Atherosclerosis-related biomarkers in women with endometriosis: The effects of dienogest and oral contraceptive therapy

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ABSTRACT

Objective: Chronic inflammation in endometriosis is associated with increased risk of future cardiovascular disease; however, no studies have investigated the cardiovascular risk of women who have undergone hormonal therapy for endometriosis. We investigated atherosclerosis-related biomarkers in women with and without endometriosis and the effects of dienogest (DNG) and oral contraceptive (OC) therapies.

Study design: In this cross-sectional study, 109 women with endometriosis and 42 control women without endometriosis were enrolled. The endometriosis group was divided into the untreated (n = 34), DNG therapy (n = 33), and OC therapy (n = 42) groups. Lipid profile serum levels, inflammatory marker such as high-sensitivity C-reactive protein, oxidative stress markers such as oxidized low-density lipoprotein and diacron-reactive oxygen metabolites, and atherosclerosis indicators (cardio-ankle vascular index [CAVI] and ankle-brachial pressure index [ABI]) were measured.

Results: The median treatment duration was 28 months in the DNG group and 32.5 months in the OC group. Triglyceride levels were higher in the OC group than in the other three groups ($P < 0.05$). Regarding markers of inflammation and oxidative stress, log high-sensitivity C-reactive protein and diacron-reactive oxygen metabolites levels were higher in the untreated group than in the control group ($P < 0.05$), and these markers were further increased in the OC group (log high-sensitivity C-reactive protein: $P < 0.05$; diacron-reactive oxygen metabolites: $P < 0.01$), but not in the DNG group. There was no difference in the CAVI and ABI among all groups. Spearman correlation revealed a positive correlation between duration of OC therapy and CAVI ($\rho = +0.49$; $P = 0.002$), but no correlation between the duration of DNG therapy and CAVI ($\rho = -0.04$; $P = 0.81$).

Conclusions: Inflammation and oxidative stress markers are increased in women with untreated endometriosis. Treatment with OC, but not with DNG, further increases these levels. There was a positive association between the duration of OC administration and atherosclerosis risk for women with endometriosis. Our results suggest that DNG could be administered to endometriosis without the increased atherosclerosis risk and short-term OC administration for endometriosis is not harmful, however, atherosclerosis risk should be strictly observed.

Introduction

Endometriosis is a chronic inflammatory disorder defined as the presence of endometrial tissue outside the uterus, predominantly within the peritoneal cavity, causing pelvic pain, dysmenorrhea, and infertility [1].

In a recent, large, prospective cohort study in the United States, the Nurses' Health Study II [2], endometriosis was associated with increased risk of coronary heart disease. Moreover, a cross-sectional baseline survey, the Japan Nurses' Health Study [3], showed that women with endometriosis were at higher risk for cerebral infarction and angina pectoris. Cardiovascular events in patients with endometriosis are attributed to chronic inflammation, oxidative stress induced by endometriosis [4–6], and surgical treatment such as hysterectomy or oophorectomy or both [2,7].

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The cardio-ankle vascular index (CAVI) and ankle-brachial index (ABI) are atherosclerosis-related indices reflecting arterial stiffness and stenosis, respectively. CAVI is a novel parameter independent of blood pressure (BP); its usefulness for detecting cardiovascular disease (CVD) has been established recently [8]. ABI is useful for detecting the presence of atherosclerosis [9]. Therefore, both indices are associated with atherosclerotic risk factors and predict subsequent cardiovascular morbidity and mortality [8,10].

Hormonal therapy for endometriosis has been recently developed; the effectiveness of dienogest (DNG) [11] and oral contraceptives (OCs) [12,13] for endometriosis has been established. These therapies are long term, sometimes until menopause. However, no study has evaluated the effects of hormonal therapy on atherosclerosis leading to CVD risk in endometriosis patients.

Here, we investigated the effects of DNG and OC therapy on atherosclerosis by measuring CAVI and ABI of Japanese women with endometriosis. Additionally, we measured markers of inflammation and systemic oxidative stress to explore factors related to atherosclerosis.

