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Topics of heart disease in women

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Editorial

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Impact of heart disease on women in Latin America

Impacto de las cardiopatías en la mujer de Latinoamérica

Gabriela Borrayo-Sánchez,* Adriana Puente-Barragán,‡ Claudia Almonte,§ Eduardo Meaney¶

Cardiovascular diseases (CVD) are the leading cause of mortality in women worldwide, responsible for 35% of all deaths worldwide and 18.6 million deaths annually, mainly affecting women from middle and low-income countries. Most deaths (> 50%) are secondary to ischemic heart disease. In Latin America (LATAM), every 9 minutes, a woman dies from CVD, and contrary to what is commonly considered by the general population, CVD is responsible for five times more deaths than breast cancer.[1,2]

The «traditional» cardiovascular risk factors (CVRFs) equally favor the development of CVD in both genders. However, in Latin America (LATAM), high blood pressure, dyslipidemia, and diabetes mellitus are the CVRFs with the most significant impact on the development of CVD in women, increasing the risk of developing ischemic heart disease from 1.5 to 2.0 times more than in men. These peculiarities arise due to biological differences (linked to sex, age, race, ethnicity, and family background) and, on the other hand, due to differences linked to gender or social determinants (socioeconomic and employment level, education, status). In addition, sociocultural, interpersonal, and family relationships determine the existence of «emerging or underrecognized» risk factors (depression, stress, immunological diseases, oncological treatments, environmental pollution) and the presence of «unique or little recognized» risk factors (menopause, hormone replacement therapy, menarche, polycystic ovaries, hypertensive disorders of pregnancy). The importance of knowing how to recognize these risk factors in women is to timely detection of these conditions that increase cardiovascular risk up to 4 to 7 times during the different stages of a woman's life.[3]

Even though, in recent decades, there has been a reduction and control of risk factors and the development of various scientific advances, women continue to die from CVD due to various existing gaps in its diagnosis and treatment. Furthermore, socioeconomic

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deprivation contributes substantially to the global burden of CVD in women, which remain understudied, underrecognized, poorly diagnosed, inadequately managed, and underrepresented in most cardiovascular clinical trials. In addition, the poor understanding of the pathophysiological mechanisms and the natural history of CVD linked to gender remain controversial and deficiently understood. This fact may contribute to increased mortality from myocardial infarction in young women in recent years.[4]

It is necessary to increase awareness in the general population and in the medical community about the importance of timely diagnosis and management of CVD in women. As well as make a «call to action» to design and implement clear and urgent prevention strategies and multidisciplinary and comprehensive management, which guarantees access and delivery of equitable health services, and an improvement in the quality of medical care, to reduce mortality secondary to CVD in LATAM[5] women.

One in 3 women in Latin America is aware that heart disease is their leading cause of death. They may be more likely to develop cardiovascular diseases a decade earlier than those not from that geographical area.

The woman assumes the role of caretaker and superwoman, attending to the needs of everyone around her and postponing her own. The food she prepares for her family is usually not so healthy, and the more she adheres to the traditions of industrialization or junk food, the quality of the diet decreases significantly. Campaigns that combat cardiovascular risk factors such as smoking, an unhealthy diet rich in saturated fats, alcoholism, and a sedentary lifestyle have identified other factors that affect cardiovascular disease in women. Events such as diabetes and hypertension in pregnancy, menopause before age 45, endometriosis, autoimmune diseases, and polycystic ovary syndrome, among other conditions, increment CV risk substantially. Unfortunately, many women affected by those potentially dreadful conditions do not consider that they have a high risk and therefore do not pay enough attention to their health care.

The need to collect regional and local data to effectively treat cardiovascular diseases in women is highlighted due to the variations, recognition, and effective treatment required for them.

The purpose of having written this supplement focused on cardiovascular disease in women is to publicize further the gender-specific characteristics of traditional and emergent risk factors, as well as the clinical, epidemiological, pathophysiological, therapeutic, and prognostic differences of cardiovascular disease in women.

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Chapter 1

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Epidemiological impact of cardiovascular diseases in women

Impacto epidemiológico de las enfermedades cardiovasculares

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INTRODUCTION

Cardiovascular disease (CVD) in women is a public health problem since it represents the leading cause of mortality and morbidity worldwide. It was responsible for 35% of all deaths in women in 2019.[1]

Cardiovascular conditions, including those related to the circulatory system, ischemic heart disease (IHD), and stroke, are estimated to cause 2 million deaths annually in the Americas, according to data from PAHO 2019.[2]

Latin America (LA) has experienced rapid but uneven economic and social changes in recent decades. Although the general health status of the population, especially women, has improved, there is a marked difference between low- and middle-income countries.[1]

The epidemiological transition, with the consequent population aging, the growth of cities, and the increase in the prevalence of unhealthy lifestyles, have contributed to the rise in CVD morbidity and mortality in women.[3] Many factors contribute to this scenario. The existing inequity in preventing, detecting, and managing CVD in both sexes is relevant.

CARDIOVASCULAR MORBIDITY IN WOMEN

Regarding morbidity, IHD and stroke are the leading causes of Disability Adjusted Life Years (DALYs) in women *(Figure 1)*.[2]

We must consider that other causes of heart disease are important in Latin America, such as Chagas disease and rheumatic fever, which cause myocarditis, cardiomyopathy, and arrhythmias. These conditions have a high prevalence rate that varies between regions such as Argentina and Costa Rica (10/100,000 inhabitants).[2] Notably, approximately 1,125,000 women of reproductive age are infected with Chagas disease.[4,5]

Rheumatic heart disease is also endemic in Latin American countries, presenting DALY rates per 100,000 inhabitants ranging between 137 in Bolivia, 85 in Brazil, and 5.2 in Colombia, affecting women during their childhood and reproductive life.[2-6]

In addition to traditional and non-traditional cardiovascular risk factors, socio-cultural factors specific to the region must be considered in women as aggravating risks for their health. For example, the change in the conventional role of women as mothers and homemakers to workers out of the home has created an additional barrier to maintaining a healthy lifestyle, adding a high-stress load in both work areas.

On the other hand, access to health care is inequitable. Latin American indigenous women or women of African descent have worse health outcomes and shorter life expectancy than non-indigenous or Afro-descendant women due to poor quality of medical care.[1]

CARDIOVASCULAR MORTALITY IN WOMEN

CVDs cause the greatest mortality burden in the Americas, among men and women,

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being the most critical specific pathologies, coronary heart disease, and stroke. Age-adjusted CVD mortality rates in women decreased from 203.3 deaths (95% CI: 176.0 to 227.1) per 100,000 population in 2000 to 137.2 deaths (95% CI: 110.3 to 165.5) per 100,000 population in 2019. In general terms, in recent decades, in most countries, there has been a decrease in the mortality rate, attributable to the reduction in smoking[3] and improved access to diagnosis and treatment, except in the Dominican Republic, where it has increased.[3]

If we compare the ten leading causes of mortality in women in the Americas in 2019, we found ischemic disease as the first cause with a rate of 95.8 per 100,000 inhabitants, in third place, stroke (50.3 per 100,000) and ninth place, breast cancer (21.2 per 100,000).[7]

Coronary or ischemic heart disease is the most important specific cause of death in women, also presenting a marked variation between countries (180.4 per 100,000 in Haiti and 24.8 per 100,000 in Chile).[7]

The mortality rate of rheumatic disease per 100,000 inhabitants varies between 12.6 in Haiti and 3.6 in Bolivia, being lower than 0.5 in other countries such as Chile, Argentina, Colombia, and Venezuela *(Figure 2)*.[7]

CONCLUSION

CVDs are a public health problem in women in the Americas, which must be approached from a perspective of social determinants with particular emphasis on the inequalities that are observed depending on the level of development of the countries.

We are concerned that morbidity and mortality from different cardiovascular causes affect mainly women who live in poorer areas, so we believe that it is necessary to focus actions and resources on campaigns that improve prevention and access to therapies that address all stages of the female life cycle.

