REVIEW ARTICLE

Coronary Artery Disease in Women: Getting to Know Gender Related Disparities

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Abstract

Coronary artery disease (CAD) and ischemic heart disease (IHD) are often indistinctly used terms. Both combined have generated, over the past years, concerns about sex disparities in their presentation. From an epidemiological perspective, females have several disadvantages regarding the prevention, diagnosis, and treatment of CAD. Most of the general cardiovascular risk factors affect women more frequently, or with a higher morbidity and mortality association. Besides, atypical manifestations of the disease and uncommon forms of CAD represent a diagnostic challenge for clinicians. Even if current treatments for CAD have no apparent sex bias, women representation in clinical trials and treatment patterns analyzed in clinical practice refuse this statement. Several disparities are caused by inevitable sex-particularities, but many of them are more social, cultural, and dogmatic beliefs that have to be addressed and overhaul.

Introduction

Cardiovascular diseases (CVD) arise as one of the leading causes of death worldwide, taking an estimated 17,9 million lives each year.[1] Between 1990 and 2010, the global prevalence of CVD in women decreased but in the last years, there has been a significant increase, especially in highly populated countries. This rise should be an important call to action to develop more programs aimed at women's cardiovascular health.[2] With this data, the United Nations General Assembly, through the Sustainable Development Goals, set the target to reduce premature mortality from non-communicable diseases by a third until 2030 (relative to 2015 levels), in which IHD is one of many targets. This goal is aimed to be reached with country-specific decisions involving health system interventions, finance, and policies that could improve the management of non-communicable diseases.[3]

For Latin America, the epidemiological transition regarding population aging, unhealthy diets, increased smoking habits, and physical inactivity, according to the Pan American Health Organization, has made IHD the leading cause of death in Latin American women. They also estimate that the prevalence of CAD will triple over the next 20 years, with higher mortality rates in women compared to men. Moreover, the traditional roles for these women in domestic labor create a barrier to a healthy lifestyle and physical activity.[2]

Historically, the guidelines and data concerning CAD have been retrieved mainly from results obtained from studies on men.[4] This lack of inclusion has generated a selection bias, leaving women with specific risk factors, diagnoses, and symptoms aside from the general knowledge of specialists, general practitioners, and medical students. With this review, we aim to expose the differences between men's and women's CAD, so that the existing disparities can be known, and many underdiagnosed women can receive early diagnosis and treatment.

Epidemiology

CAD affects around 1.72% of the population worldwide, meaning that almost 2 in 100 people will

Keywords

Coronary Disease; Female; Risk factors.

suffer from it during their lifetime; unfortunately, the prevalence has increased over the past years along with population aging.[5] In the United States, nearly 1 in 4 deaths is caused by CVD,[6] and for women, 1 in every 3 deaths is caused by CVD.[7-8] In Mexico, data remains discouraging, as CVDs accounted for 20.8% of all deaths in 2020, being the first cause of death for both men and women, even above COVID-19. Interestingly, CVDs worldwide are slightly less prevalent in women between 35–64 years of age compared with men, nonetheless, this statistical difference disappears in people >65 years old.[9] This is relevant as CAD is the most prevalent form of CVD in the world.[5]

Over the years, there has been a consensus in the literature on a clearly higher rate of mortality and complications due to myocardial infarction (MI) in women than in men.[10] Trials like TRANSLATE-ACS (treatment with adenosine diphosphate [ADP] receptor inhibitors: a longitudinal assessment of treatment patterns and events after acute coronary syndrome [ACS]) suggest that differences in outcomes of MI are completely independent of sex.[11] However, an analysis of the French Nationwide Hospital Database revealed a 30% excess of mortality in women with MI, even when adjusted for age and comorbidities.[12] The reasons for such differences are variable and multifactorial.