Materials and methods

Subjects

A cross-sectional study was conducted between 2013 and 2019. We enrolled a total of 151 premenopausal women aged 20–50 years who visited the outpatient clinic of Kyoto Prefectural University of Medicine Hospital. Of the 151 women, 109 were diagnosed endometriosis (endometriosis group). Endometriosis was defined as unilateral or bilateral ovarian endometrioma clinically diagnosed by transvaginal ultrasonography and magnetic resonance imaging. The endometriosis group was assigned to the following subgroups: (i) Those patients without any hormonal therapy during the period before laparoscopic surgery for ovarian endometrioma or before fertility treatment were assigned to the untreated group (n = 34). (ii) Those patients clinically determined deep endometriosis (DE) with symptoms such as chronic pelvic pain were assigned to the DNG group (n = 33). And (iii) those who did not wish immediate conception and had no suspicion of DE were assigned to the OC group (n = 42). The remaining 42 were enrolled as healthy controls (control group). The control group included healthy volunteers or medical checkup examinees. The DNG group used DINAGEST® tablets (1 mg dienogest) twice daily. In the OC group, 18 patients used LUNABELL® LD (0.035 mg ethinylestradiol and 1 mg norethisterone; Nippon Shinyaku Co., Tokyo, Japan), 5 used LUNABELL® ULD (0.02 mg ethinylestradiol and 1 mg norethisterone; Nippon Shinyaku Co., Tokyo, Japan), 17 used Yaz® (0.02 mg ethinylestradiol and 3 mg drospirenone; Bayer Co., Tokyo, Japan), and 2 used MARVELON 28® (0.03 mg ethinylestradiol and 0.15 mg desogestrel; Merck Sharp & Dohme Co., Tokyo, Japan) cyclically. The median duration of DNG therapy was 28 months, but that of OC therapy was 32.5 months (Table 1). Exclusion criteria were pregnancy; hysterectomy; treatment with GnRH agonists; cancer history; history of venous thrombosis; treatment for hypertension, hyperlipidemia, or diabetes; history of myocardial infarction; and cardiovascular surgery or intervention. The risk and benefit of all treatment options including the risk of deep venous thrombosis were explained to the patients. Written informed consent was obtained from each subject before participation. The study was approved by the institutional review board of Kyoto Prefectural University of Medicine (ERB-C-1217).

Table 1
Clinical and biochemical characteristics of the study group.

	Control group (n = 42)	Endometriosis group		
		Untreated (n = 34)	DNG (n = 33)	OC (n = 42)
Age (years)	34.0 ± 8.1	37.2 ± 6.9	42.1 ± 5.9	39.9 ± 6.8
Age (years), median (range)	32 (20−50)	39 (21−47)	43 (29−50)**†	41 (26−49)**
Height (cm)	161.3 ± 5.9	160.9 ± 5.6	159.1 ± 5.6	160.4 ± 4.7
Weight (kg)	54.2 ± 8.0	54.1 ± 9.1	53.5 ± 9.0	52.3 ± 6.2
BMI (kg/m²)	20.9 ± 2.8	20.9 ± 3.9	21.0 ± 3.0	20.3 ± 2.3
Gravidity; median (range)	0 (0−4)	0 (0−5)	0 (0−3)	0 (0−2)
Parity; median (range)	0 (0−3)	0 (0−2)	0 (0−2)	0 (0−2)
Menstrual cycle				
Menstrual phase, n (%)	2 (4.8)	4 (11.8)	—	—
Proliferative phase, n (%)	18 (42.9)	19 (55.9)		
Secretory phase, n (%)	22 (52.4)	11 (32.4)		
Smoking				
No, n (%)	36 (85.7)	28 (82.4)	32 (97.0)	36 (85.7)
Past, n (%)	5 (11.9)	3 (8.8)	0 (0.0)	4 (9.5)
Current, n (%)	2 (4.8)	3 (8.8)	1 (3.0)	2 (4.8)
Duration of therapy (month), median (range)	—	—	28 (7−108)	32.5 (2−97)
Systolic BP (mmHg)	114.2 ± 12.4	119.1 ± 13.8	124.3 ± 17.0*	120.0 ± 14.3
Diastolic BP (mmHg)	71.1 ± 10.1	76.6 ± 10.3	80.4 ± 14.3**	77.5 ± 11.8
WBC (/μL)	6020 ± 1440	6030 ± 1390	5550 ± 1460	5800 ± 1270
Hemoglobin (g/dL)	13.3 ± 1.0	12.6 ± 1.4*	13.5 ± 1.1†	13.1 ± 1.4
Platelet (×10⁴/μL)	25.0 ± 4.6	27.4 ± 7.0	24.1 ± 5.1	26.7 ± 5.2
FPG (mg/dL)	95.4 ± 13.0	99.1 ± 19.0	93.0 ± 10.0	91.5 ± 10.4
CA19-9 (mg/dL)	10.8 ± 9.1	32.6 ± 40.7	14.5 ± 21.5	12.6 ± 15.0
CA-125 (mg/dL)	14.6 ± 7.1	65.4 ± 67.0**	18.5 ± 14.5††	18.8 ± 19.0††
TC (mg/dL)	196.1 ± 35.0	189.1 ± 29.7	175.9 ± 21.5*	191.1 ± 28.9
HDL-C (mg/dL)	76.5 ± 14.1	70.1 ± 15.9	67.8 ± 18.0	75.8 ± 14.8
LDL-C (mg/dL)	105.3 ± 29.2	102.9 ± 24.2	93.0 ± 16.3	92.7 ± 26.1
Log TGs	1.81 ± 0.21	1.87 ± 0.21	1.82 ± 0.18	2.02 ± 0.21**†‡

