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ASSOCIATION OF ENDOMETRIOSIS WITH CARDIOVASCULAR EVENTS THE ROLE OF SYSTEMIC INFLAMMATION AND GONADOTROPIN-RELEASING HORMONETHERAPY

Rimma Gagikovna Antonyan[1], Elena Maksimovna Klekovkina[2], Anastasia Sergeevna Moskovskaya[3], Maria Dmitrievna Arkhipova[4], Vera Mikhailovna Cherkina[5], Ivan Alekseevich Barannikov[6], Ziyarat Salimsoltanovna Isaeva[7]

[1]Saratov State Medical University named after V. I. Razumovsky, BolshayaKazachiast., 112 Saratov, 410012 Russia, ORCID: https://orcid.org/0009-0004-6151-7625
[2]Saratov State Medical University named after V. I. Razumovsky, BolshayaKazachiast., 112 Saratov, 410012 Russia, ORCID: https://orcid.org/0009-0001-3098-4800
[3]The Chuvash state university named after I. N. Ulyanov», Cheboksary, Russia, 15 Moskovsky Prospekt, 428014, ORCID: https://orcid.org/0009-0000-9927-7760
[4]South Ural State Medical University, Vorovskogo St., 64, Chelyabinsk, Chelyabinsk region, 454092, ORCID: https://orcid.org/0009-0008-1603-9141
[5]National Research Moscow State University of Civil Engineering,129337, 26, Yaroslavskoye Shosse, Moscow, Russia
[6]Federal State Budgetary Educational Institution of Higher Education «Astrakhan State Medical University" Medical Faculty, 414000, Astrakhan, Bakinskaya str. 121, ORCID: https://orcid.org/0000-0002-8100-9992
[7]Astrakhan State Medical University ,121, Bakinskaya Street, Astrakhan, Russia, 414000, https://orcid.org/0009-0001-0962-3349

ABSTRACT

The aim of the study was to evaluate the association of endometriosis in women of reproductive age with cardiovascular events, as well as to analyze the role of systemic inflammation and gonadotropin-releasing hormone (GnRH) agonist therapy.A single-center observational study was conducted that included 110 patients with laparoscopically confirmed endometriosis who were treated in a Novosibirsk hospital. Clinical and demographic characteristics, traditional cardiovascular risk factors, history of cardiovascular events, levels of highly sensitive C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), as well as the presence and duration of GnRHagonist therapy were evaluated. The primary endpoint was a combined indicator, including myocardial infarction, ischemic stroke, transient ischemic attacks, episodes of unstable angina and hospitalization for hypertension decompensation. Cardiovascular events were reported in some patients and were associated with an older age, an increased body mass index, a higher incidence of hypertension, and more pronounced systemic inflammation in terms of hs-CRP, IL-6, and TNF-α levels. GnRH agonist therapy, especially with a duration of ≥ 6 months, was associated with an increased incidence of cardiovascular events. In a multivariate logistic regression, increased hs-CRP and long-term GnRHagonist therapy maintained an independent association with cardiovascular events after adjusting for age, body mass index, and hypertension. The results obtained emphasize the importance of endometriosis as a condition associated with increased cardiovascular risk, and indicate the important role of systemic inflammation and hormone therapy in the formation of an unfavorable cardiovascular profile in women of reproductive age. A comprehensive interdisciplinary approach involving a gynecologist and a cardiologist, early risk stratification and individualization of therapy are needed.

KEYWORDS: endometriosis, cardiovascular diseases, systemic inflammation, C-reactive protein, interleukin-6, tumor necrosis factor-α, gonadotropin-releasing hormone, GnRH agonists, cardiovascular risk.

INTRODUCTION

Endometriosis is a chronic estrogen–dependent inflammatory disease characterized by the presence of foci of endometrioid tissue outside the uterine cavity. According to epidemiological studies, endometriosis is detected in about a tenth of women of reproductive age and is one of the leading causes of chronic pelvic pain and infertility. In Russian clinical practice, endometriosis is considered as a systemic disease accompanied by local and systemic inflammation, increased oxidative stress, changes in the lipid profile and impaired vascular reactivity [1].