For instance, women have historically represented no more than 30% of people enrolled in clinical studies.[13] A previous review of 150 CAD studies used for the development of clinical guidelines for women and men, determined that of the 801,198 participants, only 31% were women. Moreover, no sex-specific analyses were addressed regarding female-specific important physiological factors (pregnancy, hormonal fluctuations, etc.). Data from men were then simply extrapolated to determine female guidelines.[14] The same problem arose when concerning interventional cardiology studies, for so, many of the therapeutic options like stents were considered to be much more beneficial in men, even if no such assertions were confirmed.[10] A clear deficit of women in trials was once again the real problem. In fact, according to a study performed by the American National Heart Association, women benefited from percutaneous interventions, stent placement, and coronary angioplasty equally as men.[15] Despite these findings, women were less likely to receive treatment guidance, preventive therapeutics,[16] aggressive medical treatments,[17] and cardiac rehabilitation,[18] even when comparing patients of both sexes with exactly the same cardiovascular risk

factors such as diabetes, dyslipidemia, hypertension, among others.

Traditional risk factors

Compared to traditional cardiovascular risk factors, women tend to be more affected by common risk factors of both sexes, have less probability to achieve adequate control of them, and have additional ones that are women-specific, such as those related to pregnancy or menopause.

One of the most well-known and relevant risk factors is hypertension, which is more prevalent in women, affecting 25% of the female population worldwide and contributing to 14.3% of the total female deaths (compared to 11.4% in men).[19] Another recent study demonstrated that women older than 65 years with hypertension had a considerably worse prognosis and higher risk of cardiovascular events.[20] Besides that, only 23% of women compared to 38% of men older than 80 years of age in the United States managed to maintain a blood pressure goal of 140/90 mmHg or less.[21] Finally, among female patients, dyslipidemia has the highest Population Attributable Risk (PAR) at 47.1%, compared with all other known risk factors for CVD.[22] In fact, postmenopausal women have a dramatic rise in low-density lipoprotein (LDL) cholesterol with a decline in high-density lipoprotein (HDL) levels, increasing drastically their risk for CAD (Figure 1).[23]

Biological risk factors

There are biological female-specific risk factors that can compromise the life of pregnant women and the wellness of products of conception. The most studied risk factors for CAD in this population are preterm delivery, preeclampsia, gestational hypertension, gestational diabetes mellitus (GDM), the capacity of losing weight after delivery, autoimmune diseases, and even depression.[7] For instance, the severity degree of preeclampsia is correlated with the severity of CVD later in life. Additionally, as for autoimmune diseases, rheumatoid arthritis increases 2 to 3 times the risk for MI, while systemic lupus erythematosus increases the risk by 9 to 50 times.[8] Also, women with obesity have a higher risk of developing CAD (64%) than their male counterparts (46%),[24] and when diabetes coexists, they exhibit a higher risk of MI with a higher mortality rate.[7] The rates of obesity are higher in women in all age groups.[25,26] Compared to men, women with a body mass