Values are presented as mean ± standard deviation. *P < 0.05, **P < 0.01 vs control group. †P < 0.05, ††P < 0.01 vs untreated endometriosis group. ‡P < 0.01 vs DNG group. BMI, body mass index; BP, blood pressure; DNG, dienogest; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; OC, oral contraceptive; TC, total cholesterol; TGs, triglycerides; WBC, white blood cells.

Sample collection and Laboratory analysis

We calculated body mass index (BMI) by dividing weight (kg) by height squared (m²). Data regarding the last menstrual period, gravidity, parity, medication use, and smoking were recorded. Table 1 shows the menstrual cycle of blood collection in the control group and the untreated group. OC users provided their blood samples to avoid withdrawal bleeding. Blood was collected after 12 h of fasting. Fasting plasma glucose, CA-125, CA19-9, serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs) were measured using enzymatic methods. Low-density lipoprotein cholesterol (LDL-C) was calculated using Friedewald's formula: LDL-C = (TC) – (HDL-C) – (TG/5). Serum high-sensitivity C-reactive protein (hs-CRP) was measured with a nephelometric assay; oxidized low-density lipoprotein (ox-LDL) was measured using enzyme-linked immunosorbent assay (SRL, Inc., Tokyo, Japan).

Measurement of diacron-reactive oxygen metabolites

Serum was obtained from blood samples by centrifugation at 3000 rpm for 5 min at 4 °C. Diacron-reactive oxygen metabolites (d-ROMs) tests were performed using fresh serum and the Free Radical Analytical System 4 (FRAS 4®; Wismerll Co. Ltd. Tokyo, Japan). Briefly, the serum was added to an acidic buffered solution (R1 reagent) in a cuvette; then, a colorless oxidizable chromogenic mixture (R2 reagent) was added. After mixing well and setting the cuvette in the analyzer, absorbance change at 505 nm was calculated. Normal values are between 250 and 300 Carratelli units (U CARR); 1 U CARR corresponds to 0.8 mg/L H_2O_2 solution. During d-ROMs testing, concentration of hydroperoxides generated by oxidation of organic molecules, such as proteins, amino acids, peptides, glucosides, lipids, and nucleotides in the blood, is measured; therefore, it is a marker of comprehensive oxidative stress.

Measurements of CAVI and ABI

CAVI and ABI were measured using a VaSera VS-1000 vascular screening system (Fukuda Denshi Co., Tokyo, Japan). Briefly, after 10 min of bed rest in the supine position, CAVIs were obtained from brachial and ankle pulse wave forms and systolic BP (SBP) and diastolic BP (DBP). The stiffness parameter was calculated using the following formula: CAVI = a [(2ρ/ΔP)·ln(Ps/Pd)·PWV2] + b, where ρ is the blood density, ΔP is the change in BP, Ps is SBP, Pd is DBP, PWV is the pulse wave velocity between the aorta and ankle, and a and b are scale conversion constants [14].

ABI was obtained based on SBP of the upper (brachial arterial) and lower (tibial arterial) BP and calculated by dividing ankle SBP by brachial SBP.

