# The effect of dienogest treatment on anti-Mullerian hormone in patients with endometrioma: a 12-month follow-up study

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## *Abstract*

**Objective:** To assess the effect of dienogest treatment on endometrioma (OMA) size, serum anti-Mullerian hormone (AMH) levels and associated pain over a 12-month follow-up period.

**Material and Methods:** A longitudinal cohort study of 104 patients with OMA who were treated with dienogest, between January 2017 and January 2020. Of the included patients, each had a 12-month follow-up period with transvaginal or pelvic ultrasound and measurement of serum AMH concentration at the sixth and twelfth months of follow-up. The alteration in OMA size in the sixth and twelfth months of treatment was the primary outcome measure and the alteration in AMH concentration over the same period was the secondary outcome measure. The only exclusion criterion was having surgical intervention for OMA during the follow-up period (n=44). In patients with bilateral OMA (n=21), the change in size of the largest OMA was considered in the analysis.

**Results:** A total of 60 patients with a mean ± standard deviation (SD) age of 31.5±8.0 years were included. The mean ± SD OMA size on the day the dienogest was started was 46.3±17.4 mm and the mean AMH level was 3.6±2.4 ng/mL. After six months, the mean OMA size had decreased to 38.6±14.0 mm, with a median difference of 7.8 mm [95% confidence interval (CI): 3.0 to 12.6; p=0.003]. The mean AMH level was 3.3±2.7 ng/mL at 6 months follow-up (95% CI: -0.2 to 0.8; p=0.23) and the average difference was 0.3 ng/mL. At the 12$^{th}$-month visit, when compared with the beginning of the treatment, OMA size had again significantly decreased by a median of -8.9 mm (95% CI: -2.9 to -14.9; p=0.005), and the decline in median AMH was also significant (-0.9 ng/mL, 95% CI: -0.1 to -1.7; p=0.045). The initial mean ± SD visual analog scale pain score at the commencement of dienogest treatment was 6.3±3.4. The mean values at the sixth and twelfth months of dienogest therapy were 1.08±1.8 and 0.75±1.5, respectively (both p<0.001 compared to baseline).

**Conclusion:** At the sixth and twelfth months of dienogest treatment a significant decrease in OMA size and reported pain scores were observed, whereas the AMH concentrations did not change significantly. (J Turk Ger Gynecol Assoc 2024; 25: 102-6)

**Keywords:** Endometrioma, anti-Mullerian hormone, dienogest, pelvic pain, ovarian reserve

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## Introduction

Endometriosis is a chronic disorder that affects approximately 2-10% of women throughout the reproductive years (1,2). Whereas endometriosis is often associated with pain-related symptoms, including dysmenorrhea, dyspareunia, and dyschezia, a significant portion of women do not have any symptoms (3,4). Among patients with endometriosis, 17-44% may have visible ovarian endometrioma (OMA) on ultrasonography (US) that represents a more severe stage of the disease, according to the revised American Society of Reproductive Medicine staging (5,6). OMA may be associated

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with infertility and hence approximately 40% of infertile women with endometriosis are reported to have visible OMA cysts (7).

The optimal management of OMA during the reproductive years is controversial. The preferred strategy depends on the patient's age, desire for childbearing, severity of pain-related symptoms, presence of bilaterality, and suspicion of malignancy (8,9). Given the high success rate for pain-related symptoms and lack of any harm to the ovarian reserve, medical treatments may be considered in patients with moderate-severe symptoms who do not have any desire to preserve fertility. Among the available medical treatment options, combined contraceptive pills or progestin-only drugs, with or without non-steroidal anti-inflammatory drugs, may be the first choice due to the low complication rate and high patient compliance (10). Although dienogest is one of the options within the group of progestin-only drugs, there are constrained statistics approximately its effect on the scale of the OMA and therefore serum anti-Mullerian hormone (AMH) concentration in the course of 365 days of compliance with up.

In the present study, the aim was to investigate if there were statistically significant changes in the volume of OMA, AMH levels and associated symptoms at one-year follow-up in patients with OMA on dienogest.

## Material and Methods

### Patients and study design

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (approval number: 2021/09-30, date: 20.04.2021). Informed consent was obtained from all patients participating in the study.

In the current observational cohort study, consecutive patients with a diagnosis of OMA and treated with dienogest (Visanne, Bayer, İstanbul, Turkey) between January, 2017 to January, 2020 at university department of obstetrics and gynecology were recruited. The inclusion criteria were being between the ages of 20 and 45 years, no patient desire to preserve fertility, and the preferred medical treatment was dienogest alone. The exclusion criteria were history of any surgical treatment (cystectomy, cyst aspiration/fenestration or sclerotherapy) before the study period, use of the combined contraceptive pill in the three months preceding the study and suspicious of malignancy as suggested by US.

