



Effects of Dienogest Only Treatment on Lipid Profile

Dienogest Tedavisinin Lipid Profili Üzerindeki Etkileri

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ABSTRACT

Objective: Metabolic effects of dienogest (DNG) may lead to unintended lipid levels, which may predispose to cardiovascular diseases. The main objective of this study was to reveal effects of DNG only treatment on lipid profile.

Methods: Thirty three otherwise healthy women with diagnosed endometriosis were started on 2 mg dienogest/day oral treatment. Blood samples were taken before and after 6 months of therapy to measure triglycerides (TG) low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and total cholesterol levels. Exclusion criteria were withdrawal from DNG treatment, pregnancy, women with incomplete medical records or who were lost to follow-up, allergies for DNG, need for laparoscopy during the 6-month of medical treatment, having familial lipid disorders, and body mass index (BMI) >30 kg/m².

Results: There was no significant difference regarding total cholesterol, HDL, and LDL levels between the blood samples taken before and after DNG treatment. However, TG levels were significantly higher at 6th-month blood samples than the pre-DNG blood samples (94 vs. 75, p=0.03). The mean age was 31.4±4.8 years, gravidity was 1.8±1.3, parity was 1.6±1.1, and BMI was 24.6±1.8 (kg/m²).

Conclusion: Our results suggest that DNG treatment increases TG levels. The metabolic effects of DNG should be clarified as being widely used among women as a progestin-only regimen. Alterations in lipid metabolism may affect the use of this drug in patients with metabolic syndrome or hyperlipidemia.

Keywords: Dienogest, hyperlipidemias, progesterone, endometriosis

ÖZ

Amaç: Dienogest (DNG) kullanımı kan lipid seviyelerinde istenmeyen değişikliklere sebep olarak kardiyovasküler hastalık riskini artırabilir. Bu çalışmanın amacı tek başına DNG kullanımının lipid profiline olan etkisini araştırmaktır.

Gereç ve Yöntem: Endometriosis tanısı almış ve ek hastalığı bulunmayan 33 hastaya 2 mg/gün dozunda DNG tedavisi başlanmıştır. Tedavi başlangıcından önce ve tedavinin 6. ayında venöz kanda trigliserid (TG), düşük yoğunluklu lipoprotein (LDL) kolesterol, yüksek yoğunluklu lipoprotein (HDL) kolesterol ve total kolesterol seviyeleri ölçülmüştür. Dışlanma kriterleri ise şunlardır: Tedaviyi bırakmak, gebelik, eksik tıbbi kayıtlar, DNG alerjisi, medikal tedavi sırasında operasyon geçirmek, ailevi lipid hastalığı bulunması ile vücut kitle indeksi (VKİ) > 30 kg/m².

Bulgular: Total kolesterol, HDL kolesterol ve LDL kolesterol seviyelerinde tedavi öncesi ve sonrası arasında anlamlı fark gözlenmemiştir. TG seviyelerinde ise DNG tedavisi öncesi ve 6. ay arasında anlamlı fark mevcuttur (94 vs. 75, p=0,03). Ortalama yaş 31,4±4,8, gravide 1,8±1,3, parite 1,6±1,1, ve VKİ 24,6±1,8'dir (kg/m²).

Sonuç: Çalışmamızın sonuçları DNG tedavisinin TG seviyelerini yükselttiğini göstermektedir. DNG, yalnızca progesteron içeriği ile yaygın bir şekilde kullanılmaktadır ve metabolik etkileri hakkında daha net bilgilere ihtiyaç duyulmaktadır. Bu molekülün kullanımında lipid profilinde görülen değişimler, metabolik sendrom veya ailesel hiperlipidemi gibi ek hastalıkları olan kadınların ilacı kullanması hakkındaki durumu da değiştirebilir.

Anahtar Kelimeler: Dienogest, lipid profili, progesteron, endometriozis

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INTRODUCTION

Endometriosis is a chronic disease affecting approximately 10% of reproductive-age women (1). It can cause various problems, such as chronic pelvic pain, infertility, dyspareunia, and dysmenorrhea (1). To manage this common complex disorder, medical and surgical treatments are could be used. Although surgery seems to be a quick treatment option, the current data are contrary since the recurrence rates could be as much as 40-50% and may also diminish ovarian reserve (2). Medical treatment is commonly referred to as the first-line option, especially in adolescents, with a previous history of endometriosis surgery and low ovarian reserve to achieve pain control.