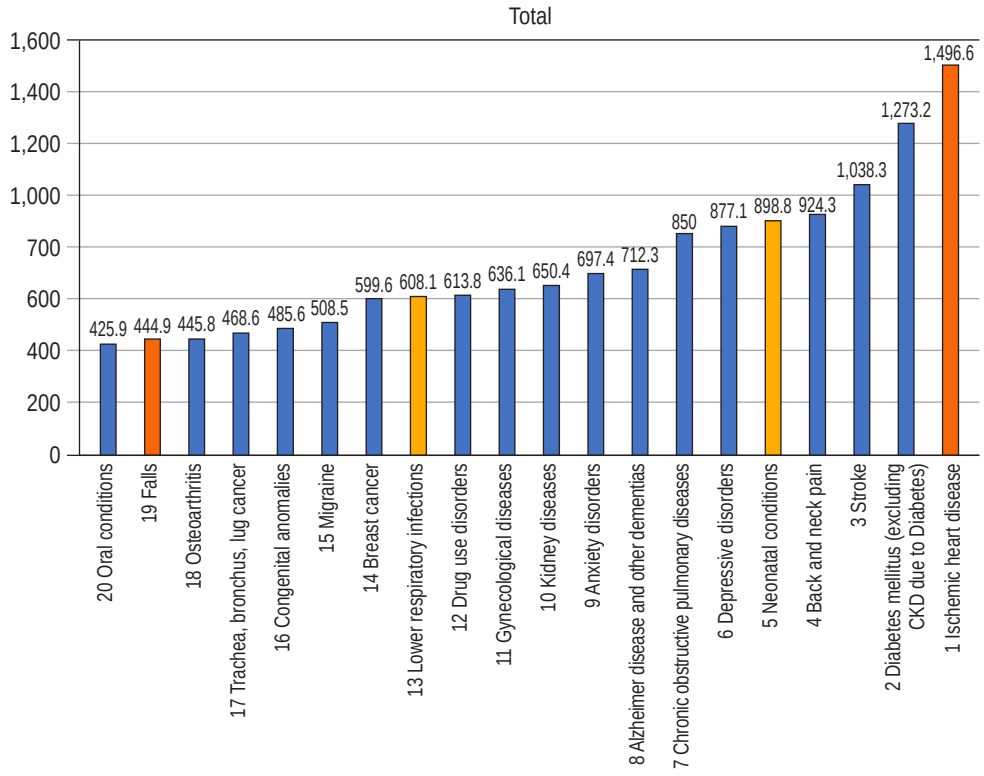

Figure 1: Cardiovascular disease mortality rates in women adjusted for age in Latin America, 2019. Adapted from: Pan American Health Organization; 2021.[2]

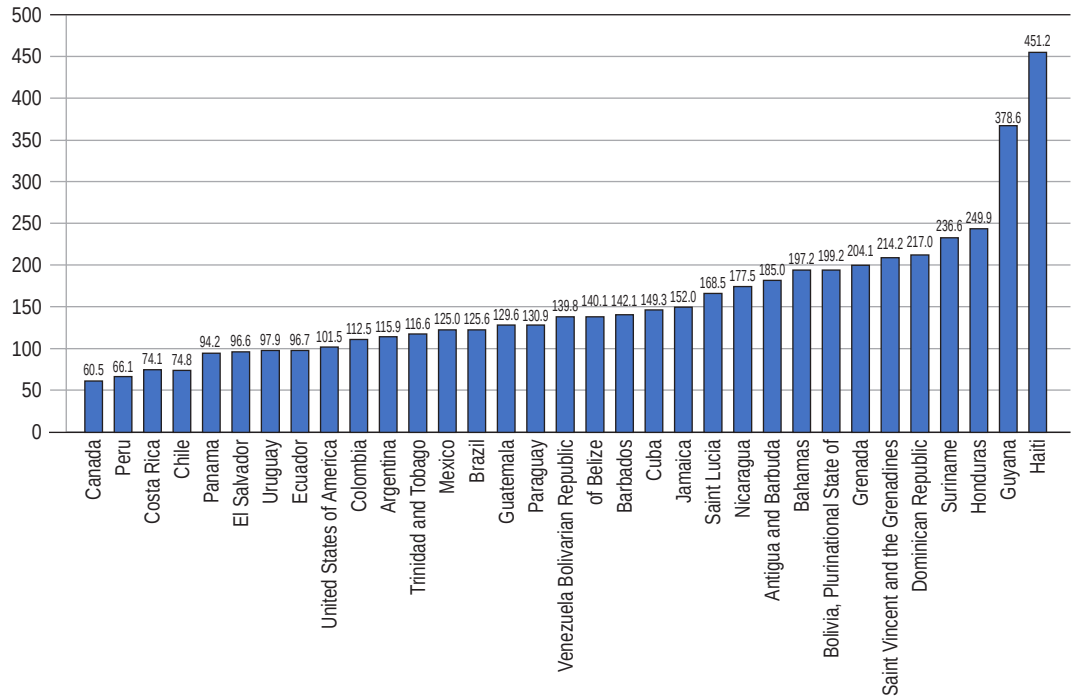

Figure 2: Cardiovascular disease mortality rates in women adjusted for age in Latin America, 2019. Adapted from: Pan American Health Organization; 2021.[2]

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Chapter 2

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Screening for congenital heart disease

Tamizaje de las cardiopatías congénitas

Iván Romero-Rivera,* Angélica Grullón,* Demián Herrera*

INTRODUCTION

Congenital heart defects (CHDs) are present in approximately 9 per 1,000 live newborns (NBs), representing 28% of all congenital malformations. It is estimated that there are 1.35 million live newborns with CHDs worldwide.

CHDs screening requires knowledge of the symptoms and the tests that can be performed for this purpose.

Most of them, like ventricular septum defect (VSD), do not have fetal and postnatal repercussions and may present heart failure (HF) later, depending on the size of the defect. Other heart diseases may have clinical expression after birth, such as atrial septal defect (ASD) or patent ductus arteriosus (PDA), which are essential for intrauterine life. Still, their persistence after birth can produce symptoms of HF. The *foramen ovale* is almost universal in the first hours of life but may remain patent in up to 25% of adults. Other heart diseases are challenging to detect in the fetus, for example, coarctation of the aorta (Co Ao). This condition can cause severe symptoms in the NB or remain latent until adulthood, with significant arterial hypertension in the upper limbs and complications, such as cerebral aneurysms or dilatation of the ascending aorta, generally in cases associated with the bicuspid aortic valve.

Some CHDs produce severe symptoms of HF in the NB, such as the total anomalous connection of the pulmonary veins with the right atrium, mainly when there is obstruction of the collecting duct. Others may present with cyanosis and metabolic acidosis, such as complete transposition of the great arteries (TGA) or pulmonary atresia. In these cases, keeping the ductus arteriosus (DA) patent is essential to allow survival. Tetralogy of Fallot (TOF) generally presents cyanosis later when the pulmonary obstruction becomes important and produces hypoxic crises.

One of the most feared CHDs, due to poor evolution and high mortality even with treatment, is the hypoplastic syndrome of the left ventricle (LVHS) and the ascending aorta. Since the flow of the lower limbs depends on the DA and has low saturation, greater cyanosis is seen in the inferior extremities than in the upper limbs (differential cyanosis). Other severe heart diseases, such as interruption of the aortic arch, also present this sign. These cases decompensate in the first week of life due to the spontaneous closure of the DA. This difference in saturation between the upper and lower limbs may indicate more severe heart diseases in NBs. This fact supports the principle for performing the pulse oximetry test in these babies.

PULSE OXIMETRY TEST

The test must be performed in the first 24 to 48 hours of life, with adequate equipment, for asymptomatic newborns born with gestational age > 35 weeks. The test consists of measuring oximetry with a pulse oximeter in the right hand (pre-ductal measurement) and one of the lower limbs (post-ductal measurement). The result can be positive, negative, or equivocal *(Figure 1)*.