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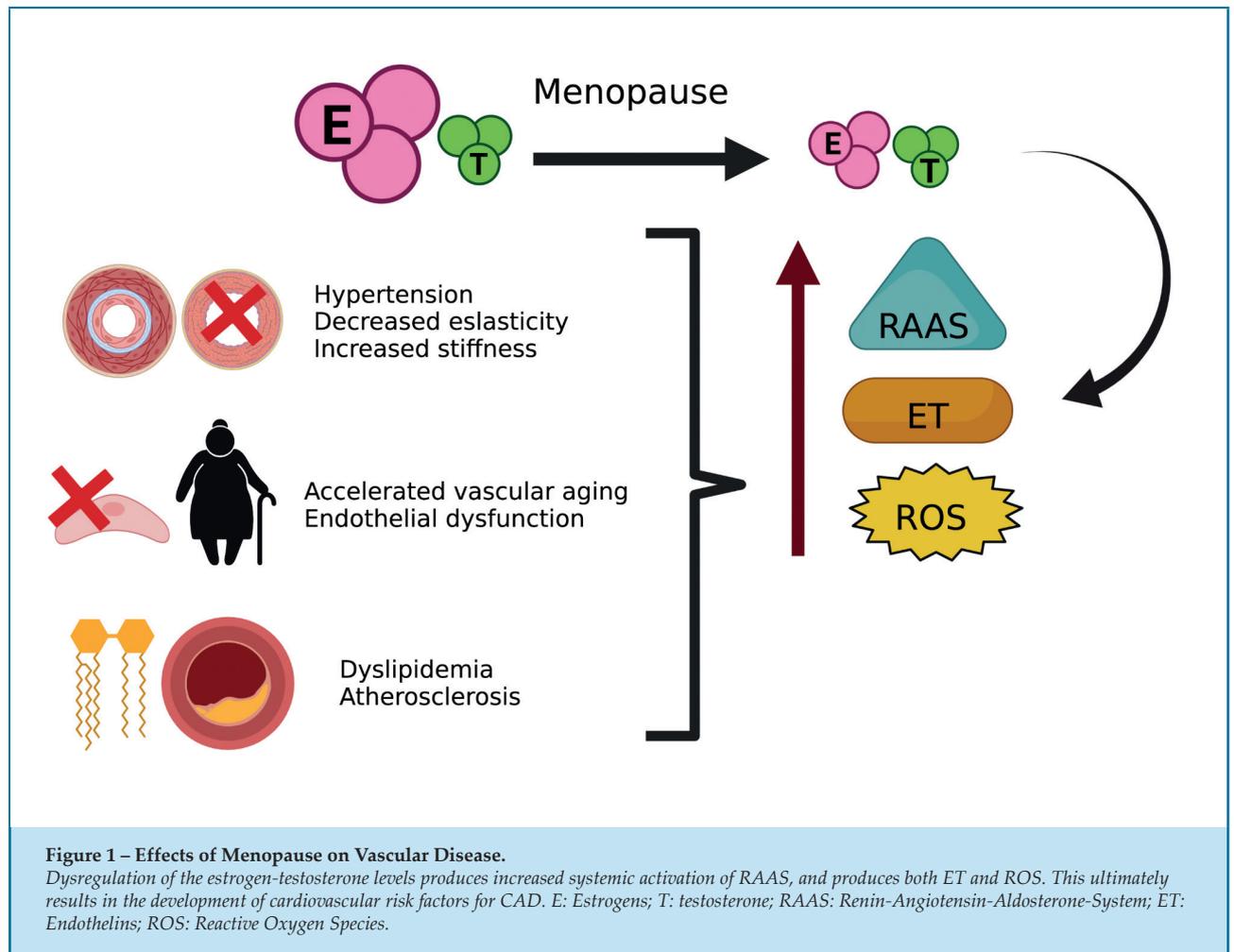Int J Cardiovasc Sci. 2023;36:e20220022
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Figure 1 – Effects of Menopause on Vascular Disease.
Dysregulation of the estrogen-testosterone levels produces increased systemic activation of RAAS, and produces both ET and ROS. This ultimately results in the development of cardiovascular risk factors for CAD. E: Estrogens; T: testosterone; RAAS: Renin-Angiotensin-Aldosterone-System; ET: Endothelins; ROS: Reactive Oxygen Species.

index (BMI) >30 have a higher relative risk for CAD.[25,26] A meta-analysis made by Huxley et al. showed that smoking increased the risk for CVD in women from all age groups, except for the group from 30–44 years old.[27] It is then clear that biological differences among sexes have an impact on the prevalence, physiopathology, and clinical manifestations of CVDs (Figure 2).

Social risk factors

Gender is defined as the group of characteristics, including norms, behaviors, and roles of women and men that are socially constructed.[28] Gender differences among women and men arise from sociocultural practices as lifestyle, nutrition, and behavior.[7] Social female-specific risk factors for CVDs that have been described so far are inactivity, sedentary lifestyle, and smoking habits.[7,23,27,29] Physical inactivity is a risk factor that varies between genders. It has been reported that women have a higher tendency to present sedentary lifestyles than men (33.2

vs 29.9%, respectively),[30] since their teenage years.[7,31,32] Inactivity and sedentary behavior are risk factors for obesity, as well as for CVD.[23,29] Smoking is associated with atherosclerosis, MI, and sudden cardiovascular death.[33,34] Women smokers have a greater risk of developing CAD and dying from IHD.[35,36] It is also important to note that the concomitant use of oral contraceptives while smoking results in an increased risk of MI, stroke, and venous thromboembolism.[37,38] Women present a 25% higher risk for CAD by smoking (Figure 2).[27]