Cardiovascular diseases remain the leading cause of death for women in the Russian Federation. In recent years, more and more attention has been paid to specific risk factors specific to the female population [5]. These factors include pregnancy complications, premature menopause, polycystic ovary syndrome, autoimmune diseases, and endometriosis.

A number of large-scale studies and meta-analyses have demonstrated the association of endometriosis with an increased risk of coronary heart disease, stroke, arrhythmias, and major cardiovascular events [6]. It has been shown that women with endometriosis have a higher risk of coronary heart disease and cerebrovascular pathology than women without this diagnosis, and the risk of major adverse cardiovascular outcomes may increase by 15-20% [7].

Chronic systemic inflammation is considered to be a key link between endometriosis and cardiovascular diseases [11]. In patients with endometriosis, elevated levels of pro-inflammatory cytokines (IL-6, TNF-α, IL-8, IL-17, etc.) are detected both in the peritoneal fluid and in the systemic bloodstream, which is accompanied by increased levels of hs-CRP and activation of endothelial dysfunction [12]. These mechanisms contribute to atherogenesis, increased rigidity of the vascular wall and the development of thrombogenicity.

Drug therapy of endometriosis is of additional importance. Gonadotropin-releasing hormone agonists, which cause reversible drug-induced hypoestrogenism, are widely used in Russian practice. The experience of using GnRHagonist in oncology, in particular in prostate cancer, has demonstrated a possible increase in cardiovascular risk during long-term therapy, which is associated with an adverse effect on lipid metabolism, blood pressure, body weight, and carbohydrate metabolism [13]. However, data on the effect of GnRH agonist on cardiovascular risk in women with endometriosis are limited, and the role of systemic inflammation in this context remains poorly understood.
For domestic clinical practice, it is important to obtain our own data on the relationship between endometriosis, systemic inflammation, and cardiovascular events, taking into account population characteristics, the prevalence of risk factors, and the treatment regimens used [10].

MATERIALS AND METHODS OF RESEARCH

The study was performed in the format of a single-center observational study at a gynecological hospital in Novosibirsk. The protocol was approved by the local ethics committee, and all participants signed informed voluntary consent.
The study included 110 women of reproductive age with laparoscopically and, if indicated, histologically confirmed endometriosis. The age of the patients ranged from 18 to 49 years. The inclusion criteria were the presence of clinically and surgically confirmed signs of endometriosis, regular follow-up with a gynecologist, and the availability of medical documentation. The exclusion criteria included the presence of an active oncological process, severe systemic inflammatory and autoimmune diseases of a different nature, congenital heart defects with pronounced hemodynamic significance, as well as refusal to participate in the study.
Data collection was carried out by analyzing medical records and a standardized survey. Age, body mass index, blood pressure, hypertension, dyslipidemia, type 2 diabetes mellitus, tobacco smoking, and a family history of early cardiovascular diseases were recorded. The gynecological history, the duration of symptoms of endometriosis, the stage according to laparoscopy, and the presence of concomitant gynecological pathology were evaluated. Information about hormone therapy was analyzed separately, including the use of GnRHagonist, the duration of courses, the drugs used, and the time interval between the end of therapy and inclusion in the study.
Cardiovascular events were assessed retrospectively according to medical records (hospital discharge, instrumental examination results, cardiologist and neurologist conclusions) and clarified during the interview of patients. The combined endpoint included myocardial infarction, ischemic stroke, transient ischemic attacks, episodes of unstable angina with documented myocardial ischemia, and hospitalizations for hypertension decompensation.
Laboratory assessment of systemic inflammation was performed with determination of hs-CRP, IL-6 and TNF-α in blood serum. Blood sampling was performed in the morning on an empty stomach, and food was excluded 8-12 hours before the study. The blood samples were centrifuged, the serum was frozen before analysis and examined in batches in a certified hospital laboratory using standardized commercial kits in accordance with the manufacturer's instructions.
For statistical analysis, continuous variables were checked for compliance with a normal distribution. Depending on the nature of the distribution, the data were presented as the mean and standard deviation, or the median and interquartile range. The groups were compared using the Student's t-test or the Mann–Whitney test. Categorical variables were compared using the $\chi 2$ criterion or Fisher's exact criterion. Logistic regression with step-by-step inclusion of variables was used to identify independent associations between clinical and laboratory parameters and the presence of cardiovascular events. Age, body mass index, arterial hypertension, hs-CRP, and the duration of GnRH therapy were introduced into the model. The value of $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSIONS