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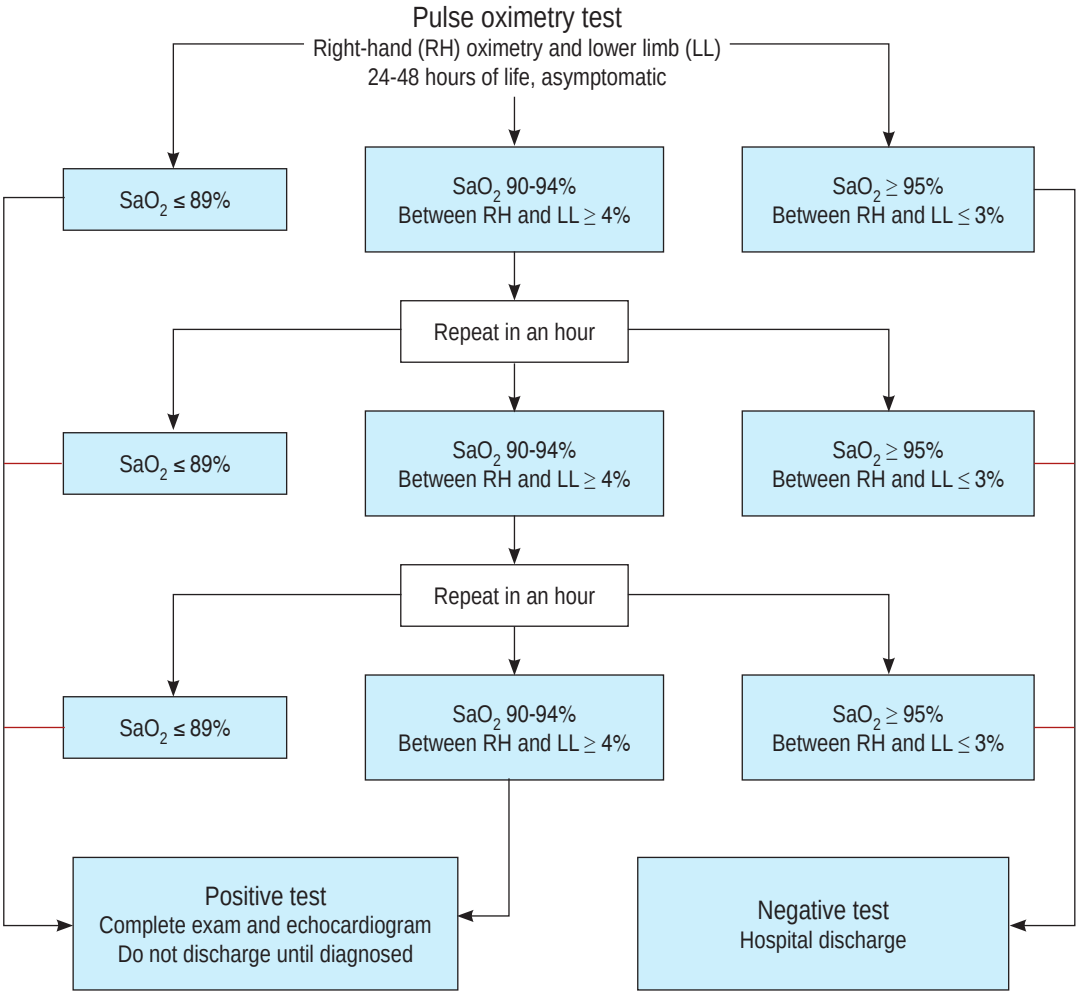

Figure 1: Pulse oximetry test, showing a positive test in the left column, negative in the right, and doubtful in the central part.
SaO_2 = oxygen saturation obtained by a pulse oximeter. RH = right hand. LL = lower limb.

SYMPTOMS AND SIGNS IN THE NEWBORN

CHDs can be acyanotic, with blood flow going from the left chambers (with greater saturation) to the right (with less saturation), as occurs in VSDs, ASDs, and PDAs. In these cases, pulmonary flow increases, and heart failure (HF) could manifest. If pulmonary stenosis (PS) is associated, and depending on the degree of obstruction, the pulmonary flow decreases, and the flow through the defect is reversed, going from the right to the left chambers, causing cyanosis and not HF, as in TOF. Single chambers (i.e., single ventricle) present a mixture of saturated and unsaturated blood with cyanosis and absence or with different degrees of HF, depending on the presence and degree of PS. Pure obstructions, such as isolated PS, are acyanotic, and left-sided obstructions can cause HF, depending on the degree of the obstructive lesion.

Hypoxemia and cyanosis are manifestations of DA-dependent heart disease, such as pulmonary atresia and TGA. As lung diseases sometimes present these symptoms, a test can be performed with 100% oxygen inhalation for 15 minutes. If the pO_2 and arterial oxygen saturation increase to > 250 mmHg or 97%,

respectively, it must be a pulmonary condition, not a cardiac one. A cardiac disease must be where there is no improvement with oxygen inhalation.

Severe heart diseases such as LVHS can cause low cardiac output and severe HF with DA closure, significant fatigue with feeding, excessive sweating, pale skin, progressive tachypnea, and low pulse amplitude. Therefore, these pictures must be differentiated from neonatal sepsis.

On physical exam, can be found tachypnea (RR > 70 bpm), hypoxemia with arterial O_2 saturation < 95%; heart rhythm disturbances, rate > 180 bpm or < 90 bpm, visible or palpable precordial impulses, hyperphonesis of cardiac bullae; low pulse amplitude (low output) or asymmetry (CoAo) and pathological heart murmurs.

CHDs can occur isolated (90%), or associated with chromosomal abnormalities (5%) and genetic syndromes (3%), with the possibility of transmission of approximately 3 to 10% in isolated defects and up to 50 to 75% in some genetic syndromes.

Some chromosomal alterations, such as trisomy 18 (Edwards syndrome) and 13 (Patau syndrome) are associated with complex cardiac malformations with short life expectancy. Trisomy 21 or Down syndrome presents heart disease in half of the cases, the most frequent being VSD, the common atrioventricular canal, and TOF less frequently, susceptible to surgical correction and long-term correction survival.

Other syndromes are caused by the absence of a chromosome, such as Turner syndrome (45X), which is associated with aortic coarctation or partial chromosome abnormalities, such as 22q11.2 deletion or DiGeorge syndrome, which may present conotruncal abnormalities severe, such as truncus arteriosus.

Autosomal genetic transmission can be dominant and recessive. Among the multiple diseases with cardiac involvement and this type of transmission, we have the Noonan, Marfan, and Holt-Oram syndromes, among others. Therefore, the presence of a syndrome with cardiac compromise can lead to the diagnosis of CHDs.

Thus, neonatal screening for CHD must consider symptoms, the pulse oximetry test already incorporated into the newborn routine in some countries, and the presence of family syndromes or diseases that involve the transmission of cardiac malformation.

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Chapter 3

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Obesity since childhood as a risk factor

Obesidad desde la infancia como factor de riesgo

Mardia López-Alarcón,* José Ramón Gómez-Mancebo,‡ Martha B Sánchez-Zambrano§

INTRODUCTION

Obesity (OB) is a public health problem. Its prevalence in women is higher than in men. The consequences related to cardiovascular diseases (CVD), type 2 diabetes mellitus (DM2), hypertension, and others, involve increased morbidity and mortality. In addition, pregnant women should have a more significant number of complications during pregnancy, as well as intergenerational transmission of OB to their children. Being a reversible cardiovascular risk factor, OB can be treated.

OBESITY IN CHILDHOOD AND ADOLESCENCE

The most frequent cardiovascular risk factors (CVRF) associated with obesity in childhood include an increase in body mass index (BMI), elevated concentrations of serum lipids, high blood pressure, rapid weight gain, and severe obesity. All these factors predict subclinical atherosclerosis, heart disease, and increased morbidity and mortality in adulthood.[1] Pediatric obesity is a consequence of chronic positive energy balance and programming during fetal life and lactation, among other causes.[2]

The worldwide frequency of overweight/obesity (OW/OB) in adolescents is 17 and 32%, respectively, similar in boys and girls.[3] Likewise, the pathophysiology of pediatric obesity is the same in boys and girls. However, in adolescents, OW/OB acquires greater relevance in girls due to the risk of complicated pregnancies. Latin America and the Caribbean have the second highest adolescent pregnancy rate (66.5 births per 1,000 girls aged 15-19).[4] This fact is significant from a clinical and public health point of view because obese pregnant girls have a greater risk of miscarriage, gestational diabetes, preeclampsia, preterm birth, depression, and birth complications and are less likely to be able to breastfeed their babies.

In addition, through the placenta and milk, these girls transmit biochemical and metabolic information to the product, programming an imbalance in the hormones of hunger and satiety, greater adiposity, inflammation, insulin resistance, and a greater risk of obesity in adulthood, becoming a vicious circle.

To prevent pediatric obesity, the World Health Organization (WHO) recommends acting from an early age, promoting adequate weight at the beginning of pregnancy, exclusive breastfeeding for six months, and adopting a healthy lifestyle. It is advisable to increase the consumption of fruits, vegetables, whole grains, and nuts, limit the intake of fats, refined sugars, and industrialized foods, change saturated fats to unsaturated ones, and eliminate the consumption of trans fatty acids. In addition, salt intake should be limited, ensuring it is iodized. Other therapeutic lifestyle changes include avoiding smoking, engaging in moderate physical activity for at least 60 min a day, limiting screen time and sedentary activities, and promoting good sleep habits.[5]

For the treatment of obesity in children and adolescents, the scientific evidence

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suggests, instead of restrictive diets, changes in lifestyle that include diet, exercise, and behavior modifications (eating habits, exercise, sleep). Furthermore, the greater the intensity of the intervention, it is expected to achieve more significant weight loss and a more remarkable improvement in cardiovascular risk.[3]

OBESITY IN WOMEN OF CHILDBEARING AGE

OB is a prevalent, preventable, and reversible risk factor (RF). During the last decades, the prevalence of OW/OB has progressively increased, reaching pandemic dimensions. According to WHO estimates,[5] in 2016, 1.9 billion adults aged 18 years and older had excess weight. Of these, 650 million were obese. Thirty-nine percent (39% of men and 40% of women) of adults aged > 18 had OW, and 13% (11% of men and 15% of women) had OB.