Psychological factors

Underlying psychological factors may contribute to the physiopathological process of CVDs. In women, angina is related to the phenomenon of mental stress ischemia (MSI), a transient myocardial ischemic response to mental stress.[39] Mental stress tends to further affect the cardiovascular system in women compared to their male counterparts.[40] Psychological stressors like

Figure 2 – Risk factors for CAD associated to women.
CAD: coronary artery disease.
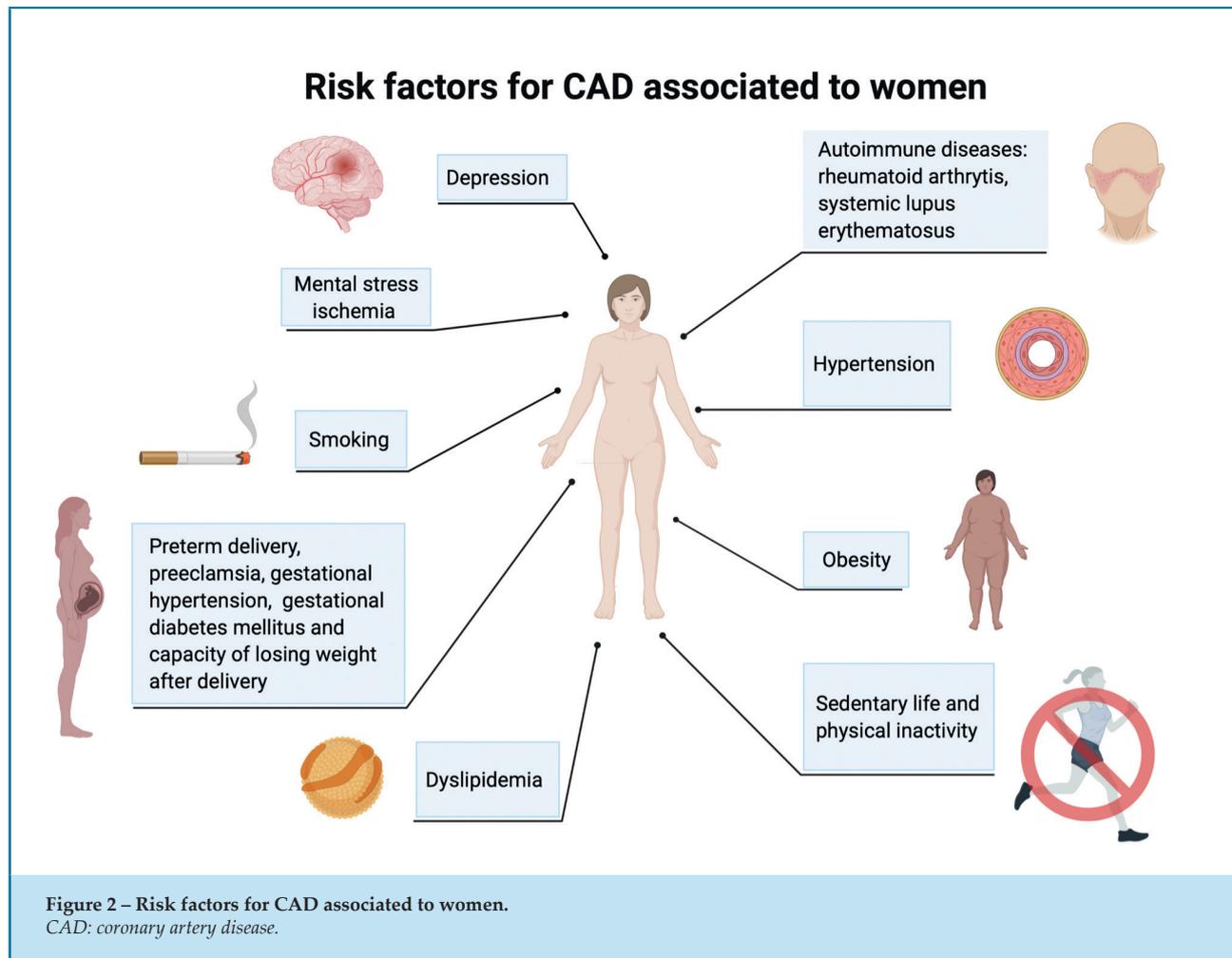
anxiety and anger may provoke vasoconstriction and microcirculatory dysfunction resulting in ischemia and microvascular angina in women.[40,41] Finally, women tend to suffer a worse psychological outcome after a CVD.[42] An example of this is the higher rate of depression following cardiac events in young women.[43] Most of the time, sex differences linked to biological characteristics can be controlled, yet can't be changed. Highlighting the impact of gender-related characteristics on CVD results is very important because these are risk factors that can be changed and managed by women for a better prognosis. It would be important to find gender-related risk factors specific for different CVDs, such as CAD.