The study included 110 women with endometriosis. The average age was about thirty-six years, and the median body mass index was in the range of normal or slightly elevated values. A significant part of the patients had arterial hypertension and other traditional cardiovascular risk factors, which corresponded to the modern structure of comorbidity in women of reproductive age with chronic gynecological diseases.
Cardiovascular events included in the combined endpoint were reported in some patients. When comparing groups with the presence and absence of cardiovascular events, differences in age, body mass index, duration of symptoms of endometriosis, and frequency of hypertension were revealed. These characteristics are presented in table 1.

Table 1. Clinical and demographic characteristics of patients with endometriosis depending on the presence of cardiovascular events

Indicator	Without CC events (n = 90)	CC events (n = 20)	p
Age, years	35,1 ± 4,2	39,8 ± 4,6	0,001
Body mass index, kg/m2	24,6 ± 3,1	27,1 ± 3,4	0,004
Duration of symptoms of endometriosis, years	5,1 ± 2,7	7,2 ± 3,0	0,002
Arterialhypertension, %	19	55	0,001
Activesmoking, %	21	40	0,08

Table 1 shows that patients with cardiovascular events were older, had a higher body mass index, and were more likely to suffer from hypertension. These observations are consistent with the idea that even in relatively young women, traditional risk factors remain crucial in the development of cardiovascular complications. Such a profile is especially important for the practice of the Russian Federation, as it allows timely identification of patients who need more active cardiological monitoring and correction of risk factors.

Next, the levels of markers of systemic inflammation and the parameters of AHRH therapy were evaluated depending on the presence of cardiovascular events. The results are presented in table 2.

Table 2. Markers of systemic inflammation and GnRH agonist therapy in patients with endometriosis

Indicator	Without CVevents (n = 90)	CVevents (n = 20)	p
hs-CRP, mg/l, median [IQR]	1,4 [0,9–1,9]	3,9 [3,3–4,6]	<0,001
IL-6, pg/ml, median [IQR]	2,1 [1,5–2,9]	4,3 [3,3–5,4]	<0,001
TNF-α, pg/ml, median [IQR]	8,7 [7,5–10,1]	12,3 [10,8–13,9]	<0,001
AnyGnRHagonisttherapy, %	28	60	0,006
Duration of GnRH therapy ≥ 6 months, %	15	45	0,003

It is noted that patients with cardiovascular events have higher levels of hs-CRP, IL-6 and TNF-α than patients without events. This picture confirms the role of chronic systemic inflammation in the formation of cardiovascular risk in endometriosis and is consistent with data from foreign and domestic studies, which consider endometriosis as a systemic disease with activation of proinflammatory cascades and atherogenic mechanisms. A significant proportion of patients with long-term GnRH therapy in the group with cardiovascular events indicates a possible adverse effect of prolonged drug-induced hypoestrogenism on the state of the cardiovascular system.

Logistic regression was performed to evaluate independent factors associated with cardiovascular events [2]. The model included age, body mass index, presence of arterial hypertension, hs-CRP level, and long-term GnRH therapy. The results are presented in table 3.

Table 3. Factors associated with cardiovascular events in patients with endometriosis

Variable	Odds ratio (OR) 95%	Confidence interval	p
Age, over 1 year	1,10	1,02–1,20	0,015
Body mass index, per 1 kg/m2	1,08	1,00–1,18	0,049
Arterialhypertension (yes/no)	2,90	1,10–7,60	0,031
hs-CRP, per 1 mg/l	1,25	1,05–1,50	0,011
aGnRH therapy ≥ 6 months (yes/no)	2,80	1,05–7,40	0,039

According to these data, an increase in hs-CRP and long-term GnRH therapy maintain an independent association with the presence of cardiovascular events even after age, body mass index, and hypertension are taken into account. This highlights that in women with endometriosis, inflammatory and hormonal components are added to the traditional cardiovascular risk factors, which must be taken into account when risk stratification and management tactics are selected.