According to the NHANES[6] study, from 2015 to 2018, in adults > 20 years old, the prevalence of OB in men was 39.9% and 41.1% in women. On the other hand, severe OB (BMI ≥ 40 kg/m^2) affected 6.2% of men and 10.5% of women. The prevalence in women was higher in Black people and Hispanics.

According to age, the prevalence of OB in adults between 20-39 years was 40.4%, and 42.8% between 40-59 years, with no significant differences between men and women. There are more than twice as many obese adults in the Americas as in the rest of the world, with women being the most affected (prevalence of 29.6 and 24% in men and women, respectively).[7]

High BMI is a RF for the leading non-communicable diseases such as cardiovascular disease, DM2, osteoarthritis, and some types of cancer.[6] OB is a chronic, complex disease characterized by excess body fat, which in the long term, has medical complications that reduce life expectancy.[8] In addition, environmental, genetic, biological, and socioeconomic factors are involved.[9] For the control of OW/OB, the recommendations aim to achieve changes to healthier lifestyles. Only women who do not reach the established goals will require pharmacological and surgical treatment.[10]

CONCLUSION

OB is highly prevalent from childhood, increasing with age. This condition is associated with high morbidity and mortality, particularly from non-communicable diseases. The Americas is the region with the highest rate of OB compared to the rest of the world, with greater affectation in children and women, for which programs at the governmental, institutional, and individual levels are required to achieve control of this pathology.

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Chapter 4

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Cardiovascular risk in adolescent women

Riesgo cardiovascular en mujeres adolescentes

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INTRODUCTION

Cardiovascular disease is the leading cause of death worldwide, which occurs in both men and women, with an increasing incidence.

When looking at the natural history of the disease, it is essential to note that the atherosclerosis process, in many cases, begins early in life, either during childhood or later in adolescence. Moreover, it is a process with well-defined causes since there has recently been an increase in the prevalence and the earlier appearance of cardiovascular risk factors (CVRFs).[1] which tend to be prolonged towards adult life. Therefore, early diagnosis and prevention, even before adolescence, can influence the present time of children and adolescents and their future.

CARDIOVASCULAR RISK IN ADOLESCENTS

Family history plays an essential role in adolescents with a positive inherited-family history, who present more significant vascular damage, such as thickening of the carotid intima and media layers, which may or may not be accompanied by signs of endothelial dysfunction.[2] Hypertensive disorders during pregnancy and low birth weight also have adverse consequences beyond the gestational period, generating a greater predisposition to cardiovascular disease in adult life. Taking this into account, at the Argerich Hospital in Buenos Aires, Argentina, early manifestations were studied in adolescents born or not to mothers with high blood pressure (HBP) during pregnancy. It was observed that regardless of what happened during pregnancy, men presented greater vascular stiffness and left ventricular thickening, indicative of early remodeling.[3]

Although CVRFs are more prevalent in adults than adolescents, obesity or overweight, hypertension, dyslipidemia with a predominance of increased LDL-cholesterol and glucose intolerance, or type 2 diabetes can be found in the latter.

Many of these factors are secondary to an inadequate diet and a sedentary lifestyle, typical of modern society. Because of the increment of the mentioned risk factors, there is a higher rate of metabolic syndrome, which affects women to a greater extent.[4]

There are other CFRFs, such as smoking which, although its trend is declining, it is noteworthy that in the 2018 Global School Health Survey, it was observed that in female adolescents, both tobacco and alcohol consumption were higher than in men.[5]

There are risk factors specific to the female gender, such as polycystic ovary syndrome, a pathology associated with hyperandrogenism, predisposing these patients to develop CVRFs, such as hypertension, diabetes, and a higher incidence of obesity even in such early stages.[6]

In adolescence, cardiovascular disease is not the first cause of death, but identifying CVRFs is essential to avoid its continuation in adult life.

DIAGNOSIS AND PREVENTION

The timely diagnosis and identification of CVRFs in adolescence are vital for preventing cardiovascular diseases. Therefore, the

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inclusion of a general clinical examination focusing on cardiovascular risk will be the cornerstone of identifying relevant variables in children and adolescents. Moreover, it must be systematically motivated to perform a good clinical history and a physical examination that includes the identification of murmurs or clinical data of hormonal changes at early ages in female adolescents. Blood pressure must be measured, as weight and height (according to standardized percentiles for age) and body mass index, classifying the existence of overweight and obesity.[7]

Implementing new strategies for evaluating young populations and identifying risk factors will generate more effective interventions, mainly from our profession. It is also proposed to measure other variables, such as cholesterol concentrations, and psychological analysis in search of depression, stress, and anxiety. Also, the assessment of abrupt hormonal changes in girls and gynecological studies, and the estimation of the thyroid profile, will help us to identify cardiovascular risk in a large percentage of the adolescent population and thus carry out effective therapeutic and guidance interventions.[8]

Strategies should include regular physical activity and promoting healthy eating in schools and homes to reduce risk. In addition, family communication should be facilitated in cases of depression or anxiety, as well as by asking for guidance in the psychological sphere at schools.

There is no doubt that childhood and adolescence are the ideal age to carry out strategies to promote healthy habits due to the extraordinary plasticity of the brain at an early age. Furthermore, the school environment is favorable, given that it is where they spend much of their time for several years. Therefore, motivation and prevention campaigns are an essential basis for the strategy, and the level of motivation should never drop in this regard.[9,10]

It is difficult to fight against video games and the Internet, one of the biggest current distractions for young people. Notwithstanding, many strategies are carried out worldwide to promote sport and reduce obesity and sedentary lifestyle rates.

When physical activity is stimulated by promoting maxims such as «you will be happier», the results are better than rational reasons such as «you will be healthier». However, current strategies only make explicit health improvements that represent the practice of physical exercise. Therefore, both benefits are obtained by promoting the effects on the emotional sphere.

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Chapter 5

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Pregnancy and cardiovascular risk

Embarazo y riesgo cardiovascular

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INTRODUCTION

Cardiovascular diseases are among the leading causes of maternal death.[1] These entities complicate between 0.2 and 4% of pregnancies, and this prevalence is increasing. On the one hand, girls with congenital heart disease reach childbearing age thanks to partial or total surgical correction of the heart disease; on the other hand, assisted fertilization techniques have extended maternal age with older mothers with more significant comorbidities. Finally, the increase in the prevalence of cardiovascular risk factors (CVRFs) in women of any age also operates as an additional factor.[2,3] Latin America also adds another scourge, the Chagas-Mazza disease. According to data from the World Health Organization (WHO), 60 million people are at risk of suffering from it,[4] and 20-30% of them will develop heart disease. The impact on women is related to heart disease and the additional risk of vertical transmission.

EVALUATION OF THE GLOBAL RISK OF PREGNANT WOMEN WITH HEART DISEASE

The risk of possible complications during pregnancy is related to multiple factors, such as:

1. The type of underlying heart disease
2. Ventricular and valvular function
3. Pre-gestational functional class
4. The presence of cyanosis
5. The presence of CVRFs
6. Obstetric history
7. Maternal age

The risk calculation must be personalized, integrating all the variables.[5] The hemodynamic changes of pregnancy, i.e., increased cardiac output and heart rate and decreased vascular resistance, will influence heart disease and may aggravate it.[6,7] Sometimes, the diagnosis of maternal heart disease is established during pregnancy because these changes decompensate the underlying disease.

Therefore, the pre-pregnancy consultation is of great value since it allows the estimation of the individual risk, requesting complementary studies, planning the surgical correction, and establishing a multidisciplinary follow-up team.

1. Type of maternal heart disease

The most widely used current tool to estimate maternal and fetal risk is the modified World Health Organization (WHO) Risk Scale published in 2018 by the WHO[8-10] *(Table 1)*. It considers 5 categories, each of which gives a range of risk.

