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Cardiovascular risks and endothelial dysfunction in reproductive-age women with endometriosis

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Endometriosis is a prevalent gynecological condition, affecting around 10% of reproductive-age women. Inflammatory processes associated with endometriosis may contribute to endothelial dysfunction. Increased skin accumulation of advanced glycation end-products (AGEs), reflecting arterial stiffness, potentially links endometriosis with elevated risk of cardiovascular events. We hypothesized that patients with endometriosis have impaired endothelial function as well as increased arterial stiffness and AGE skin accumulation, compared to healthy controls. We compared endothelial function, arterial stiffness, and levels of AGEs in patients suffering from endometriosis and in healthy controls. The study included 45 women aged 20 to 40: 21 patients with endometriosis and 24 healthy controls, matched in terms of age, BMI, and blood pressure values. Endo-PAT 2000 device was used for non-invasive assessment of (i) endothelial function, expressed as Reactive Hyperemia Index (RHI), and (ii) arterial stiffness, expressed as Augmentation Index (AI) and Augmentation Index at 75 heart beats/min (AI@75). Endothelial dysfunction was defined as an RHI value ≤ 1.67. AGE Reader device was used for non-invasive evaluation of skin AGE level accumulation. Patients with endometriosis had lower mean RHI values (1.69 ± 0.54 vs. 2.02 ± 0.48, $p = 0.037$) and a higher prevalence of endothelial dysfunction, (52.4% vs. 20.8%, $p = 0.027$) compared to healthy controls. Skin AGE level was higher in patients with endometriosis, compared to controls (2.00 ± 0.57 vs. 1.70 ± 0.24, $p = 0.013$). There were no significant differences in AI and AI@75 between the two groups. Patients with endometriosis have impaired endothelial function and higher AGE skin accumulation, which are well-established preclinical manifestations of increased cardiovascular risk. There is a great need for comprehensive cardiovascular risk assessments in women with endometriosis to prevent the development of potential atherosclerotic-based complications.

Keywords Endothelial dysfunction, Cardiovascular risk, Endometriosis, EndoPAT 2000, AGE reader

Endometriosis is a chronic, inflammatory gynecological condition characterized by the presence of endometrial-like tissue outside of the uterine cavity, commonly affecting the pelvic peritoneum, the ovaries, the rectovaginal septum, the bladder, and the bowel[1,2]. The disease affects approximately 10% of reproductive-age women and is estimated to impact around 190 million women globally[3]. Endometriosis manifests with chronic pelvic pain, dysmenorrhea, dyspareunia, and gastrointestinal disturbances[1,2]. Severe symptoms dramatically diminish the quality of life of the affected women[4,5]. Furthermore, endometriosis can also lead to infertility[1,2].

The pathogenesis of endometriosis remains a subject of ongoing research, with several hypotheses proposed, including retrograde menstruation, coelomic metaplasia and immune system dysfunction[6]. Research on the pathogenesis and mechanism underlying this condition reports elevated levels of inflammatory cytokines, including interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-alpha in serum and peritoneal fluid[7]. These cytokines trigger chronic inflammatory processes, causing damage to the vascular endothelium and atherosclerosis. The endothelium, an active monolayer of cells lining the lumen of vessels, is an integral

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regulator of vascular homeostasis through the modulation of vascular tone, smooth muscle cell proliferation, hemostasis processes, and immune cell migration[8]. Endothelial dysfunction refers to a condition where there is reduced production or availability of nitric oxide, or an imbalance between endothelium-derived relaxing and contracting factors. Notably, endothelial dysfunction can be reversed with the treatment of cardiovascular risk factors and serves as an independent predictor of cardiac events[9]. Endothelial dysfunction as a recognized early sign of atherosclerosis, can be assessed by measuring reactive hyperemia, which indicates alterations in peripheral arterial tone and reflects arterial stiffness, thereby helping to predict future cardiovascular risk[10]. Except for endothelial dysfunction, skin accumulation of advanced glycation end-products (AGEs) is associated with metabolic alterations and the aging processes and may also reflect an elevated cardiovascular risk[11,12]. AGEs represent a diverse category of bioactive compounds resulting from the nonenzymatic interaction between reducing sugars and aminoacids found in proteins and other macromolecules[13,14]. AGEs formed within the body contribute to arterial stiffness through the process of cross-linking collagen within the arterial wall[13,15]. Simultaneously, endogenously formed AGEs activate the receptor for AGEs (RAGE), initiating a subsequent cascade that ultimately results in low-grade inflammation[13,16].