Physiopathology

Recently, important findings regarding the pathophysiology of CAD among women revealed several particularities and sex-dependent aspects. For instance, cardiovascular changes observed in both sexes that are associated with age are 1) development of greater diameter in central elastic arteries, 2) thickening of both intimal and medial laminae (especially the latter), 3) greater collagen deposition and elastin degradation/fragmentation, 4) loss of vascular smooth muscle cells (VSMC), 5) hypertrophy and migration to the lamina intima of the remaining VSMC, and 6) hypertrophy of endothelial cells.[44] Concerning women, the most important age-related changes in the cardiovascular system occur after menopause. As estrogens decline drastically and androgens slowly, endothelins' expression increases (vasoconstrictors), the renin-angiotensin-aldosterone system activates, and oxidative stress increases in a considerable way. Furthermore, vascular aging is accelerated due to endothelial dysfunction, dyslipidemia, loss of arterial elasticity – with respective increased arterial stiffness –, increased pulse wave, hypertension, and atherosclerosis (Figure 1).[19]

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With regard to relevant female-specific pathophysiological processes of obstructive CAD, women – especially the younger ones – tend to present a higher frequency of plaque erosion rather than rupture. Despite presenting less involvement of inflammatory components, plaque erosion generates a more dangerous type of remodeling, showing a higher deposition of VSMC, proteoglycans, and fibrotic tissue. In addition, even if this notable difference between plaque erosion and rupture is lost over time (since as women enter into the post-menopause period, they start to present more plaque rupture), it is important to keep this in mind as it is a diagnostic and therapeutic challenge due to its lower frequency.[10]

Moreover, an interesting entity called the Yentl syndrome, that was identified more than a decade ago, remains as a valid statement: when women´s clinical presentation resembles men´s pattern (mostly regarding traditional obstructive CAD presentation), they are much more likely to be treated in the same way, even if the pathology or condition might be different.[45] Despite often having a similar clinical presentation as obstructive CAD, women are more inclined to present non-obstructive CAD as a cause for IHD. Non-obstructive CAD can be observed in pathologies such as Takayasu arteritis, coronary microvascular dysfunction, vasospasms, vasomotor abnormalities, and spontaneous coronary artery dissection.[7,23] In this way, women tend to present more ischemic findings spotted by biomarkers or stress tests, rather than coronary obstruction findings, especially among young women.[46] Furthermore, even if non-obstructive CAD represents a less frequent cause of MI worldwide,[23] the Women's Ischemia Syndrome Evaluation (WISE) trial determined that over 50% of women presenting signs or symptoms of IHD have no apparent epicardial coronary stenosis.[47] Constituting then, a far less frequent finding, non-obstructive CAD is more difficult to treat and diagnose appropriately. Thus, it is important for future clinicians to avoid the use of "CAD" and "epicardial coronary obstruction" as synonyms.

As for pregnancy, some other related physiological changes could potentially be involved in the appearance of CAD, that are the increase in blood volume, hypertrophy of VSMC, loss of vascular intercellular matrix, among others.[23]

Clinical manifestations

Women tend to be ten years older than men at the time of CAD diagnosis due to the fact that they have a later symptom onset. As mentioned before, women present more evidence of ischemia with less obstructive findings compared with men.[48] Angina is a common manifestation in both genders,[49] but female patients tend to present atypical symptoms more often. In a study of 515 women, 43% did not have chest pain at the time of evaluation. In fact, the most commonly observed symptoms were dyspnea (58%), weakness (55%), and fatigue (43%).[26] Moreover, these symptoms do not occur necessarily after physical effort, but they can also be triggered after emotional stress.[49]