2. Evaluation of the functional class

Functional class (FC) is an independent risk factor for maternal-fetal mortality. Women in FC I have a mortality of less than 1%, while those in FC IV reach up to 15%. For its part, the fetal risk is 20 to 30% in FC IV, in addition to increased morbidity due to prematurity, low birth weight, spontaneous abortion, and congenital heart disease.

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FC can be evaluated with a stress test or the measurement of natriuretic peptides (BNP or NT-proBNP). An NT-proBNP concentration > 128 pg/mL at 20 weeks of gestation predicts late events during pregnancy.[11,12]

3. Cardiovascular risk factors

Pregestational CVRFs increase maternal-fetal risk during pregnancy and for the rest of a woman's life. Furthermore, increasing maternal age is associated with a higher prevalence of CVRFs. The cumulative burden of CVRFs is associated with a higher risk of maternal cardiovascular complications, premature birth, and fetal death. Therefore, in the postpartum period, it is relevant to evaluate all women in the risk category in the puerperium and at 6 to 12 months postpartum. Instructions must be given about lifestyle changes, and implementing treatment of CVRFs has to be

Table 1: Modified World Health Organization risk scale.

Class	Pathology	Maternal event rate (%)
I No increased risk of mortality Low morbidity	• Small or mild uncomplicated injury including pulmonary stenosis, patent ductus arteriosus, or mitral valve prolapse Repaired simple lesions: atrial or ventricular septal defects, ductus arteriosus, and anomalous pulmonary vein return Isolated ventricular or supraventricular extrasystoles	2.5-5
II Slight increase in mortality risk A moderate increase in morbidity risk	• Unrepaired atrial or ventricular septal defect Repaired Tetralogy of Fallot Arrhythmias	5.7-10.5
II–III Intermediate increase in mortality risk	• Mild deterioration of the LVEF (> 45%) Hypertrophic cardiomyopathy Native valve disease not considered class I or IV Marfan syndrome without aortic dilatation Bicuspid aortic valve with dilated aorta < 45 mm Repaired coarctation of the aorta	10-19
III Significant increase in maternal mortality or serious morbidity	• LVEF deterioration (30-45%) Previous peripartum cardiomyopathy Mechanical prosthesis Systemic right ventricle Fontan circulation Cyanotic heart disease (unrepaired) Other complex congenital disease Moderate aortic dilatation: 40-45 mm in Marfan, 45-50 in the bicuspid valve, < 50 in Fallot	19-27
IV High risk or contraindicated pregnancy	• Pulmonary hypertension of any cause Severe LV dysfunction (LVFE < 30% or FC III-IV) Previous peripartum cardiomyopathy with impaired residual LVEF Severe obstruction of the left cavities (aortic valve area < 1 cm^2 or peak gradient > 50 mmHg or mitral valve area < 1.5 cm^2) Marfan syndrome with aortic dilatation > 45 mm. Bicuspid aortic valve with aortic dilatation > 50 mm Severe coarctation of the aorta severa Ehler Danlos and severe re-coarctation	40-100

LVEF = left ventricle ejection fraction.

Table 2: PAHO/WHO recommendations for the elimination of mother-to-child transmission (MTCT).

Moment	Interventions
Pregnancy	Routine screening in all pregnant women
	Care and follow-up in seropositive
Delivery	Parasitological tests in neonates of infected mothers (umbilical cord blood)
Maternal and child care	Treatment of mothers after childbirth
	Serological tests in children from 8 months
	Treatment in children before the year and serological follow-up
Other interventions	Diagnosis and treatment in girls and women of childbearing age
	Screening in newborn siblings with Chagas disease

done, informing about the implications for a future pregnancy and the increase in CVD risk.[13-16]

4. The obstetric history

The history of adverse evolution in previous pregnancies confers a higher risk of new events or complications, such as abortion or stillbirth, preeclampsia, gestational diabetes, placental abruption, or peripartum cardiomyopathy. At the other extreme, the absence of complications in previous pregnancies could indicate good tolerance to the stress of pregnancy.

5. Maternal age

Maternal age is not considered in the scales that assess the risk of cardiovascular complications in patients with heart disease. However, evidence shows that pregnancies in women over 35 are associated with more significant direct obstetric complications. In mothers over 40 years of age, the risk of cardiovascular complications increases markedly by preeclampsia, stroke, and coronary artery dissection.

PRE-PREGNANCY CONSULTATION

Pre-pregnancy evaluation in patients with heart disease allows:

1. To assess the maternal-fetal risk linked to heart disease.
2. To optimize the pre-gestational conditions of the risk factors.
3. To detect heart disease plausible for surgical correction.
4. To establish the interdisciplinary cardio-obstetrics team.
5. To define the level of complexity of the care center for the mother and the newborn.
6. To perform maternal treatment for Chagas disease.

Contact with the health system in these conditions is an ideal time to recommend lifestyle changes that will impact the mother and the offspring.

Likewise, it allows modifying contraindicated medication during pregnancy, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor antagonists (ARBs), opting for drugs of proven innocuousness.

CHAGAS DISEASE AND PREGNANCY

Given the high prevalence of this entity in Latin America and its growing detection in North America and Europe due to migratory currents, research is imperative to reduce vertical transmission and congenital Chagas[4,17] *(Table 2)*.

Most women of childbearing age with positive serology are asymptomatic. In those with heart disease, the entity does not differ from other populations with rhythm disturbances or conduction disorders, dilated cardiomyopathy, ventricular dysfunction, and apical aneurysm with a thromboembolic risk. Neonatal congenital Chagas is usually asymptomatic, and early detection allows a cure rate close to 100%.

The indicated screening will be:

1. In the mother: 2 quantitative reagent tests IIF, ELISA, HAI, or particle agglutination.
2. In children: identify the parasite with micro hematocrit in the newborn and search for antibodies with serological tests from 10 months of life.

Follow-up during pregnancy of the patient with heart disease

The design of the follow-up and treatment plan will be marked by the type of maternal heart disease and the obstetric and fetal-neonatal conditions, for which the integration of a multidisciplinary team is valuable *(Table 3)*. On the other hand, the level of complexity of the health center where the mother and child are cared for will be assessed, considering adequate neonatology for extremely premature infants.[8]

Timing and mode of termination of pregnancy in patients with heart disease

The delivery time will depend on the maternal-fetal conditions trying to reach fetal maturity without putting the mother's life at risk by

Table 3: Follow-up strategies according to WHO category.

Clase	I	II	II-III	III	IV
Prenatal care Minimal follow-up visits Ending	Low complexity One or two during the current gestation Delivery in a high complexity center	Low complexity Once quarterly Delivery in a low complexity center	Referral center Bimonthly Delivery in a referral center	High complexity Monthly or bimonthly Delivery in a high-complexity center	High complexity Monthly Delivery in a high-complexity center

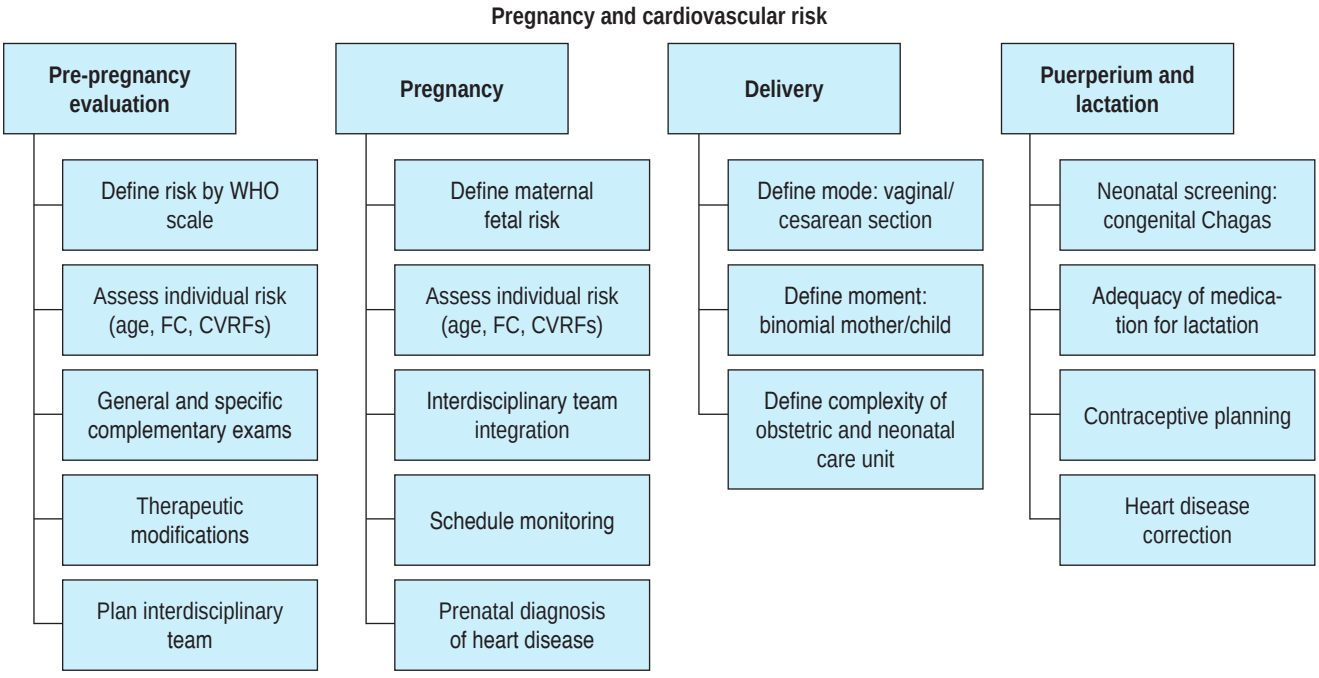

Figure 1: Conceptual framework of pregnancy and cardiovascular risk.
FC = functional class. CVRFs = cardiovascular risk factors.