Statistical analysis

All data are presented as mean ± standard deviation (SD). Differences in variables between subgroups were analyzed using analysis of variance (ANOVA) and Tukey-Kramer's test was used as a post-hoc test to determine specific group differences when there was normal distribution, and were analyzed using the Kruskal-Wallis test and Steel-Dwass test were used as the post-hoc test when parameters did not exhibit normal distribution. Cross-table analyses were performed using the Chi-square test (with and without Yates correction) as appropriate. Hormonal therapy durations were compared using the Mann-Whitney *U*-test. To approximate the normal distribution of TGs, ox-LDL, and hs-CRP, natural log transformation was performed (log TGs, log ox-LDL, and log hs-CRP). Maximum CAVI and minimum ABI of the bilateral

values were used. Multiple regression analysis was performed to identify independent factors associated with d-ROMs and CAVI. CAVI was compared among the four groups using analysis of covariance (ANCOVA) and adjusting for mean age as a covariable. Correlations between CAVI and hormonal therapy duration were analyzed by Spearman rank-order correlation coefficients (ρ). For all comparisons, *P* < 0.05 was considered statistically significant. All statistical analyses were conducted using GraphPad Prism 5 software (version 5.04; San Diego, CA, USA).

Results

Subjects

Table 1 shows the clinical characteristics of the study groups. The median age was not different between the control group and untreated group, but it was significantly higher in the DNG group than in the control group and untreated group; it was also significantly higher in the OC group than in the control group. SBP
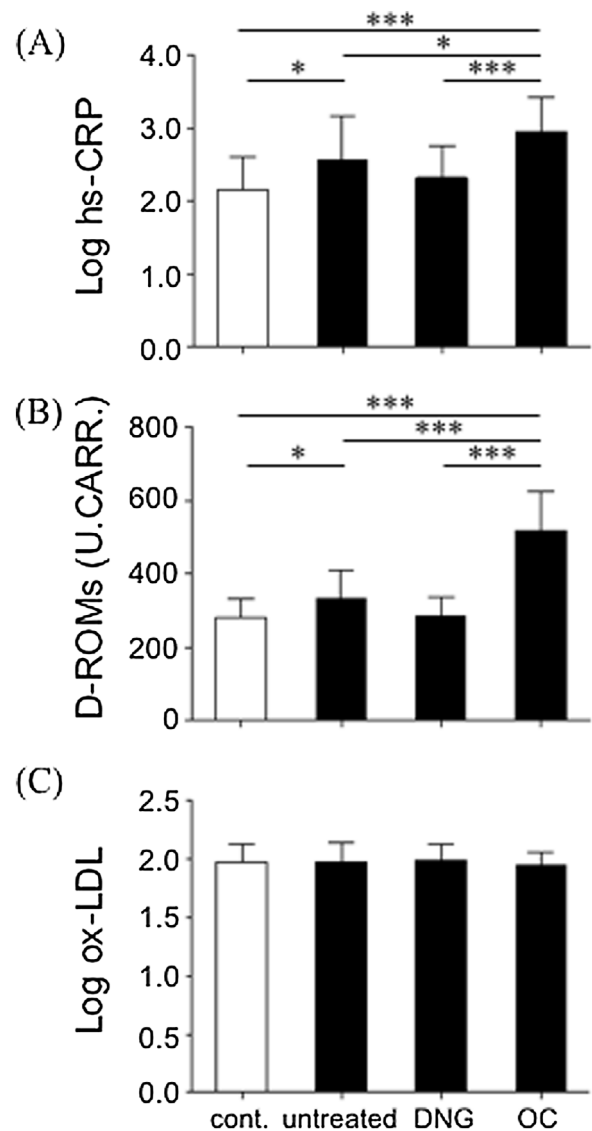

Fig. 1. (**A**) Log high-sensitivity CRP (hs-CRP), (**B**) diacron-reactive oxygen metabolites (d-ROMs) test, and (**C**) log oxidized low-density lipoprotein (ox-LDL) of patients with untreated endometriosis, those using dienogest (DNG) therapy, those using OC therapy, and the control group. Values are presented as mean ± standard deviation (SD).

was significantly higher in the DNG group, and DBP was significantly higher in the DNG group and OC group compared to the control group.

