treatment group.

Conclusion

Patients who receive dienogest following conservative surgery for endometriosis have a significantly lower rate of recurrence, better pain control, and less side effects than their untreated counterparts or those receiving treatment with hormonal suppressive drugs or oral contraceptives. In view of our findings, further studies are needed to determine the feasibility and side effects of long-term treatment with dienogest, to identify whether a particular group of patients is more likely to benefit from dienogest, and to specify the optimal postoperative medical regimen associated with less disease recurrence.

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Table 1: Summary of the main results of included studies

Study	Research design	Dienogest (G1)		Control (G2)			Recurrence (G1)/(G2)	Pain	Side Effects
		No.	FU	Received treatment	No.	FU			
Adachi et al., 2016	Retrospective	40	21	Expectant management	41	18.6	(0)/(8)	G2>G1	--
Takaesu et al., 2016	Prospective	55	24	Goserelin/ No treatment	134: 55/79	24	(4)/(8,17)	Reduced in patients receiving Dienogest & Goserelin	Goserelin more than Dienogest
Imanaka et al., 2017	Retrospective	59	35	No treatment	67	28	(3)/(21)	Reduced in G1	--
Koshiba et al., 2018	Retrospective	27	60	Oral contraceptives/ No treatment	115: 32/83	60	(1)/(12,3)	Not stated	Not stated
Ozaki et al., 2020	Prospective	35	12	Low-dose sustained-release goserelin acetate	35	12	(0)/(0)	Not stated	Not stated
Overall		216	28.5	Hormonal suppression/ No treatment	392: 163/229	29.3: 30.4/28.5	(8)/(28,41)	G2 more than G1	G2 more than G1

FU: Mean follow up period (in months) G1: Dienogest Group G2: Control Group