Dienogest (DNG) is an Food and Drug Administration-approved gestagen that could be used to treat endometriosis-related pain with its anti-androgenic effects. It is widely used for endometriosis treatment, and its progestin component could be found in combined oral contraceptive (COC's) formulations. DNG could be recommended as the initial treatment to reduce chronic pelvic pain and dysmenorrhea in suspicion of endometriosis (3).

DNG has known side effects such as menstrual irregularities, weight gain, and decreased bone mineral density (4). Regarding the effects of progestins on lipid levels change through different generations of gestagens. The first and second-generation progestins could lower high-density lipoprotein (HDL) levels but increase low-density lipoprotein (LDL)-cholesterol and triglyceride (TG) levels (5). However, new generation progestins such as desogestrel have opposite effects on HDL and LDL levels than older generations (6). The fourth-generation progestin, DNG, has a moderate antigonadotrophic activity and does not bind to cortisol-binding-globulin or sex-hormone-binding-globulin (7). A study, evaluating the pharmacological prospects of the DNG concluded that the molecule does not alter lipid levels significantly (7). Although current literature has some evidence regarding the metabolic effects of DNG containing OC's, there is still a lack of evidence considering the effects of DNG on lipid profile.

Therefore, this study evaluated the effect of DNG on lipid profiles in patients with endometriosis.

METHODS

This prospective observational study consisted of 33 otherwise healthy women diagnosed with endometriosis-revised American Society of Reproductive Medicine classification I-IV with either laparoscopically or

sonographically in an endometriosis clinic of a tertiary hospital between January 2018 and June 2018. After obtaining Bakirkoy Dr. Sadi Konuk Training and Research Ethics Committee approval of where the study occurred (decision no: 2018-01-21, date: 08.01.2018), the study was conducted, and the guidelines of the Helsinki Declaration on human experimentation were followed. Written consent was obtained from all participants.

Inclusion criteria were as follows: 18-45 years old, prescribed a minimum of 6 months of DNG treatment and agreeing to participate in this study. Exclusion criteria were withdrawal from DNG treatment, pregnancy, women with incomplete medical records or who were lost to follow-up, allergies for DNG, need for laparoscopy during the 6-month of medical treatment, having familial lipid disorders, and body mass index (BMI) >30 kg/m².

The patients were assessed with a complete medical history and ultrasound examination. The age, parity, BMI, and main presenting symptoms of the patients and laboratory results were noted. The fasting blood samples were taken from the antecubital vein to measure total cholesterol (TC), TG, HDL cholesterol, and LDL cholesterol levels before starting DNG treatment. All women had a 2 mg/day oral DNG treatment for the next 6 months. After completing the medical therapy, all patients were scheduled for a control blood test to evaluate serum lipids.

Statistical Analysis

The analysis was performed using SPSS (version 20.0; SPSS Inc., Chicago, IL, USA) software. Kolmogorov-Smirnov test was used to analyze the normality of continuous variables. The homogenous data were presented as mean \pm standard deviation, and non-homogenous continuous values were presented as median-interquartile range. The Wilcoxon test was used to compare the paired groups. A $p < 0.05$ value was considered statistically significant.

RESULTS

The study comprised thirty-three women who received DNG treatment for 6 months. The mean age was 31.4 ± 4.8 years, gravidity was 1.8 ± 1.3 , parity was 1.6 ± 1.1 , and BMI was 24.6 ± 1.8 (kg/m²). The main presenting symptoms were dysmenorrhea in 19 (57.6%) women, dyspareunia in 10 (30.3%) women, and dyschezia in 4 (12.1%) women (Table 1). There was no significant difference regarding TC, HDL, and LDL levels between the blood samples taken before and after DNG treatment. However, TG levels were significantly higher at 6th-month blood samples than the pre-DNG blood samples (94 vs. 75, $p = 0.03$) (Table 2).