Laboratory measurements

Plasma CA19-9 and CA-125 were significantly higher in the untreated group. Log TG levels were higher in the OC group than in other groups. No significant differences were found in TC, HDL-C, and LDL-C levels among groups (Table 1). As regards to markers of inflammation and oxidative stress, log hs-CRP and d-ROMs levels were significantly higher in the untreated group than in the control group ($P < 0.05$) and even higher in the OC group (log hs-CRP: $P < 0.05$; d-ROMs: $P < 0.01$). In contrast, there were no differences between the DNG and control group or between the DNG and untreated groups (Fig. 1A, B). There was no difference in log ox-LDL (Fig. 1C). Next, we examined factors associated with d-ROMs. Table 2 summarizes the results of a multiple regression analysis of the correlation between d-ROMs and clinical variables. Log hs-CRP was an independent predictor of d-ROMs for all subjects (β coefficient = 0.5939; $P < 0.001$). Additionally, a correlation between d-ROMs and OC therapy (β coefficient = 0.5526; $P < 0.001$) or log hs-CRP (β coefficient = 0.3897; $P < 0.001$) was observed in all women with endometriosis.

Correlation of CAVI with clinical variables and duration of hormonal therapy

Table 3 summarizes the results of multiple regression analysis of the correlation between CAVI and clinical variables. Correlations between CAVI and age (β coefficient = 0.4806; $P < 0.001$), BMI (β coefficient = −0.2891; $P < 0.001$), and log TG levels (β coefficient = 0.2170; $P = 0.017$) were observed in all subjects, and correlations between CAVI and age (β coefficient = 0.4437; $P < 0.001$) and BMI (β coefficient = −0.2208; $P = 0.038$) was observed in all women with endometriosis. Age was a major independent predictor of CAVI; therefore, we used this confounder to adjust CAVI in subsequent analyses. There was no difference in the mean CAVI adjusted for age and ABI among the groups (Fig. 2). Additionally, in the OC group, we found no significant difference among these and the type of OC (data not shown). Spearman rank-order correlation coefficients revealed a positive correlation between OC therapy duration and CAVI (ρ = +0.49; $P = 0.002$); however, there was no significant correlation between DNG therapy duration and CAVI (ρ = −0.04; $P = 0.81$) (Fig. 3).

Comments

It is generally accepted that inflammation and oxidative stress are important factors in atherosclerosis development. To our knowledge, this is the first study investigating the effects of hormonal therapy on atherosclerosis-related indices of women with endometriosis. Our study determined the effects of DNG and OC therapies on systemic inflammation, oxidative stress, and subsequent atherosclerotic changes in Japanese women with endometriosis.

In this study, log hs-CRP and d-ROMs levels increased in women with untreated endometriosis when compared with women without endometriosis. OC therapy further promoted these parameters, whereas DNG therapy did not show any further increment of these markers. Considering the levels of serum hs-CRP and d-ROMs positively correlate [15], inflammation in endometriosis may increase serum d-ROMs levels. There are a few reports that serum oxidative stress markers were increased in women with endometriosis when compared with women without endometriosis [16,17]. Our results were compatible with those of previous reports.

Table 2

Results of a multiple regression analysis of the correlation of d-ROMs with clinical variables for all subjects and women with endometriosis.

Variable	β coefficient	95 % CI	P-value
All subjects[§]			
Age (years)	−0.0644	−3.36 to 1.23	0.36
BMI (kg/m^2)	−0.0363	−7.10 to 4.06	0.59
Mean BP (mmHg)	−0.0808	−1.50 to 0.46	0.30
LDL-C (mg/dL)	0.1577	−0.04 to 0.95	0.07
Log TGs	0.1143	−20.7 to 153.8	0.13
Log hs-CRP	0.5939	96.1–164.5	< 0.001
Endometriosis[¶]			
Age (years)	−0.0539	−3.58 to 1.40	0.39
BMI (kg/m^2)	0.0887	−1.58 to 9.31	0.16
Mean BP (mmHg)	−0.1152	−1.81 to 0.40	0.21
LDL-C (mg/dL)	0.1184	−0.34 to 1.56	0.20
Log TGs	−0.0692	−139.2 to 52.2	0.37
Log hs-CRP	0.3897	57.9–127.1	< 0.001
DNG administration	−0.0503	−60.2 to 30.5	0.52
OC administration	0.5526	108.7–199.2	< 0.001

[§] Model: $R^2 = 0.509$, adjusted $R^2 = 0.484$, $P < 0.001$.
[¶] Model: $R^2 = 0.739$, adjusted $R^2 = 0.713$, $P < 0.001$. CI = confidence interval; CRP, C-reactive protein; D-ROM, diacron-reactive oxygen metabolite. Abbreviations are the same as in Table 1.