A higher incidence of ischemic heart disease, cerebrovascular disease, heart failure, dyslipidemia, arrhythmias and all-cause mortality have been reported among patients with endometriosis, compared to matched healthy controls[17–21,23,25]. So far, endothelial cell function, arterial stiffness and AGEs skin accumulation have not been studied in women with endometriosis. We hypothesized that patients with endometriosis have impaired endothelial function, increased arterial stiffness and higher AGE skin accumulation, compared to healthy controls. We aimed to evaluate endothelial dysfunction, arterial stiffness and skin AGEs accumulation as preclinical manifestations of increased cardiovascular risk in patients with endometriosis.

Materials and methods

Patients

Study participants were recruited from the 2nd Department of Obstetrics and Gynecology of Medical University of Warsaw between December 2021 and April 2022. Eligibility criteria included (i) women between 20 and 40 years of age, (ii) a diagnosis of endometriosis confirmed at least in transvaginal ultrasound (TVUS), and (iii) no evidence of clinically overt atherosclerosis-related cardiovascular disease. The diagnostic criteria for endometriosis were based on specific sonographic features identified during TVUS. For ovarian endometriomas, the key features included: the presence of at least one unilocular (single-chambered) cyst with homogeneous, low-level, "ground-glass" echogenicity and thickened walls, typically without internal vascularity. For deep infiltrating endometriosis (DIE), sonographic features included hypoechoic nodules or masses in the rectovaginal septum, uterosacral ligaments, or posterior vaginal fornix; hypoechoic thickening or nodules in the bladder wall, particularly in the posterior aspect; and hypoechoic, irregular thickening of the bowel wall, especially in the rectosigmoid colon. In several patients, endometriosis was also confirmed through MRI or surgery. Asymptomatic patients were not included in the study. Exclusion criteria included (i) pregnancy and breastfeeding, (ii) presence of malignancy, (iii) concomitant chronic diseases affecting endothelial function (i.e., hypertension, diabetes mellitus, chronic kidney disease). The control group consisted of healthy women with no abnormalities in ultrasound, matched for age and body mass index (BMI), with the same exclusion criteria as the study group.

The study protocol was approved by the bioethics committee of the Medical University of Warsaw (no. of approval: KB/211/2021). The study was performed in accordance with the Declaration of Helsinki. All patients provided written informed consent to participate in the study.

Assessment of endothelial dysfunction and arterial stiffness

Endothelial function and arterial stiffness were assessed using a noninvasive diagnostic device, the EndoPAT 2000 (Itamar Medical Ltd., Caesarea, Israel). Participants were instructed to abstain from caffeine and smoking for at least 12 h prior to the test. Upon arrival, patients rested for 15 min, during which data on coexisting diseases, age, weight, height and blood pressure were collected. Before initiating the evaluation, the patient was instructed to remain in a supine position. Finger probes were attached to the index fingers of both hands to record the baseline pulse amplitude. A blood pressure cuff was applied to the nondominant arm to create reactive hyperemia during further measurements. The reactive hyperemia procedure consists of a 3–10 min baseline recording, 4.5–5.5 min of blood flow occlusion to one arm using an upper arm blood pressure cuff, and 3–5 min of recording after cuff release. The anticipated response involves an increase in the PAT signal amplitude following occlusion. The system's software automatically generates the PAT score, which is essentially the ratio of the post-occlusion to pre-occlusion average signal amplitude, adjusted for baseline levels and any systemic variations. Based on pulse wave analysis of the signal, EndoPAT 200 device calculates several scores: the Reactive Hyperemia Index (RHI), Augmentation Index (AI) and Augmentation Index at 75 beats/min (AI@75) providing a quantitative assessment of endothelial dysfunction (RHI) and arterial stiffness (AI, AI@75). The RHI is determined by the ratio of post- to pre-occlusion PAT signals in the occluded arm, compared to the same ratio in the control arm, with adjustments for the baseline vascular tone of the occluded arm. The RHI categorizes endothelial function as normal with $RHI > 1.67$ or abnormal (endothelial dysfunction) with $RHI \leq 1.67$. EndoPAT 2000 also calculates the heart rate from the PAT signals in the baseline region of interest. RHI provides a quantitative assessment of endothelial dysfunction. AI is an indicator of arterial stiffness, derived from pulse wave analysis using the EndoPAT 2000 device. Iis calculated from the PAT pulses at the base-line period of the occluded arm, by averaging multiple valid pulses and finding the systolic peak (P1) and the backward reflected peak (P2) and then using the formula: (P2-P1)/P1. Since AI is influenced by heart rate, the result is then corrected to a standard of AI at heart rate of 75BPM (AI@75)[22,23].