prolonging the pregnancy. Vaginal delivery is always preferred, resulting in less blood loss and a lower risk of infection and venous thromboembolism. Elective cesarean section is of no benefit to the mother and should be considered when:

1. There is an obstetric indication for fetal distress.
2. In women taking oral anticoagulants.
3. In the presence of heart failure or hemodynamic decompensation.
4. Severe symptomatic aortic or mitral stenosis.
5. Severe forms of pulmonary hypertension.
6. Bicuspid aortic valve with an aortic root greater than 45 mm in diameter.
7. Marfan syndrome with an aortic root greater than 40 mm in diameter.

CONCLUSIONS

Pregnancy in women with heart disease challenges the treating team. It requires an individualized evaluation and interdisciplinary follow-up that, in the ideal scenario, should begin in the pre-gestational stage. In addition, pregnancy provides a valuable opportunity to indicate lifestyle modifications that will impact maternal and offspring cardiovascular health *(Figure 1)*.

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Chapter 6

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Cardiovascular risk scales in women

Escalas de riesgo cardiovascular en la mujer

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INTRODUCTION

The estimation of cardiovascular risk (CVR) continues to be a significant challenge for preventing cardiovascular disease (CVD) in both men and women. Current guidelines on CVD prevention are based on individual evaluations applied to epidemiological risk tables. As Latin America lacks sufficient information to make its risk scales, it is necessary to extrapolate those derived from different studies in non-representative populations, constituting this a severe limitation.

Women have unique cardiovascular risk factors (CVRFs) and unrecognized CVRFs that significantly impact CVR. Therefore, determining their risk is complex.

In the American Heart Association (AHA) CVD prevention guidelines for women, an algorithm for risk classification is proposed, taking into account some exclusive CVRFs, and defining three categories: high risk, at risk, and optimal risk based on in the presence of documented CVD, traditional CVRFs, incorporating a history of pregnancy complications, the presence of autoimmune diseases, central obesity, and functional exercise capacity.[1] In 2011, the term «ideal cardiovascular health» was introduced, defined as the absence of clinical CVD and ideal concentrations or levels of total cholesterol (TC < 200 mg/dL), blood pressure (< 120/80 mmHg), and fasting blood glucose (< 100 mg/dL), plus a healthy lifestyle.[2] This strategy allows those who, in the conventional evaluation, would not qualify to receive preventive treatments to be re-categorized and benefit from early and intensive preventive interventions.

The Reynolds score was validated in a significant population of women. In addition, it showed great power to reclassify both men and women at higher or lower risk, adding the family history of acute myocardial infarction (AMI) and high-sensitivity c-reactive protein (CRP) to conventional CVRFs. However, it also did not include women-specific CVRFs.[3]

The risk calculator proposed by the ACC/AHA (ASCVD Risk Estimator) does not include data from the Latino population and cannot be applied to people that are not Caucasian or Afro-American.[4]

The European Systematic Coronary Risk Evaluation system (SCORE) recently introduced the SCORE2 and the SCORE OP (Older Persons). It involved data from around 700,000 participants without previous CVD between 1990 and 2009. They establish four European regions with various levels of risk, provide estimates of fatal and non-fatal CV events, and consider diabetes mellitus (DM), correcting shortcomings of the previous SCORE. This model adjusts the specific risk by gender, based on cohorts of 66% of women, and includes individuals older than 65 with the SCORE OP. Importantly, it takes non-HDL cholesterol instead of TC or HDL-C, which could better discriminate the long-term risk of CVD, especially in young individuals. However, the disadvantage is that it does not consider women's CVRFs.[5] The INTERHEART score, based mainly on the PURE study (Prospective Urban Rural Epidemiology), was validated in seven regions of the world, differentiating among low-, moderate-, and high-income countries, including a good number of Latino

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populations. In addition, it incorporates variables such as diet, exercise, depression, and stress, which are not considered in other scores.[6]

Finally, the WHO developed a risk prediction model for fatal and non-fatal events (AMI and stroke), adapted for low and middle-income countries, applicable to 79 countries in 21 regions. Latin America was divided into five regions: Caribbean, Central, Andean, Tropical, and South. It has gender-specific models, and it is currently recommended by the WHO for the Americas region.[7]

Age is the non-modifiable CVRF that most affects all risk calculators. For this reason, CVR is underestimated in young people, especially women, when the risk estimation is limited to 10 years, which is the usual period for most scores. The US National Health Survey, with a median age of 44, found that 82% of the surveyed people were at low risk at ten years. However, when extended to a lifetime risk estimate (LTR), almost two-thirds of this population was reclassified as high-risk.[8]

Women-specific CVRFs are present at young ages or in pre-menopause, where the calculated CVR is generally low. For example, a study in young women with a history of pre-eclampsia, who evaluated CVR at ten years, 30 years, and LTR, compared with healthy controls, found a high CVR at ten years in 18.2% in patients with pre-eclampsia vs 1.7% of controls, at 30 years 31.3 vs 5.1%, and the projected CVR LTR 41.4 vs 17.8%, respectively.[9] This is a clear example of the usefulness of using the LTR in young women with a history of specific CVRFs.

Algorithm for estimating cardiovascular risk in women *(Figure 1)*.[10] Women who have had CVD or those with evidence of atherosclerotic disease without a previous event should be treated with secondary prevention goals.