Several studies have demonstrated that OC use for healthy women increases oxidative stress [18–20]; however, mechanisms remain unclear. One possible explanation is that, in contrast to E2, ethinylestradiol (EE) does not protect endothelial cells against oxidative stress and does not increase nitric oxide (NO) production [21]. Another possibility is that OC use increases CRP levels [22]. The elevation of CRP during OC use has been described as a direct effect of hepatocyte CRP synthesis, rather than the inflammatory response [23], however, a recent study showed that increased CRP during OC use reflects a true increase in inflammation when plasma PTX-3 levels are measured [24]. CRP increases the production of reactive oxygen species, directly promotes endothelial cell inflammation, and induces the secretion of chemokines, thereby accelerating the atherosclerotic processes [25].

In the present study, there was no difference in either age-adjusted CAVI and ABI among the groups. However, we further found that there was no correlation between CAVI and DNG therapy duration, but there was a positive correlation between CAVI and OC therapy duration. In other words, these findings suggest that vascular structural changes have not yet emerged in

Table 3

Results of a multiple regression analysis of the correlation of CAVI and clinical variables for all patients and women with endometriosis.

Variable	β coefficient	95 % CI	P-value
All subjects[§]			
Age (years)	0.4806	0.03 to 0.07	< 0.001
BMI (kg/m^2)	−0.2891	−0.12 to −0.04	< 0.001
Mean BP (mmHg)	0.1051	−0.003 to 0.01	0.25
LDL-C (mg/dL)	−0.0648	−0.005 to 0.003	0.53
Log TGs	0.2170	0.15 to 1.46	0.017
d-ROMs (Carratelli units)	0.0267	−0.0009 to 0.001	0.77
Endometriosis[¶]			
Age (years)	0.4437	0.03 to 0.08	< 0.001
BMI (kg/m^2)	−0.2208	−0.11 to −0.003	0.038
Mean BP (mmHg)	0.1674	−0.004 to 0.02	0.25
LDL-C (mg/dL)	−0.1085	−0.012 to 0.006	0.48
Log TGs	0.2026	−0.18 to 1.66	0.11
d-ROMs (Carratelli units)	−0.2433	−0.004 to 0.0007	0.19
DNG administration	−0.0525	−0.53 to 0.35	0.68
OC administration	0.2097	−0.21 to 0.89	0.22

[§] Model: $R^2 = 0.356$, adjusted $R^2 = 0.320$, $P < 0.001$.
[¶] Model: $R^2 = 0.333$, adjusted $R^2 = 0.253$, $P < 0.001$. CI = confidence interval; CRP, C-reactive protein; d-ROM, diacron-reactive oxygen metabolite. Abbreviations are the same as in Table 1.
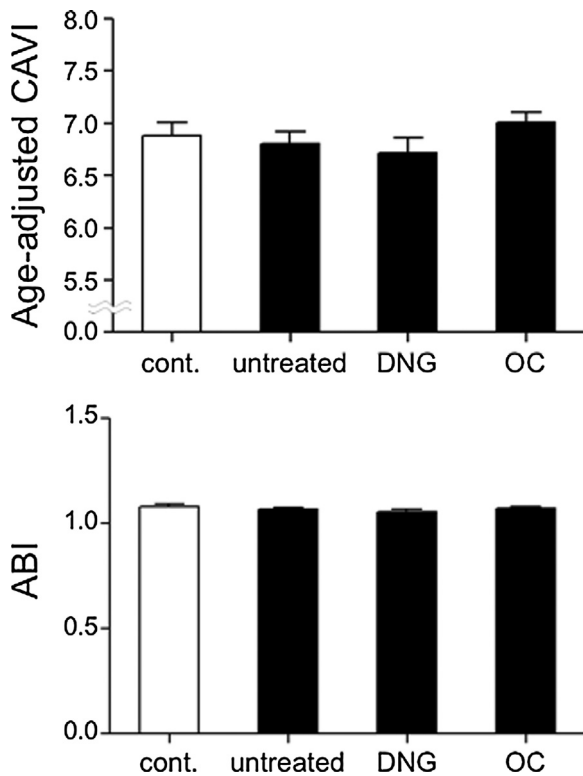
Fig. 2. Comparison of the adjusted CAVI and ABI between four groups. CAVI was adjusted for age. Values are presented as mean ± standard deviation. The adjusted CAVI and ABI were compared using one-way analysis of variance (ANOVA) followed by the Tukey-Kramer's test for multiple comparisons. CAVI, cardio-ankle vascular index; ABI, ankle-brachial index.
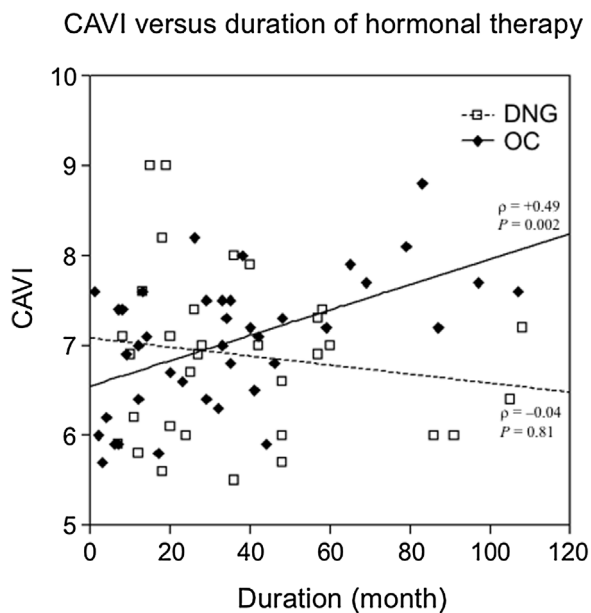