Table 1. Demographic data of patients

n=33	Mean ± SD	
Age	31.4±4.8	
G	1.8±1.3	
P	1.6±1.1	
BMI	24.6±1.8	
Main presenting symptom	Dysmenorrhea	19 (57.6%)
	Dyspareunia	10 (30.3%)
	Dyschesia	4 (12.1%)

SD: Standard deviation, BMI: Body mass index

DISCUSSION

Our study revealed that DNG treatment might only increase TG levels. However, no significant difference was observed regarding TC, HDL, and LDL levels in pre-and-post DNG treatment.

The current medical treatment options for managing endometriosis have various limitations due to their likely side effects. Considering the metabolic side effects of the medications used for treating endometriosis, earlier generation progestins and danazol, which have androgenic effects, reported to have negative effects on serum lipid profiles (8). The medroxyprogesterone acetate, one of the commonly used progestins recommended in the treatment of endometriosis, could increase free and TC levels while substantially decreasing HDL cholesterol (8). Another agent with androgenic effects, danazol, also decreases HDL cholesterol and increases LDL cholesterol and TG levels (9). These unintended effects on serum cholesterol levels could further lead to an increased cardiovascular disease risk (9).

DNG, is a four-generation progestin containing non-ethylestrone, has anti-androgenic effects (10). The efficacy of DNG in endometriosis-related pelvic pain was demonstrated by multiple randomized placebo-controlled studies and recommended worldwide as the first-line treatment (3,4). Strowitzki et al. (3) conducted a placebo-controlled study in patients with endometriosis-associated pelvic pain. They evaluated the effect of 2 mg DNG on TG, TC, HDL, and LDL levels in both DNG and control groups. They reported a slight increase toward upper limits of TG levels in the DNG group than in the placebo group. TG baseline levels were 0.96 and increased to 1.11 in the DNG group, whereas baseline TG levels of the placebo group were 0.99 and increased to 1.08. However, they concluded that all lipid levels did not differ significantly and remained within normal limits pre- and post-treatment in both study groups. Schindler et al. (5) conducted a study with high

Table 2. Median and interquartile range of both groups. Significant p-values are in bold letters

	Pre dienolest (median-IQR)	6 th month control (median- IQR)	p-value
Total cholesterol	178 (31)	169 (33)	0.88
Triglyceride	75 (52)	94 (51)	0.03
HDL	46 (13)	47 (11)	0.77
LDL	107 (38.5)	112 (28)	0.35

IQR: Interquartile range, HDL: High-density lipoprotein, LDL: Low-density lipoprotein

dose DNG (20 mg) and found no effect on LDL, TG, and TC levels, yet HDL levels were slightly increased. Our results may differ from the abovementioned studies that higher TG levels were observed after DNG treatment in our study. We may speculate that lower DNG levels could lead to higher TG levels due to its lower anti-androgenic effects compared to higher doses of DNG.

To date, there is only one study conducted in 1989 by Köhler et al. (11) compared blood lipid levels in patients who received DNG treatment due to endometriosis. They evaluated 84 endometriosis patients who received DNG 2 mg/day treatment. The blood samples were taken before, 1, 3, and 6 months of DNG treatment. They concluded that no statistically significant difference in lipid samples taken in different time periods. However, they suggest a tendency toward lower levels of HDL and TG; higher levels of LDL.

Wiegratz et al. (12) found a significant increase in TG levels in women receiving DNG containing COC's. They conducted a randomized controlled trial and four groups were randomly assigned differently expressed COC's. These tablets were monophasic combinations of 30 mg ethynyl estradiol (EE)+2 mg DNG, 20 mg EE+2 mg DNG, 10 mg EE+2 mg estradiol valerate (EV)+2 mg DNG, 20 mg EE+100 mg levonorgestrel (LNG). Three of these drugs contained DNG as the progestin component, and one included LNG. They reported a 40-60% rise in TG levels in DNG containing groups that were more pronounced in 20 EE/DNG and 30 EE/DNG than with 20 EE/EV/DNG, whereas only a 20% non-significant increase was observed in LNG-containing ones. Wiegratz et al. (12) also suggested that the difference between HDL levels in women on LNG or DNG containing pills arises from the HDL-reducing effect of LNG-containing pills. Although it was not a significant increase, there was a slight increase in HDL levels, which is also compatible with our study. It is known that EE reduces the catabolism of HDL2 by decreasing plasma hepatic lipase activity. subgroup. This effect of EE is counteracted

by androgenic progestines. However, the lack of increase in HDL2 suggests that, DNG might have a slight inhibitory function on the abovementioned EE effect despite its anti-androgenic nature. Considering this, it could be postulated that the effects of any progestin on metabolic activity should be considered individually.