Skin AGE level accumulation was measured using AGE Reader device (DiagnOptics Technologies BV, Groningen, The Netherlands), which utilizes fluorescence spectroscopy, emitting a specific wavelength of light onto the skin. This light causes AGEs present in the skin to fluoresce, emitting light of a different wavelength. The emitted fluorescence is then detected and analyzed by the device. Typically, the forearm is chosen as the measurement site. An arm cuff is applied to stabilize the area and block external light interference.

The measurement process typically takes a few minutes to complete. Once the measurement is complete, the device provides a numerical value representing the level of AGE accumulation in the skin. Two measurements were taken at a time, from which an average was calculated[22].

Working principles of EndoPAT 2000 and AGE Reader are shown in Fig. 1.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (version 27.0). Shapiro-Wilk test was used to examine the normality of the distribution. Normally distributed values were compared using Student's t-test. Non-normally distributed values were compared using Mann-Whitney U test. P-value below 0.05 was considered statistically significant.

Results

Demographics and clinical evaluation

A total of 45 patients participated in the study, 21 in the study group and 24 in the control group. Baseline characteristics of the study population are presented in Table 1. There were no differences between the groups in terms of age, BMI, average systolic blood pressure or average diastolic blood pressure.

Endothelial function and arterial stiffness assessment

The mean RHI was lower in patients with endometriosis, compared to healthy controls (1.7 ± 0.5 vs. 2.0 ± 0.5, respectively; $p = 0.037$). Endothelial dysfunction, defined as an RHI value ≤ 1.67, was observed more often in the study group ($n = 11$, 52.4%), compared to control group ($n = 5$, 20.8%) ($p = 0.027$). The mean value of skin autofluorescence measured using AGE Reader was higher in the study group, compared to the control group (2.00 ± 0.6 vs. 1.70 ± 0.2 respectively, $p = 0.013$). The AI and AI@75 were comparable in both groups. The results of the assessment of endothelial function and arterial stiffness in the study group and in healthy controls are presented in Table 2. Comparison of the results between both groups is illustrated in Fig. 2.

Discussion

To our knowledge, this is the first study evaluating endothelial function, arterial stiffness and AGEs skin accumulation in reproductive-age women with endometriosis. The results of the study demonstrate a higher prevalence of endothelial dysfunction and higher AGEs skin accumulation among patients with endometriosis, compared with healthy controls, indicating higher cardiovascular risk in this population.

Endometriosis as a chronic, inflammatory condition, continues to be a subject of ongoing research. Scientists are investigating the influence of endometriosis on several organ systems, and also mechanisms behind its development and progression. In recent years, several studies showed the increased risk of cardiovascular diseases in endometriosis. In a retrospective matched cohort study including 56 090 patients with endometriosis