Fig. 3. Spearman rank-order correlation coefficients between CAVI and duration of hormonal therapy. CAVI is significantly associated with administration duration of OC therapy duration (ρ = +0.49; P = 0.002) but is not significantly associated with that of DNG therapy (ρ = −0.04; P = 0.81.). CAVI, cardio-ankle vascular index; DNG, dienogest; OC, oral contraceptive.

women with endometriosis, and short-term OC administration does not contribute to atherosclerosis in endometriosis.

Two studies have investigated the effects of OCs on atherosclerotic changes in women without endometriosis. The first study indicated that after approximately 18 months of hormonal contraceptive use by healthy young women, flow-mediated dilatation (FMD) in hormonal contraceptive users was decreased compared to that in nonusers [26]. The second study showed that after approximately 4 years of OC administration, FMD (%) was significantly reduced and the common carotid intima-media thickness (ccIMT) increased in OC users compared to nonusers [27]. Considering the natural course of atherosclerosis, it seems to take longer than the duration of OC administration in the present study (approximately 30 months) to develop arterial stiffness.

Although no study has investigated the relationship between d-ROMs and CAVI, two contradictory studies have reported regarding the relationship between d-ROMs and structural parameters of subclinical atherosclerosis. In the first study, the IMT was correlated with d-ROMs in a population with hypercholesterolemia [28]. In the second study, the IMT was not correlated with d-ROMs in healthy people and those with mild disease conditions [29]. This discrepancy was likely to attributable to the differences in subject backgrounds and age. Similarly, in this study, all subjects were younger than 50 years of age and excluded for diseases at risk for endothelial function (diabetes, hypertension, hyperlipidemia, etc.), therefore, the change in CAVI may be slight, and statistical differences may not have been detected.

The current study has some limitations. The small sample size and the short duration of medication and observation make it difficult to lead to the conclusive clinical significance of hormonal therapy on atherosclerosis. Additionally, because this study is a cross-sectional design, the baseline data of participants is lacking and the causal relationship cannot be examined using the obtained findings. Despite these weak points, the differential effect of OC and DNG on inflammatory and oxidative stress biomarkers is still meaningful. Therefore, prospective studies with more subjects and longer durations of hormonal administration are desired to determine the cardiovascular risk of women with endometriosis.

In conclusion, the markers of inflammation and oxidative stress are increased in women with untreated endometriosis compared to women without endometriosis. OC therapy further promotes inflammation and oxidative stress, but DNG therapy does not. Although hormonal therapy for approximately 3 years or less does not promote atherosclerosis risk, there is a positive association between OC therapy duration and atherosclerosis risk in women with endometriosis. Therefore, DNG can be used without the increased atherosclerosis risk. OC administration for endometriosis may not be harmful for a short period, however, the risk of atherosclerosis should be strictly observed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eurox.2020.100108.

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