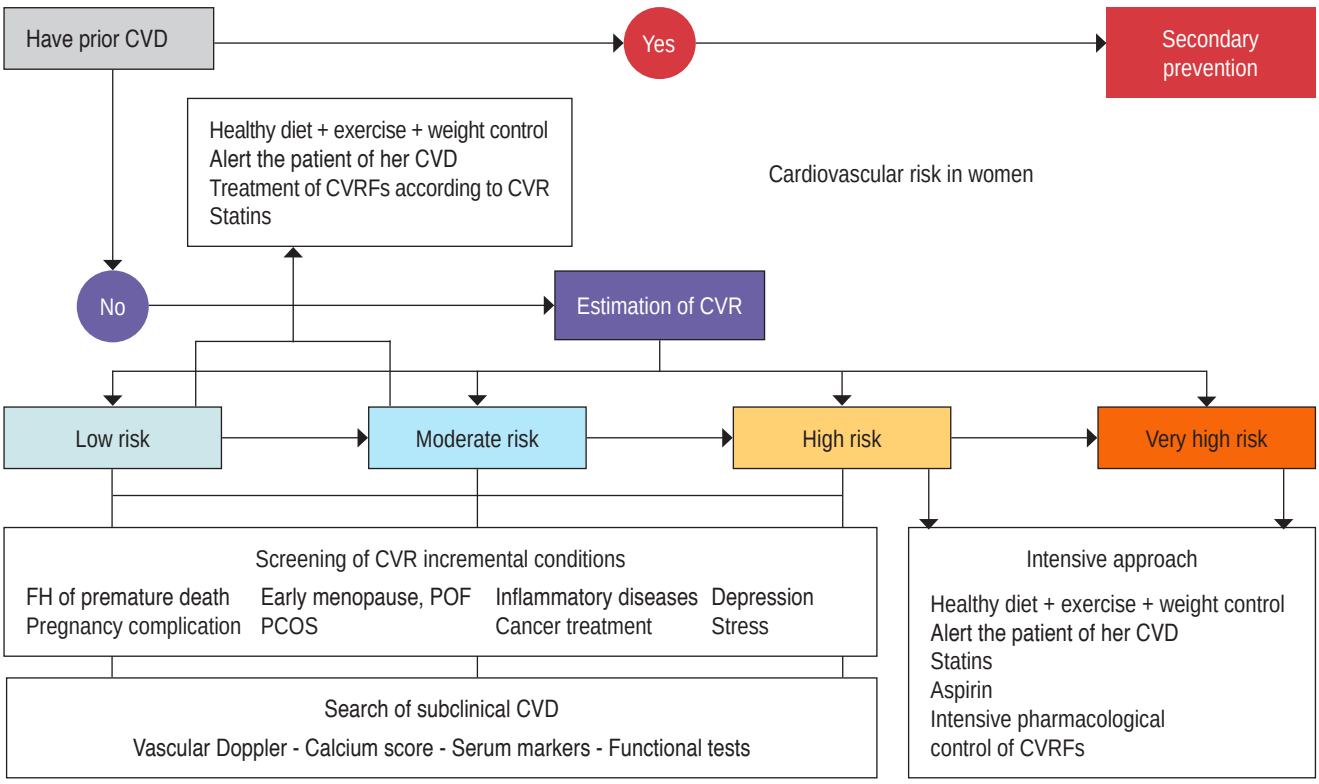

Figure 1: Algorithm for estimating cardiovascular risk in women.
CVD = cardiovascular disease. CVRFs = cardiovascular risk factors. CVR = cardiovascular risk. FH = family history. POF = premature ovarian failure. PCOS = polycystic ovary syndrome.

1. In those who have not had a previous CVD or without a diagnosis of atherosclerotic disease, the CVR should be calculated considering the traditional CVRFs. Those Latin American countries that have validated any of the above-mentioned risk estimations can use that score to determine CV risk. Those who do not have this validated tool can use the Interheart Risk Score or the Euroscore,[2] calibrated by the corresponding correction factor, or the WHO score according to their region.[5,7]
2. When presenting unique or emerging CVRF, a woman should be considered «at risk» and moved to the immediately higher risk group (intermediate, high, or very high). In its absence, it remains in the low-risk group or the one considered by the chosen calculator.
3. It is recommended to search for subclinical atheromatosis in those women at intermediate risk or with higher CVRF, with the methods available in the reference center.

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Chapter 7

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Metabolic syndrome in women

Síndrome metabólico en la mujer

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INTRODUCTION

Metabolic syndrome (MS) comprises a set of risk factors for cardiovascular disease (CVRFs) and diabetes, such as abdominal obesity, atherogenic dyslipidemia, hypertension, and increased fasting glucose. The MS is associated with a five-fold increase in the prevalence of type 2 diabetes (DM2) and a two- to three-fold increase in that of CVD.[1]

Obesity, especially the abdominal type, is associated with resistance to the effect of insulin on peripheral glucose and fatty acid utilization, a fact that can lead to the development of MS and DM2. In addition, insulin resistance, hyperinsulinemia, associated hyperglycemia, and increased adipokines can yield vascular endothelial dysfunction, abnormal lipid profile, hypertension, and vascular inflammation. All these conditions promote the development of atherosclerotic CVD. This association has been named syndrome x, death quartet, or insulin resistance syndrome.[2]

MS increases with age and is influenced significantly by gender. In people under 50 years of age, it is slightly more prevalent in men, and this situation reverses after that age. The most frequent component of MS in Mexico is abdominal obesity (76.6%), followed by low levels (60.5%) of HDL cholesterol.

In a study by Quesada et al. in which 899 women were followed up for eight years, it was observed that 34.9% were overweight, 40.5% obese, and 42.4% had MS. It was documented a 38.5% obstructive coronary disease in women with suspicion of myocardial ischemia. MS was a predictor of all-cause mortality, while overweight and obesity were protective against death, with an association between MS and BMI with death ($p < 0.0001$) and worse survival in MS with normal BMI.[3] These data are consistent with the «obesity paradox» in mortality described in ischemic heart disease and emphasize the evaluation of MS independently of BMI.

Metabolic syndrome and gender differences

The differences in the prevalence of MS and its components are determined by the distribution and characteristics of adipose tissue. An analysis of the Third National Health and Nutrition Examination Survey (NHANES III, NCEP criteria) in the US showed that abdominal obesity was the predominant feature of MS in women. In addition, the most common group (16.7%) in younger women was increased triglycerides (TG) and low HDL cholesterol. For younger men, the combination of increased TG, low HDL cholesterol, and hypertension was the most common (18.0%). Notably, this cohort essentially eliminated the gender difference in subtype distribution in older adults (> 65 years). The most common subtype, the presence of all five features, was equally prevalent in older men and women.[4]

Another differentiating point is the frequency of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). Based on analyzes of the DECODE/DECODA (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe/Asia) study groups, which included data from 13 European and 10 Asian studies, IFG is more common in

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men than in women in almost all countries, being up to 7 to 8 times higher in men aged 50 to 70 years.

Other factors for the appearance of MS are the climacteric, the use of hormonal contraceptives, polycystic ovary syndrome, which affect insulin sensitivity, glucose, and lipid metabolism, as well as those of pregnancy (gestational diabetes and hypertensive disorders of pregnancy).

Menopause and metabolic syndrome

The results of several studies indicate that postmenopausal status is associated with an increased risk of MS, regardless of aging.

During post-menopause, hormonal changes can promote metabolic changes that increase body weight and abdominal adipose tissue. Hypoestrogenism, at this stage, is associated with metabolic and vascular alterations, endothelial dysfunction, and increased oxidative stress. In Mexico, derived from the CARMELA study, the prevalence of MS of 27.4% in women of reproductive age vs. 35.5% in postmenopausal women.[5]

It has been observed that the risk of CVD increases significantly after menopause, which may be a consequence of changes in sex hormones, cardio-metabolic parameters, and chronological aging. In turn, hypoestrogenism is directly related to an increase in total cholesterol (TC), LDL-C, and apolipoprotein B, as well as an increase in the ratio of TC/HDL-C, being associated with a more atherogenic lipid profile.

This estrogen deficiency, in turn, leads to an imbalance between the factors that affect vasodilation and vasoconstriction, resulting in increased vascular resistance and high blood pressure. Furthermore, in post-menopause, coagulation factors increase (VII, VIII, fibrinogen, and antithrombin). Also, plasminogen activator inhibitor type 1 (PAI-1), the principal deterrence of fibrinolysis, is elevated in postmenopausal women compared to premenopausal ones, determining a procoagulant state.[6]

Hormonal contraceptives

The administration of combined contraceptives has been associated with increased insulin resistance, glucose intolerance, and lipid metabolism. Thus, in women with obesity and or PCOS, the risk of metabolic alterations that lead to MS[7] increases.

POLYCYSTIC OVARY SYNDROME (PCOS)

This condition has been observed in a third of women with MS. Obesity and insulin resistance are two conditions common to PCOS and MS. Therefore, it is recommended to perform tests to detect early glucose intolerance and dyslipidemia in women with PCOS, including adolescent women.[8]

MANAGEMENT RECOMMENDATIONS

The management strategy should focus on preventive measures. Therefore, it is necessary to recommend modifying the lifestyle, increasing physical activity, eating a balanced diet, avoiding smoking, reducing the consumption of alcoholic beverages, and promoting intellectual activity. However, concomitant treatment may be necessary.[9]

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Chapter 8

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Gender-based violence

Violencia de género

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INTRODUCTION

Defining health as a complete physical, mental, and social well-being, and not just the absence of disease, it is understood that those factors that involve these areas are determinants of cardiovascular risk. For example, a recent meta-analysis and systematic review documented the impact of psychological factors (including post-traumatic stress and hostility) on the development of ischemic heart disease in women [hazard ratio (HR) 1.22; 95% CI 1.14-1.30].[1]

Gender violence has various spectrums. Intimate partner violence has been associated with less healthy behaviors, higher inflammatory markers, increased cardiovascular disease (CVD), and long-term cardiovascular risk factors such as high blood pressure, diabetes, obesity, and dyslipidemia.[2,3] In a meta-analysis[4] with 640,376 women, sexual violence was associated with a high risk of CVD (HR 1.17; 95% CI 1.05-1.31), considering that the risk is maintained up to 14 years after the traumatic event. In addition, there is a strong association between the age at presentation of the trauma and cardiovascular risk, showing that a childhood with adversities has a greater possibility of CVD.