Regarding the limitations of our study, the small number of patients can reduce the reliability of our results. Although our data are consistent with the previous reports, some discrepancy exists in the current data on this subject. Therefore, prospective studies on large populations are needed.

CONCLUSION

Our results suggest that DNG treatment increases TG levels. The metabolic effects of DNG should be clarified as being widely used among women as a progestin-only regimen. Alterations in lipid metabolism may affect the use of this drug in patients with metabolic syndrome or hyperlipidemia. As a COC component, the effect of DNG may be masked by the estrogen component, and alterations caused by DNG may be speculated to be estrogen.

ETHICS

Ethics Committee Approval: After obtaining Bakirkoy Dr. Sadi Konuk Training and Research Ethics Committee approval of where the study occurred (decision no: 2018-01-21, date: 08.01.2018), the study was conducted, and the guidelines of the Helsinki Declaration on human experimentation were followed.

Informed Consent: Written consent was obtained from all participants.

Authorship Contributions

Surgical and Medical Practices: S.K., İ.A., C.K., Concept: A.F.T., S.K., İ.A., Ş.Y., C.K., Design: A.F.T., D.E.I., İ.A., E.E., Ş.Y., C.K., Data Collection or Processing: A.F.T., S.K., E.E., Ş.Y., C.K., Analysis or Interpretation: D.E.I., E.E., Ş.Y., C.K., Literature Search: A.F.T., D.E.I., İ.A., Writing: D.E.I., E.E.

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REFERENCES

1. Eskenazi B, Warner ML. Epidemiology of endometriosis. *Obstet Gynecol Clin North Am* 1997;24:235-58.
2. Römer T. Long-term treatment of endometriosis with dienogest: retrospective analysis of efficacy and safety in clinical practice. *Arch Gynecol Obstet* 2018;298:747-53.
3. 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.
4. Andres Mde P, Lopes LA, Baracat EC, Podgaec S. Dienogest in the treatment of endometriosis: systematic review. *Arch Gynecol Obstet* 2015;292:523-9.
5. Schindler AE, Henkel A, Moore C, Oettel M. Effect and safety of high-dose dienogest (20 mg/day) in the treatment of women with endometriosis. *Arch Gynecol Obstet* 2010;282:507-14.
6. Silva-Bermudez LS, Toloza FJK, Perez-Matos MC, de Souza RJ, et al. Effects of oral contraceptives on metabolic parameters in adult premenopausal women: a meta-analysis. *Endocr Connect* 2020;9:978-98.
7. Foster RH, Wilde MI. Dienogest. *Drugs* 1998;56:825-33; discussion 834-5.
8. Palomba S, Orio F Jr, Russo T, Falbo A, Cascella T, Doldo P, et al. Long-term effectiveness and safety of GnRH agonist plus raloxifene administration in women with uterine leiomyomas. *Hum Reprod* 2004;19:1308-14.
9. Herink M, Ito MK. Medication Induced Changes in Lipid and Lipoproteins. [Updated 2018 May 10]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. *Endotext* [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK326739/>
10. Sitruk-Ware R, Nath A. Metabolic effects of contraceptive steroids. *Rev Endocr Metab Disord* 2011;12:63-75.
11. Köhler G, Göretzlehner G, Brachmann K. Lipid metabolism during treatment of endometriosis with the progestin dienogest. *Acta Obstet Gynecol Scand* 1989;68:633-5.
12. Wiegatz I, Lee JH, Kutschera E, Bauer HH, von Hayn C, Moore C, et al. Effect of dienogest-containing oral contraceptives on lipid metabolism. *Contraception* 2002;65:223-9.