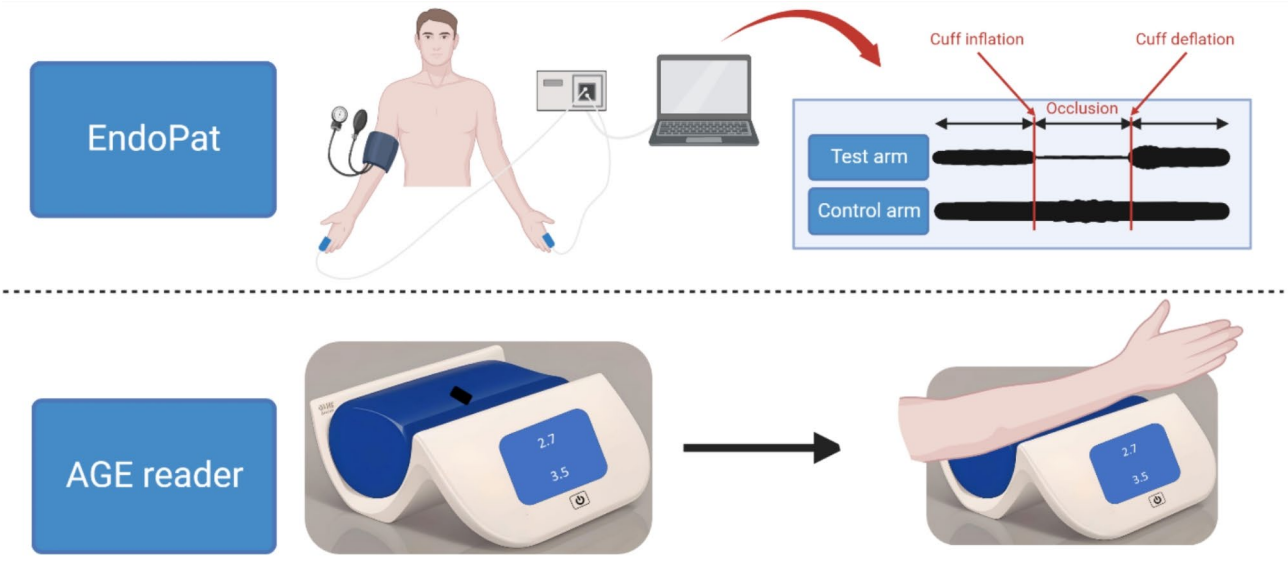

Fig. 1. Working principle of a device to measure endothelial function and arterial stiffness (EndoPAT 2000) and a device to measure skin accumulation of advanced glycation endproducts (AGE Reader). Modified based on[22]. Created with BioRender.com, licensed version (A.G.).

Parameter	Study group ($n=21$)		Control group ($n=24$)		Total ($n=45$)		p
	Mean	SD	Mean	SD	Mean	SD	
Heart rate (beats per minute)	71.5	10.1	67.7	8.5	69.5	9.3	0.180
Age (years)	31.0	5.1	30.3	5.6	30.6	5.3	0.700
Height (m)	1.7	0.1	1.7	0.1	1.7	0.1	0.161
Weight (kg)	62.3	9.5	60.7	14.6	61.4	12.4	0.667
BMI (kg/m2)	22.0	3.9	22.0	4.3	22.0	4.1	0.986
Average SBP (mmHg)	120.5	9.0	115.4	10.1	117.8	9.8	0.079
Average DBP (mmHg)	78.4	8.9	75.8	8.4	77.0	8.6	0.305

Table 1. Characteristics of the study population. BMI- Body Mass Index; SBP – systolic blood pressure; DBP-diastolic blood pressure.

Parameter	Study group ($n=21$)	Healthy controls ($n=24$)	p
RHI (mean, SD)	1.7 (0.5)	2.0 (0.5)	***0.037**
Endothelial dysfunction (%, n)	52.4 (11)	20.8 (5)	***0.027**
AGE Reader (mean, SD)	2.0 (0.6)	1.7 (0.2)	***0.013**
AI (mean, SD)	-4.2 (14.2)	1.0 (13.3)	0.215
AI@75 (mean, SD)	-6.4 (12.1)	-3.6 (12.5)	0.451

Table 2. Results of the assessment of endothelial function and arterial stiffness. AGE Reader - Advanced Glycation Endproducts measurement using AGE Reader device; RHI - reactive hyperaemia index; Ln-RHI - natural logarithm of reactive hyperemia index; AI – augmentation index; AI@75 - augmentation index at 75 beats/min; endothelial dysfunction was defined as RHI equal or below 1.67. * indicates statistical significance at $p<0.05$.