All included patients received 2 mg orally dienogest per day for at least 12 months. Data concerning the largest OMA cyst diameter on US, serum AMH measurement and visual analog scale (VAS) from 0 to 10 (0: no pain to 10: unbearable pain) were collected. Patients were asked about pelvic pain (dysmenorrhea, or non-cyclic pelvic pain) at the beginning, sixth, and twelfth months of dienogest treatment. Serum AMH was measured with the Elecsys AMH assay (Roche Diagnostic International, IN, USA.) All examination with US was conducted by a single physician (G.B.).

### Statistical analysis

A retrospective analysis of prospectively collected data was conducted using SPSS, version 23 (IBM Inc., Chicago, IL, USA). The paired t-test was employed to compare numerical values, and a statistical significance level of $p<0.05$ was used.

## Results

Of 104 patients, 44 (42.3%) were excluded and 60 patients were analyzed. The mean ± standard deviation (SD) of age was 31.5±8.0 years. Demographics of the study population are presented in Table 1. At the start of dienogest treatment, the mean largest diameter of the OMAs was 46.3±17.4 mm, and the mean serum AMH concentration was 3.6±2.4 ng/mL. The main symptoms observed among patients were: dysmenorrhea (26.7%), chronic pelvic pain (41.7%), and menstrual irregularity (13.3%). A total of 30% of the patients did not exhibit any symptoms.

After six months of treatment, the mean OMA size decreased to 38.6±14.0 mm, with a mean difference of 7.8 mm

**Table 1. Study population characteristics at baseline**

| **Characteristics** | |
|---|---|
| Number of patients | 60 |
| Age, years | 31.5±8.0 |
| Body mass index, kg/m$^2$ | 23.4±4.0 |
| **Symptoms, n (%)** | |
| Dysmenorrhea | 16 (26.7) |
| Chronic pelvic pain | 25 (41.7) |
| Menstrual irregularity | 8 (13.3) |
| Asymptomatic | 18 (30.0) |
| VAS score at baseline | 6.3±3.4 |
| **Ultrasound type, n (%)** | |
| Transvaginal | 32 (53.3) |
| Pelvic ultrasound | 28 (46.7) |
| Baseline endometrioma size, mm | 46.3±17.4 |
| Patients with bilateral endometrioma, n (%) | 21 (35%) |
| Baseline AMH, ng/mL | 3.6±2.4 |
| VAS: Visual analog score, AMH: Anti-Mullerian hormone | |

**Table 2. Comparison of mean endometrioma diameters, AMH levels and VAS scores at baseline, six months, and 12 months of treatment with dienogest**

| Measurements | Baseline | 6 months | Percentage change in mean value | p at six-months versus baseline* | 12 months | Percentage change in mean value | p-value 12 months versus baseline* |
|---|---|---|---|---|---|---|---|
| Endometrioma diameter (mm) | 46.3±17.4 | 38.6±14.0 | 16.6 | 0.003 | 37.5±15.7 | 19 | 0.005 |
| AMH level (ng/mL) | 3.6 ± 2.4 | 3.3±2.7 | 8.3 | 0.23 | 2.7±1.9 | 25 | 0.045 |
| Endometriosis-related VAS pain score | 6.3±3.4 | 1.08±1.8 | 82.8 | 0.001 | 0.75±1.5 | 88.1 | 0.001 |

*Student's t-test, values are presented as mean ± standard deviation. AMH: Anti-Mullerian hormone, VAS: Visual analog scale

[95% confidence interval (CI): 3.0 to 12.6; p=0.003]. The mean AMH level was 3.3±2.7 ng/mL, with a mean difference of 0.3 ng/mL (95% CI: -0.2 to 0.8; p=0.23).

After 12 months of treatment, the mean OMA diameter was 37.5±15.7 mm, with a mean difference of 8.9 mm (95% CI: 2.9 to 14.9; p=0.005). Similarly, the mean AMH concentration was 2.7±1.9 ng/mL, with a mean difference of 0.9 ng/mL (95% CI: 0.1 to 1.7; p=0.045) at 12 months compared to baseline. However, there was no significant difference in the OMA diameter or AMH concentration between the sixth and twelfth months of treatment measurements. OMA size at baseline, six, and twelve months of dienogest treatment was presented in Figure 1.

Serum AMH concentration at baseline, six, and twelve months of dienogest treatment was shown in Figure 2.