Diagnosis

There are several diagnostic scores and/or scales that aim to stratify and sort out CAD for each particular case. They are useful for choosing the best way of addressing the disease and elucidating the most probable outcomes. In this way, the WISE study group proposed a scheme where the microvascular function must be associated with the global risk. In asymptomatic patients, the screening of subclinical CAD should be evaluated through the Framingham Risk Score and markers of "atherosclerotic burden", such as carotid intima-media thickness, ankle-brachial index, or coronary calcium scan. For symptomatic patients, there are a variety of techniques that can be applied. Stress testing with electrocardiogram (ECG) or cardiac imaging has the greatest incremental value in symptomatic women with intermediate to high risk of CAD. The ECG exercise test is considered the initial election test in women with CAD, despite having lower sensitivity and diagnostic accuracy than in men. Stress echocardiography can assess both cardiac structure and ventricular function, providing a higher prognostic value over ECG exercise. The single photon emission computed tomography (SPECT) exhibits a more accurate diagnostic power in women with CAD, but it may give false-positive results due to breast tissue artifacts and to their lower amount of myocardial tissue compared to men. Computed tomography (CT) scan quantifies the amount of calcium in the coronary arteries, and through the score, it is possible to predict the risk of atherosclerotic CVD events.[46]

Summary and Conclusions

The recent data on sex differences in CVD show the importance of highlighting this new knowledge in clinical practice and research studies.

From biological variances to gender-related factors, there are many characteristics that influence the distinct prevalence, physiopathology, and clinical manifestations of CVDs in women. It is known that women are underrepresented in clinical trials, therefore, several assumptions about their response to treatments or diagnostic approaches have been taken for granted. Moreover, they tend to be considered less fitable candidates for several interventions, even when recent evidence supports the usefulness of those interventions in female patients. Besides, clinicians also tend to dismiss particular clinical features of diseases in women, especially regarding atypical clinical presentations or less prevalent causes of both CAD and CVDs in general. This behavior leads to the current imprecise guidelines and information regarding more than half of the population.

Even nowadays, there is a huge bias towards CVDs in women, and continuing to extrapolate data from men to women is currently known to be a harmful approach. Misleading diagnosis and both ineffective or difficult treatments could be avoided by taking into account sex-specific differences. Furthermore, knowing the specific risk factors for women can help to identify and target the information that they must receive from the health advisors, being important to differentiate between those associated with the patient's gender. It is essential to remember that even when biological particularities are important, norms, behavior, and gender roles may represent cardinal risk factors of equality. Finally, having specific considerations while studying CVD in women, and having gender-related clinical perspective will contribute to better prevention guidelines, diagnostic skills, and treatment decisions. It is necessary to focus further investigations on identifying social and gender-related characteristics that act as risk factors. The possibility of reducing and even eliminating these risk factors has great potential.

Author Contributions

Conception and design of the research: Gilabert-Garcia A, Guerrero CCV, Dagio-Cuéllar R, Bermudez-Gonzalez JL, Armenta-Moreno JI, Espinola-Zavaleta N. Acquisition of data: Gilabert-Garcia A, Guerrero CCV, Dagio-Cuéllar R, Bermudez-Gonzalez JL, Perez-Partida AM, Berarducci J, Luna-Alvarez-Amezquita J, Straface JI, Espinola-Zavaleta N. Analysis and interpretation of the data: Gilabert-Garcia A, Guerrero CCV, Dagio-Cuéllar R, Bermudez-Gonzalez JL, Espinola-Zavaleta N, Alexanderson E. Statistical analysis: Alexanderson E. Writing of the manuscript: Gilabert-Garcia A, Guerrero CCV, Dagio-Cuéllar R, Bermudez-Gonzalez JL, Perez-Partida AM, Berarducci J, Armenta-Moreno JI, Luna-Alvarez-Amezquita J, Espinola-Zavaleta N, Alexanderson E. Critical revision of the manuscript for intellectual content: Gilabert-Garcia A, Guerrero CCV, Dagio-Cuéllar R, Bermudez-Gonzalez JL, Perez-Partida AM, Berarducci J, Armenta-Moreno JI, Luna-Alvarez-Amezquita J, Espinola-Zavaleta N, Alexanderson E.

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