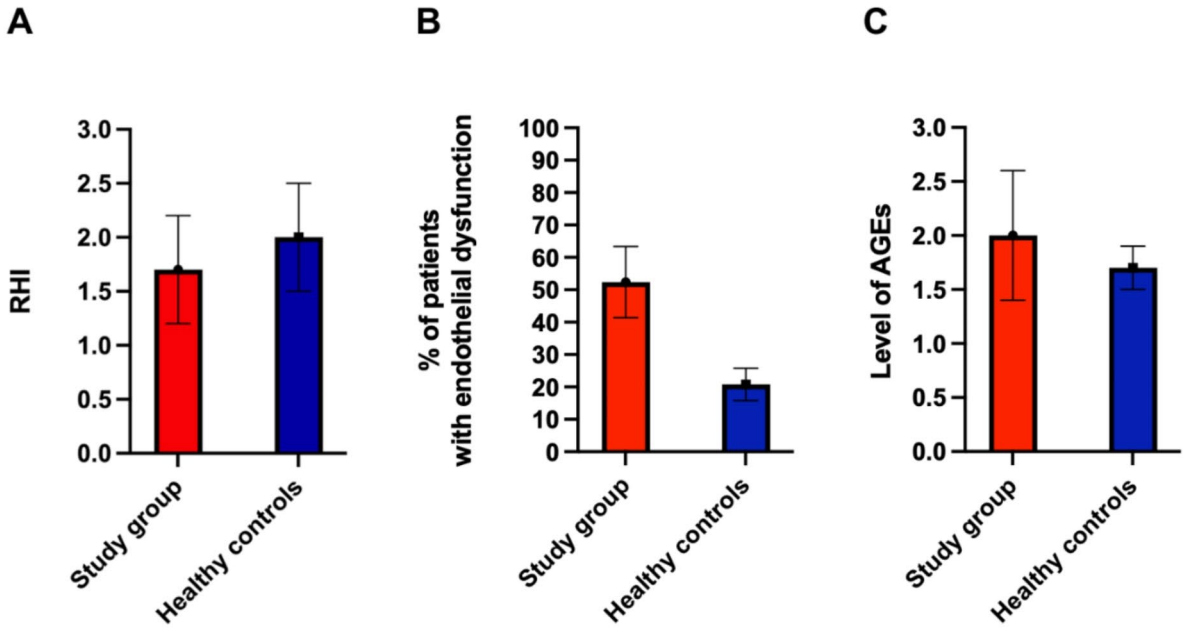

Fig. 2. Comparison of endothelial function and arterial stiffness in patients from the study group and healthy controls. **A** Comparison of mean RHI in patients with endometriosis and in healthy controls ($p=0.037$). **B** Comparison of percentage of patients with endothelial dysfunction within the group of patients with endometriosis and healthy controls ($p=0.027$). **C** Comparison of level of AGEs in patients with endometriosis and healthy controls ($p=0.013$).

and 223 669 healthy controls, women with endometriosis had increased risk of atherosclerotic-based cardiovascular diseases, including ischemic heart disease and cerebrovascular disease[24]. Two other scientific teams also confirmed the increased cardiovascular risk among patients with endometriosis[25,26]. Additionally, it was revealed that women with endometriosis had worse lipid profiles, including higher serum concentrations of total cholesterol, low-density lipoproteins and triglycerides, as well as lower levels of high-density lipoproteins, compared to controls[27]. Women with endometriosis were more likely to develop hypercholesterolemia and hypertension, both of which are also established risk factors for atherosclerotic cardiovascular disease[28,29].

Endothelial dysfunction, recognized as an early sign of atherosclerosis, is another indicator of cardiovascular risk. Multiple methods were used to assess endothelial function in patients with endometriosis, such as cardio-ankle vascular index (CAVI), laser-doppler flux (LDF) and flow-mediated dilation (FMD)[30–32]. For example, higher CAVI values and impaired LDF were found in women with endometriosis, indicating increased arterial stiffness and impaired endothelial microvascular function[30,31]. Moreover, surgical treatment of endometriosis was shown to improve FMD 2 years after the surgery, indicating improved endothelial function[32]. Despite using a different method to assess arterial stiffness, our results are consistent with those reported previously, indicating substantially increased cardiovascular risk in patients with endometriosis[30].

We have not evaluated the pathogenesis of this increased risk, but other authors postulated that it might be due to (i) increased levels of circulating extracellular vesicles (EVs) and (ii) subclinical inflammation inside the peritoneal cavity. Increased levels of EVs released from dysfunctional endothelial cells, known for their involvement in inflammation, were found especially in patients with deeply infiltrating endometriosis (DIE). Concurrently, endometrial stem cells which migrate to the peritoneal cavity in the course of endometriosis undergo differentiation into endometrial cells, which release cytokines, growth factors and adhesive proteins[33–35]. Several studies described the presence of vascular endothelial growth factor (VEGF), interleukines- interleukin-1 (IL-1), IL-8, IL-10, intercellular adhesion molecule-1 (ICAM-1), monocyte chemotactic protein-1 (MCP-1), regulated upon activation, normal T-cell expressed and secreted (RANTES), insulin-like growth factor (IGF), tumor necrosis factor β (TNFβ) and metalloproteinase-9 (MMP-9) in peripheral blood and peritoneal fluid of patients with endometriosis[34,36–42].

Since chronic inflammation is a hallmark of endometriosis, both elevated circulating EV levels and the presence of numerous pro-inflammatory mediators inside the peritoneal cavity underscore the systemic inflammatory state associated with the disease. Similar observations have been made in patients with atherosclerosis, who exhibit elevated levels of circulating EVs in the bloodstream. This association may elucidate the relationship between endometriosis and the preclinical manifestations of atherosclerosis, such as increased vascular stiffness, observed in our study population[43,44].

