

Incidence, diagnosis, and prognosis of myocarditis: does gender matter?

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Myocarditis is an inflammatory heart disease characterized by considerable variability in evolution and clinical manifestations. Although most cases resolve spontaneously, the myocardial inflammation could induce the formation of an extensive scar, resulting in left ventricular remodeling and, eventually, in a long-term evolution into dilated cardiomyopathy.¹

The pathophysiological mechanism responsible for acute myocarditis typically includes an abnormal immune-mediated response to various triggers. The specific etiology of myocarditis often remains undefined, however, the most frequently suspected causes are viral infections and/or immune reactions.² As the COVID-19 pandemic spread worldwide, a myocardial inflammation could also occur during SARS-CoV-2 infection beyond pulmonary involvement. Similarly, a temporal association between COVID-19 vaccination and myocarditis was reported, suggesting a possible relationship between them, although further studies should prove a causal association.³

In the last years, several clinical and experimental studies suggested how the pathogenesis and prognosis of myocarditis differ between the sexes; particularly, the prevalence of myocarditis shows a women to men ratio between 1:1.5 and 1:1.7.⁴ Furthermore, the myocardial acute response to inflammation, which could determine the subsequent risk of chronic evolution into dilated cardiomyopathy, seems to be influenced by sex hormones.⁴ This means that gender is a matter also for the prognosis of this inflammatory heart disease.

In this issue of the *Polish Archives of Internal Medicine*, Ozierański et al⁵ described the sex differences in the incidence, clinical characteristics, management, and outcomes of patients with a clinical diagnosis of myocarditis in Poland in the last 10 years. Notably, they used a nationwide register to identify hospitalizations with a primary diagnosis of myocarditis. Their analysis showed how the incidence of myocarditis

was higher in men rather than in women in all age groups, confirming previous data indicating myocarditis as a male-predominant disease. Moreover, the incidence of myocarditis in men significantly decreased with age. Conversely, women showed an increased incidence of myocarditis in postmenopausal age. These data indicate how sex hormones significantly influence the immune system both in physiological and pathological conditions. Indeed, estrogens exert inhibitory effects on proinflammatory T cells, resulting in a reduced cell-mediated immune response. On the other hand, they stimulate B cells, intensifying antibody response to infection, vaccines, and autoantigens. Moreover, estrogens show a general protective effect on the heart, preventing the apoptosis of cardiomyocytes, fibrosis, and cardiac hypertrophy.⁶ Contrary to that, testosterone induces a combined mechanism of inhibiting anti-inflammatory cells and activating Th1-type immune response, thus promoting the abnormal immune-mediated response involved in the pathogenesis of myocarditis.⁷

Myocarditis is a polymorphic disease characterized by large variability in clinical manifestations, which are strictly connected to the underlying inflammatory conditions and could range from subclinical or asymptomatic disease to sudden death due to severe systolic dysfunction and/or life-threatening ventricular arrhythmias.⁸ Interestingly, in the study by Ozierański et al,⁵ women showed a higher severity of cardiovascular symptoms, including heart failure and cardiomyopathy. Furthermore, a higher rate of cardiac arrhythmias, including atrial fibrillation and ventricular tachycardia, was reported in women. These results are consistent with current data showing that the severity of myocarditis symptoms is greater in women than men.⁴ Possible explanations include a higher incidence of cardiogenic shock favoring cardiac arrest, longer baseline QTc interval, and prolonged repolarization in women as compared with men.⁹

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Indeed, whereas testosterone protects from arrhythmias by shortening action potential, the reduced expression of repolarizing potassium channels and connexin 43 (which is the primary ventricular gap-junction subunit), and the fluctuating QT occurring during the menstrual cycle could induce enhanced arrhythmias vulnerability in women.⁹ Despite the lower severity of clinical presentation, men with myocarditis were more often admitted to cardiology wards, probably due to the greater frequency of cardiovascular diseases in men, including suspected myocarditis and acute and chronic coronary syndrome.¹⁰