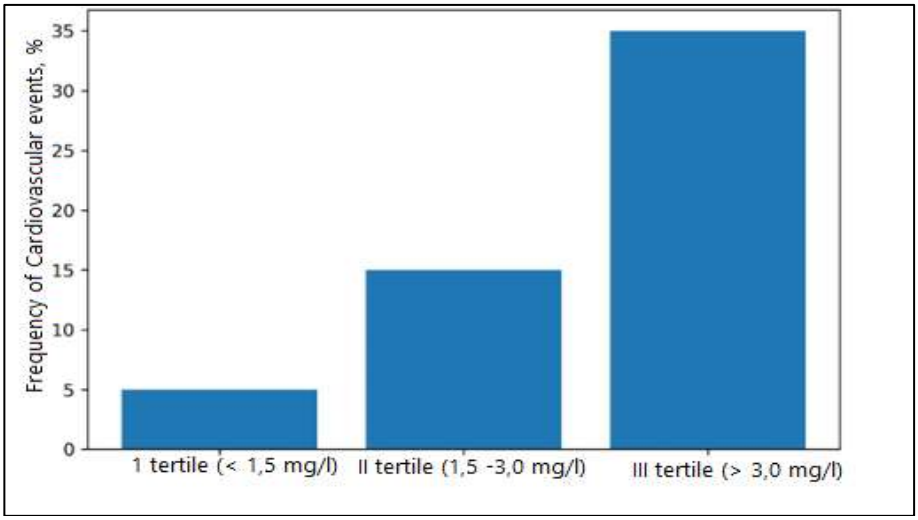

Figure 1. Frequency of cardiovascular events depending on the level of hs-CRP

To visualize the relationship between systemic inflammation and cardiovascular events, the patients were divided into three thirds according to the level of hs-CRP. Figure 1 shows a gradual increase in the frequency of cardiovascular events from the lower to the upper tercile of hs-CRP. In the group with low hs-CRP values, the frequency of events is minimal, whereas in the group with high hs-CRP values, the proportion of patients with cardiovascular outcomes increases significantly.

This stepwise relationship confirms the contribution of systemic inflammation to the formation of cardiovascular risk and is consistent with data on the prognostic value of hs-CRP in the general population. In the context of endometriosis, this allows us to consider hs-CRP as a potential additional marker for making decisions about the need for a more detailed cardiological assessment and early intervention [4].