In the study population, at the beginning of the dienogest treatment, mean ± SD VAS score was 6.3±3.4. There was a significant improvement in VAS scores at both the sixth and twelfth months compared to baseline (1.08±1.8; p<0.001 and 0.75±1.5; p<0.001, respectively). Table 2 presents the changes in the OMA dimensions, AMH levels and endometriosis-related VAS pain score at baseline, six, and 12 months.

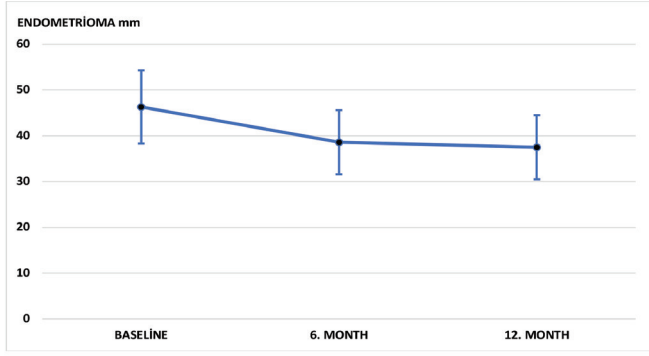


**Figure 1. OMA size (mm) at baseline, six, and twelve months of dienogest treatment (mean ± SD)**
***OMA: Endometrioma, SD: Standard deviation***

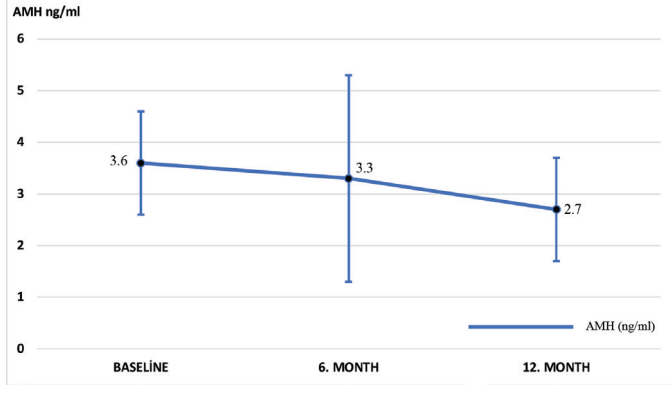


**Figure 2. Serum AMH (ng/mL) concentration at baseline, six, and twelve months of dienogest treatment (mean ± SD)**
***AMH: Anti-Mullerian hormone, SD: Standard deviation***

## Discussion

In the current study, there was a significant decrease in the largest diameter of OMA after 12 months of treatment with 2 mg of dienogest daily in which the largest proportional change was seen over the first six months of treatment. However, serum AMH concentration showed a slight and insignificant decline at the end of 12 months when compared with initial levels. Notably, endometriosis-related pain symptoms decreased significantly at both six and 12 months of treatment compared to baseline.

The optimal management for preserving ovarian reserve, reflecting the primordial follicle pool, is unclear among patients with OMA cysts. In a recent systematic review and meta-analysis, the authors reported that the presence of an ovarian OMA was associated with a decreased number of antral follicles (11). Although those findings might be attributed to the obstacles to clear visualization of antral follicles with US, Kitajima et al. (11) found that the follicular density in the ovary with OMA was significantly lower and the number of atretic early follicles were higher when compared with the contralateral unaffected ovary (12). These results suggest that there might be a genuine decrease in the number of antral follicles in women

with OMA, rather than a practical issue in the visualization. In the current analysis, based on a high inter-cycle variability of antral follicle count (13), and its inherent drawbacks, such as operator dependency, we preferred to follow the patients with AMH instead.

In the context of a comparison with non-endometriotic ovarian cysts, a systematic review and meta-analysis showed that the presence of an ovarian OMA was associated with a significant decrease in serum AMH levels when compared with otherwise healthy women (11). Furthermore, in a prospective cohort study by Kasapoglu et al. (13), it was noted that the serum AMH value decreased at the sixth month with the expectant observation of the patient with OMA (n=40), which was significantly higher than in an age-matched healthy control group (7.4%, n=40, p=0.01) (14). However, an observational cross-sectional study including 267 patients showed that serum AMH levels increased with OMA size in women without prior history of surgery (15). More recently, a follow-up study of 332 women with OMA, mainly size >6 cm, and regardless of age or bilaterality had significantly elevated preoperative AMH levels were significantly elevated, thus confirming these earlier findings (16). As high AMH concentrations in women with large ovarian OMAs have been reported in two different populations of women suffering from endometriosis by different teams, such an unexpected pattern might be explained by two hypotheses: 1) an increased leakage to the circulatory system due to increased local blood clearance boosted by an increase in ovarian blood flow associated with inflammation and neoangiogenesis in the nearby cortical tissue (15); and/or 2) expanded production of AMH from dysfunctional granulosa cells because of altered micro-environment because of increased expression of genes in the prostaglandin and corticosteroid pathways, in increased transformation of the cellular cytoskeleton, histone adjustments and DNA methylation at particular genes involved in steroidogenesis (17).