The diagnostic workup of myocarditis includes several noninvasive and invasive tests, which, through different accuracy, could help to confirm the diagnosis of suspected myocarditis.¹¹ Transthoracic echocardiography (TTE) is the first-line test to assess cardiac function and pericardial involvement. It is also crucial to rule out other cardiovascular disorders and monitor the evolution of myocarditis and response to therapy.¹² Furthermore, several studies revealed how TTE might provide remarkable prognostic information: an impaired left ventricular ejection fraction (LVEF) at the onset, a persistently reduced LVEF, and the involvement of the right ventricle are indicators of poor prognosis, associated with a high risk of long-term evolution into dilated cardiomyopathy or need for heart transplantation.¹ When acute myocarditis is highly suspected based on clinical evaluation, the use of cardiac magnetic resonance (CMR) is recommended to confirm the diagnosis. CMR provides crucial information for the diagnosis by evaluating the myocardial tissue and cardiac structures, and showing high diagnostic accuracy with the combination of post-gadolinium early and late T1-weighted and T2-weighted images.¹³ Moreover, the tissue characterization through CMR allows for an effective risk stratification of patients with suspected myocarditis, detecting the presence, the extension, and the localization of late gadolinium enhancement.¹⁴ Nevertheless, endomyocardial biopsy (EMB) remains the diagnostic gold standard of myocarditis, endorsing the diagnosis and recognizing the underlying etiology, which is fundamental to guide appropriate therapeutic strategies.¹¹ Interestingly, in the study by Ozierański et al,⁵ the use of CMR and EMB was minimal in both sexes, as they were performed in 16.7% and 0.8% of the overall population, respectively. Also, the rate of TTE performed was relatively low, particularly in women (69.8% vs 79.8% in men). Considering the large availability, the noninvasiveness, and low costs of this diagnostic tool, together with the crucial information regarding diagnosis and prognosis, it could be expected that almost all patients underwent echocardiography. In contrast, these real-world data, coming from a nationwide registry, show how the diagnosis of myocarditis is mostly related to clinical evaluation, and the use of specific instrumental tools (particularly CMR) is highly

insufficient in clinical practice, despite their fundamental role in the risk stratification.

Of note, the study showed that young women (aged 21–40 years) had a poorer short- and long-term prognosis than the corresponding men and, in both sexes, short- and long-term outcomes deteriorated with age.⁵ As mentioned above, reduced LVEF, heart failure at the onset, and arrhythmias are common predictors of poor prognosis.¹ Thus, the higher severity of cardiovascular symptoms and the greater rate of arrhythmias reported in women could partially explain the reported worst outcomes in the study. Furthermore, most study patients required rehospitalization during the 5-year observation period. Men showed a higher rate of recurrent hospitalization due to myocarditis, while women were more frequently admitted to the hospital for arrhythmias and heart failure. Analyzing the overall population of the study regardless of age, sex, and follow-up time, the patients with myocarditis showed a poorer prognosis than the age-sex-matched general population.⁵ These findings strongly suggest that the treatment of myocarditis requires significant improvement, particularly for long-term evolution and prognosis. Indeed, patients with mild symptoms of heart failure, treated with β -blockers, show an excellent prognosis, with high rate of survival and no need for heart transplantation at 5-year follow-up.¹⁵ However, gaps in evidence exist regarding new or existing immunosuppressive or immunomodulatory regimens and antiviral therapies in patients with myocarditis. Further large, prospective, randomized controlled studies are needed in order to assess optimal medical treatment duration with conventional heart failure and anti-inflammatory drugs.

In conclusion, critical knowledge gaps exist regarding diagnosis, prognosis, and treatment of acute myocarditis and its possible evolution into chronic cardiomyopathy, regardless of sex and age. In this regard, the study by Ozierański et al⁵ provides relevant information. Firstly, the inclusion of real-life patients through the nationwide database confirmed myocarditis as a male-predominant disease, more common in younger than older men, although the prognosis seems to be worse for women. Furthermore, it demonstrated how the recommended procedures (TTE, CMR, and EMB) were underperformed in clinical practice in most hospitals, despite their key role in diagnostic and prognostic evaluation. Thus, novel specific and sensitive biomarkers, besides new imaging modalities, are needed in order to standardize the management of myocarditis and short- and long-term therapeutic strategies, which currently vary largely.

ARTICLE INFORMATION

DISCLAIMER The opinions expressed by the author(s) are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

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