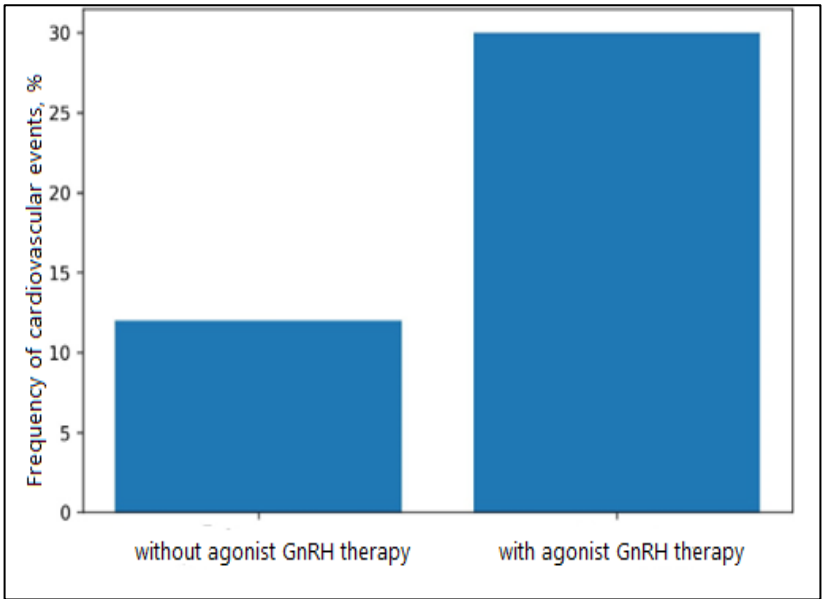

Figure 2. Frequency of cardiovascular events depending on

From GnRH agonist therapy

Figure 2 shows a comparison of the incidence of cardiovascular events in patients who did not receive GnRH therapy and in patients who received such therapy. The higher incidence of cardiovascular outcomes in women treated with GnRH may reflect both the effect of drug-induced hypoestrogenism itself on the metabolic and vascular profile, and the initially more severe course of endometriosis in patients for whom this therapy is selected.

When interpreting these data, it is important to take into account the possibility of confounding factors, including the severity of pain, the prevalence of foci, and the presence of concomitant pathology. Nevertheless, the noted association emphasizes the need for a balanced approach to prescribing long-term courses of GnRH and the expediency of a basic cardiological assessment before starting therapy in patients with risk factors [7].

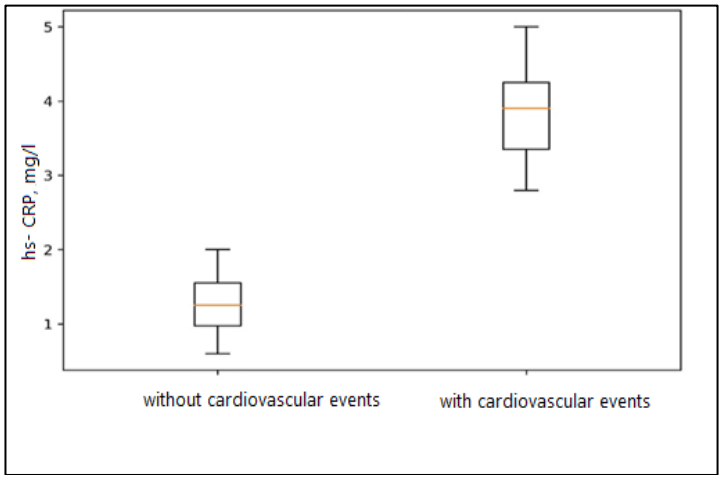

Figure 3. Distribution of hs-CRP in groups with and without cardiovascular events

Figure 3 shows the distribution of hs-CRP in groups of patients with and without cardiovascular events in a box with a mustache format. In the group with cardiovascular events, the median hs-CRP and upper quartile are higher than in the group without events, reflecting more pronounced systemic inflammation in patients with an unfavorable cardiovascular history.

This result complements the data in the tables and highlights that an increase in hs-CRP in women with endometriosis can be considered not only as a marker of disease activity, but also as a potential indicator of increased cardiovascular risk, especially when combined with traditional risk factors [3].

CONCLUSION

A study conducted on a sample of 110 women with laparoscopically confirmed endometriosis showed that some patients develop an unfavorable cardiovascular profile, including an increased incidence of hypertension, an increase in body mass index and a history of cardiovascular events. Patients with cardiovascular events have higher levels of hs-CRP, IL-6, and TNF-α, indicating severe systemic inflammation.

GnRH agonist therapy, especially with a course duration of at least six months, is associated with an increased incidence of cardiovascular events. In the logistic regression model, increased hs-CRP and long-term GnRH therapy maintain an independent association with the presence of cardiovascular outcomes after adjusting for age, body mass index, and

hypertension. These data suggest that endometriosis should be considered as a condition with a potentially increased cardiovascular risk, which is influenced by both traditional factors, systemic inflammation, and hormone therapy.
For clinical practice, this means the need for an interdisciplinary approach to patients with endometriosis, including not only gynecological correction, but also assessment of cardiovascular risk, monitoring of blood pressure, body weight, lipid profile and, if necessary, indicators of systemic inflammation. It is advisable to accompany the appointment of long-term courses of GnRH with a basic cardiological assessment and individualization of preventive measures.

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