Dienogest is a fourth-generation progestogen and the only oral, disease-specific treatment for endometriosis. Given its excessive tolerability and efficacy, dienogest has become an essential choice for the treatment of endometriosis. Studies have shown that dienogest has high specificity for progesterone receptors; it exhibits antiandrogenic, antiproliferative, antiangiogenic and anti-inflammatory effects in endometriotic implants (18,19). Although dienogest has been reported to yield a significant reduction in OMA size/volume (20) its role on the dynamics of AMH is relatively less well known. According to the only study published to date, a reduction of 40% in diameter of OMA was observed in 32 patients without any change in AMH concentration when compared with baseline levels (21). As our study with a slightly larger sample size confirmed, the lack of any drop and even the presence of a plateau in AMH concentration after six months, one may suggest that dienogest may be useful to halt or at least slow-down the classical decrease in AMH concentration in the short term.

In theory, the observed improvement in the expected decline of AMH concentration might be related to decreased inflammation and angiogenesis in nearby cortical tissue or recovery of granulosa cell function due to an altered micro-environment after administration of dienogest. Further preclinical studies are needed to address the exact interaction between the endometriotic tissue lining the internal surface of OMAs and the closely associated tissues of the ovarian cortex.

Seven out of ten women diagnosed with endometriosis have abdominal pelvic pain, dysmenorrhea, or menorrhagia. Pelvic pain significantly affects the quality of life and has an important place in the treatment of endometriosis (22). Dienogest has demonstrated equal efficacy to GnRH analogues in the treatment of endometriosis and is efficient in alleviating endometriosis-related pain (23). Strowitzki et al. (23), in a double-blind placebo-controlled study, showed that dienogest was significantly more effective than placebo in reducing endometriosis-related pelvic pain over 12 weeks in 198 women (24). In their prospective cohort study with 37 patients, Kizilkaya et al. (25) demonstrated a 31% reduction in OMA size over a three-month follow-up period among individuals receiving dienogest 2 mg/day. Furthermore, there was a significant decrease in pain scores, including a 35.5% reduction in dysmenorrhea VAS score, a 37.5% reduction in dyspareunia VAS score, and a 38.5% reduction in chronic pelvic pain VAS score (25). In the current study and concordant with the literature, a significant reduction in pain scores was observed at the sixth and twelfth months of treatment compared with baseline VAS scores.

The lack of a control group limits the possibility of drawing firm conclusions about the efficacy and effectiveness of a particular treatment or intervention. However, as there is earlier evidence of the pattern of AMH in patients without any treatment (11), we believe that the results of AMH concentrations at certain time-points after commencement of dienogest is still useful. The second limitation might be the retrospective design of the study and its inherent drawback, but the paucity of data with respect to a follow up of 12-months makes the results of the study clinically informative.

## Conclusion

In conclusion, daily administration of 2 mg of dienogest resulted in a significant decrease in the diameter of OMA after six months of treatment. Furthermore, there was a significant change in mean AMH concentrations after 12 months of treatment. This latter finding may be related to an

improvement in inflammation and angiogenesis in the nearby non-endometriotic cortical tissue.

***Ethics Committee Approval:*** *The study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (approval number: 2021/09-30, date: 20.04.2021).*