AGEs promote oxidative stress, inflammation and atherosclerosis, which all are the causes of cardiovascular disease[45,46]. Binding of AGEs to the receptor for advanced glycation end products (RAGE) results in subsequent activation of the pro-inflammatory transcription factors and stimulates chemokine secretion at inflammatory sites[47]. Concurrently, the concentration of soluble form of RAGE (sRAGE) was higher in follicular and peritoneal fluids of patients with endometriosis. sRAGE is considered to be a detoxifying agent by binding agonists of RAGE such as AGEs. The authors concluded that AGEs-RAGE regulation causes a chain reaction: the failure of apoptosis in retrograded, ectopic endometrial cells, localized angiogenesis, and an immunological tissue response that leads to the development and progression of endometriosis[48]. It is important to emphasize that the skin reflects systemic AGE levels more thoroughly than blood measurements, making it a valuable, non-invasive marker for cardiovascular risk assessment[49].

In summary, our findings are consistent with the previous evidence, indicating endothelial dysfunction and increased risk of cardiovascular disease among patients with endometriosis. Although in the described study, we have primarily focused on the cardiovascular risks associated with endometriosis, it is increasingly recognized that endometriosis is not merely a localized gynecological disorder but a systemic disease with widespread implications, largely driven by chronic inflammation. This ongoing pro-inflammatory state potentially results in widespread tissue damage. In the latest research scientists revealed potential relation between endometriosis and polycystic ovary syndrome, caused by systemic increases in kisspeptin levels, tumor necrosis factor- alpha (TNF-α), IL-6, and C-reactive protein (CRP)[50]. Molecular mechanisms by which endometriosis-associated inflammation may influence systemic health are still being studied. The nuclear factor-kappa B (NF-κB) pathway and mitogen-activated protein kinase (MAPK) pathway are considered to be responsible for the systemic spread of inflammation. The systemic effects of chronic inflammation in endometriosis are further supported by evidence showing that endometriosis is associated with an increased risk of autoimmune diseases, allergic disorders, and even certain cancers[51–54].

Given the systemic nature of endometriosis, it is essential to consider therapeutic strategies that address both the local and systemic aspects of the disease. In conclusion, while the cardiovascular risks associated with endometriosis are significant, it is important to recognize the broader systemic effects of this disease. The chronic inflammatory state induced by endometriosis not only contributes to cardiovascular risk but also has widespread implications for overall health, potentially mediated by key inflammatory molecules and pathways. Future research should continue to explore these systemic effects, with the aim of developing comprehensive treatment strategies that address the full spectrum of endometriosis-related health risks.

Strength and limitations of our study

A strength of our study was the inclusion of a well-matched control group, meticulously selected based on age, height, weight, and blood pressure. Further, we used two independent, non-invasive methods to evaluated preclinical manifestations of atherosclerosis in patients with endometriosis. The limitations of the study include a relatively small sample size and the lack of long-term follow-up, which would allow to evaluate the association between endothelial dysfunction and/or skin AGEs accumulation and cardiovascular events. For a more

comprehensive overview, it would be beneficial to also assess and compare laboratory parameters related to cardiovascular risk. Additionally, the study was conducted at a single center, which may limit the generalizability of the findings.

Conclusions

Patients with endometriosis have impaired endothelial function and increased AGEs skin accumulation, which are well-established preclinical manifestations of increased cardiovascular risk. Our results highlight the importance of comprehensive cardiovascular risk assessments and bring attention to the urgent need of comprehensive actions to prevent the development of atherosclerotic-based cardiovascular diseases in women with endometriosis. Furthermore, endometriosis, often diagnosed at a young age, may give a great opportunity for the early detection of atherosclerosis and a better risk stratification in this group of patients. There is a great need for multi-center studies involving larger cohorts of patients to validate and strengthen our findings.

Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Author contributions

J.M.S. funding acquisition, investigation, data analysis, writing—original draft preparation, figures preparation, tables preparation, project administration; Z.D. investigation, data analysis, writing—original draft preparation, tables preparation; M.K. investigation, data analysis, writing—original draft preparation; M.Z. software, funding acquisition; P.A. software, funding acquisition; M.G. methodology, software; R.G. conceptualization, supervision; M.G. conceptualization, supervision; A.G. conceptualization, methodology, funding acquisition, project administration, data analysis, writing—review and editing, supervision, E.R.W. conceptualization, methodology, supervision. All authors reviewed the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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