***Informed Consent:*** *Informed consent was obtained from all patients participating in the study.*

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## References

1. Abbas S, Ihle P, Köster I, Schubert I. Prevalence and incidence of diagnosed endometriosis and risk of endometriosis in patients with endometriosis-related symptoms: findings from a statutory health insurance-based cohort in Germany. Eur J Obstet Gynecol Reprod Biol 2012; 160: 79-83.
2. Nnoaham KE, Hummelshoj L, Webster P, d'Hooghe T, de Cicco Nardone F, de Cicco Nardone C, et al.; World Endometriosis Research Foundation Global Study of Women's Health consortium. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. Fertil Steril 2014; 101: 927-35.
3. The Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis: a committee opinion. Fertil Steril 2014; 101: 927-35.
4. Practice Committee of the American Society for Reproductive Medicine. Endometriosis and infertility: a committee opinion. Fertil Steril 2012; 98: 591-8.
5. Farquhar C. Endometriosis. Clin Evid 2004; 2391-405.
6. Chapron C, Vercellini P, Barakat H, Vieira M, Dubuisson JB. Management of ovarian endometriomas. Hum Reprod Update 2002; 8: 591-7.
7. Bulun SE, Yilmaz BD, Sison C, Miyazaki K, Bernardi L, Liu S, et al. Endometriosis. Endocr Rev 2019; 40: 1048-79.
8. Leyland N, Casper R, Laberge P, Singh SS; SOGC. Endometriosis: diagnosis and management. J Obstet Gynaecol Can 2010; 32(7 Suppl 2): S1-32.
9. Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, et al.; European Society of Human Reproduction and Embryology. ESHRE guideline: management of women with endometriosis. Hum Reprod 2014; 29: 400-12.
10. Ferrero S, Evangelisti G, Barra F. Current and emerging treatment options for endometriosis. Expert Opin Pharmacother 2018; 19: 1109-25.
11. Muzii L, Di Tucci C, Di Feliciantonio M, Galati G, Di Donato V, Musella A, et al. Antimüllerian hormone is reduced in the presence of ovarian endometriomas: a systematic review and meta-analysis. Fertil Steril 2018; 110: 932-940.e1.
12. Kitajima M, Defrère S, Dolmans MM, Colette S, Squifflet J, Van Langendonckt A, et al. Endometriomas as a possible cause of reduced ovarian reserve in women with endometriosis. Fertil Steril 2011; 96: 685-91.
13. Subirá J, Alberola-Rubio J, Núñez MJ, Escrivá AM, Pellicer A, Montañana V, et al. Inter-cycle and inter-observer variability of the antral follicle count in routine clinical practice. Gynecol Endocrinol 2017; 33: 515-8.
14. Kasapoglu I, Ata B, Uyaniklar O, Seyhan A, Orhan A, Yildiz Oguz S, et al. Endometrioma-related reduction in ovarian reserve (ERROR): a prospective longitudinal study. Fertil Steril 2018; 110: 122-7.
15. Chapron C, Marcellin L, Borghese B, Santulli P. Rethinking mechanisms, diagnosis and management of endometriosis. Nat Rev Endocrinol 2019; 15: 666-82.
16. Roman H, Chanavaz-Lacheray I, Mircea O, Berby B, Dehan L, Braund S, et al. Large ovarian endometriomas are associated with high pre-operative anti-Müllerian hormone concentrations. Reprod Biomed Online 2021; 42: 158-64.
17. Sanchez AM, Viganò P, Somigliana E, Cioffi R, Panina-Bordignon P, Candiani M. The endometriotic tissue lining the internal surface of endometrioma: hormonal, genetic, epigenetic status, and gene expression profile. Reprod Sci 2015; 22: 391-401.
18. Lamb YN. Elagolix: First Global Approval. Drugs 2018; 78: 1501-8.
19. Laganà AS, Vitale SG, Granese R, Palmara V, Ban Frangež H, Vrtačnik-Bokal E, et al. Clinical dynamics of Dienogest for the treatment of endometriosis: from bench to bedside. Expert Opin Drug Metab Toxicol 2017; 13: 593-6.
20. Vignali M, Belloni GM, Pietropaolo G, Barbasetti Di Prun A, Barbera V, et al. Effect of Dienogest therapy on the size of the endometrioma. Gynecol Endocrinol 2020; 36: 723-7.
21. Muzii L, Galati G, Di Tucci C, Di Feliciantonio M, Perniola G, Di Donato V, et al. Medical treatment of ovarian endometriomas: a prospective evaluation of the effect of dienogest on ovarian reserve, cyst diameter, and associated pain. Gynecol Endocrinol 2020; 36: 81-3.
22. Ballard KD, Seaman HE, de Vries CS, Wright JT. Can symptomatology help in the diagnosis of endometriosis? Findings from a national case-control study--Part 1. BJOG 2008; 115: 1382-91.
23. Andres Mde P, Lopes LA, Baracat EC, Podgaec S. Dienogest in the treatment of endometriosis: systematic review. Arch Gynecol Obstet 2015; 292: 523-9.
24. Strowitzki T, Faustmann T, Gerlinger C, Seitz C. Dienogest in the treatment of endometriosis-associated pelvic pain: a 12-week, randomized, double-blind, placebo-controlled study. Eur J Obstet Gynecol Reprod Biol 2010; 151: 193-8.
25. Kizilkaya Y, Ibanoglu MC, Kıykac Altinbas S, Engin-Ustun Y. A prospective study examining the effect of dienogest treatment on endometrioma size and symptoms. Gynecol Endocrinol 2022; 38: 403-6.