A multi-cohort study (53% women) documented that violence and harassment at work were associated with a 25% risk of CVD.[5] In women, violence manifested by low socioeconomic status has been associated with a 34% risk for coronary heart disease, 23% for CVD, and 21% for cerebrovascular disease.[6]

Another form of violence is that associated with the medical invisibility of women in studies on cardiovascular diseases or Yentl syndrome. Although the impact on health due to this type of violence has not been widely documented, multiple studies certify that the female gender confers the risk of receiving less treatment or correct diagnosis.[7]

Prevalence

Globally, one in three women over the age of 15 has experienced physical or sexual violence at some time in her life, with the prevalence being higher in less developed countries (37% in women between 15 and 49 years of age). Around 81,000 women and girls were murdered in 2020, 58% at the hands of their partners or relatives. These numbers equate to one woman or girl being killed by persons they know every 11 minutes.[8]

In Latin America, the prevalence of physical or sexual violence against women is 29.8%, reaching the highest figure in Bolivia at 31%. In Brazil, Panama, and Uruguay, 1 out of 7 women suffer violence.[9] In Mexico, 14% of women have been victims of physical violence, and 7 out of 100 have suffered sexual violence.[10] Emotional violence was reported in 4 out of 10 women, and economic violence in 24.5%. This type of violence includes the prohibition of working or studying, the withdrawal of money or goods. As a result of the pandemic, crimes against women increased, especially family violence reaching 80.4% of cases, and sexual crimes to a lesser extent (17.7%).[10]

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In the workplace, 14.9% declared suffering one of these conditions: certificate of weightlessness to enter work, dismissal due to pregnancy, or reduction in salary. Labor discrimination has been reported in up to 20.6% manifested by lower salary, less opportunity for promotion or fewer benefits than male peers or a reduction in salary, dismissal, or non-hiring due to age or marital status.[10]

Most CVD clinical studies have an underrepresentation of women (38.2%), excluding ethnic, racial, or elderly minorities, mainly in heart failure and those using devices or procedures. The Americas region has a higher inclusion of women compared to other regions.[11]

Although there is an increase in the presence of women in leadership positions, this is still lower compared to men. In cardiology, only 30% of women are leaders, predominantly non-experts in interventionism. This fact is explained by various sociocultural factors of the female role and access to unequal gender academic conditions for their development.[12]

Physiopathology

Gender-based violence produces stress, depression, and anxiety, predisposing behavioral risk factors (drug use, poor diet, and sedentary lifestyle).[7] Physiological mechanisms include abnormal inflammatory and neurohormonal processes, high blood pressure, glucose metabolism dysregulation, altered microvascular vasoconstrictor function, and sleep disorders. In addition, stress alters the limbic system: hypofunction of the medial prefrontal cortex (critical structure for executive function), activates the amygdala, and affects hippocampal neurons, resulting in inhibition of the parasympathetic system, activation of the sympathetic and altered baroreflex sensitivity. Consequently, there

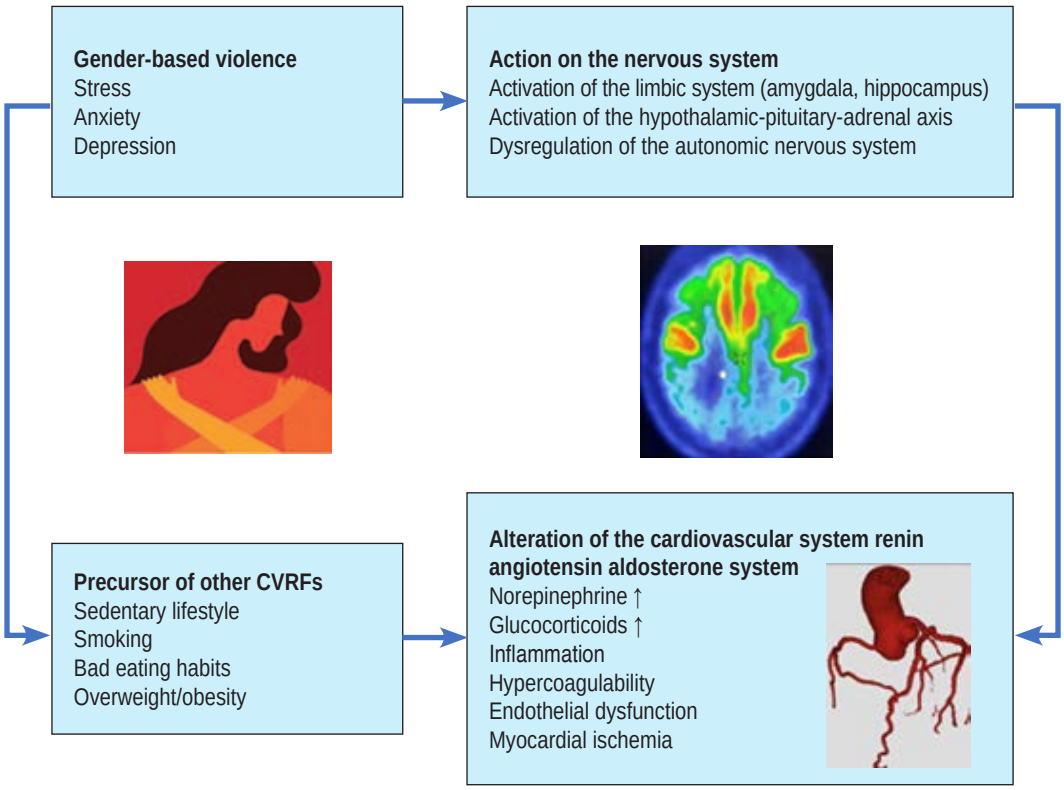

Figure 1:

Pathophysiology of gender violence as a cardiovascular risk factor. Stress and adverse experiences predispose behavioral risk factors (obesity, drug use, poor diet, sedentary lifestyle). Also, they can act on the central nervous system, increasing heart rate and blood pressure and causing ventricular hypertrophy, glucose dysregulation, cytokine production, and endothelial dysfunction. All these increase cardiovascular risk. CVRFs = cardiovascular risk factors.

Table 1: Alerts that we must consider in gender violence.

Degree of alertness	Type of violence	Aggression mechanism	Effect
Watch out! Violence is present	Psychological	The threat to harm or take away children The threat of dismissal (labor, academic)	Panic Unsafety Submission Distress Fear freezing
		The use of intimidating leering and gestures	Fear Intimidation impotence
		Blaming to provoke feelings of guilt, badness, or responsibility	Feeling of inability Low self-esteem Humiliation
		Control and stalk what you do, who you see, who you talk to, what you read and where you go Prevent you from making important decisions	Personal and social lack of protection Isolation Eliminate self- esteem Inability Undervaluation
		Deny the mistreatment or abuse that has existed Constraining social and familial contacts	Effective ambivalence Emotional dependence
		Use the visitation regime for bullying and harassment Forcing to withdraw complaints	Control Unsafety Lack of legal protection
Reaction to! Complain and ask for help	Economical	Deny information about familial income, blocking-access to them	Economic dependence
	Sexual	Sextortion	Stress Anxiety Submission
		Aggressive caresses, groping	Guiltiness Panic Submission
Get away! Your life is in danger	Physical	Lockdown at home	Isolation Lack of social protection
		Screams, insults and permanent surveillance Destruction of personal belongings, mistreatment of pets or relatives	Elimination of self-esteem Impotence Distress Anxiety
		Use of weapons to intimidate, death threat Hitting, shoving, rape	Insecurity Terror Physical deterioration
Femicide			

is a release of cytokines and endothelial dysfunction.[13] Underlying this, women have a biological predisposition to develop mental illnesses associated with hormonal conditions, in addition to the role played by the sociocultural context of risk for violence (poverty, low educational level) *(Figure 1 and Tables 1 and 2)*.

Prevention and care through public policies

The first regulations approved in Latin America were known as «First generation» laws. In 1994, the approval of the Convention of Belém do Pará, made up of 32 countries, and its subsequent ratification in 2016 marked a watershed in the designation of the duties of the State. Nine countries in the region have added social concepts such as economic and political violence, coining the term «Second generation» laws.[14]

Bolivia established the first Law, «Against harassment and political violence towards women», the first country in the region to address this issue. Mexico maintains awareness campaigns on equality between men and women through laws, including the Law to Prevent and Eliminate Discrimination. In 2021, the Regulations of the General Law on Women's Access to a Life Free of Violence were published.[15]

With lines of action such as prevention, awareness, and implementation of sanctions against gender violence, it is necessary to contribute to the empowerment of women through public policies that reduce risk factors in the family, school, work, community, and institutional spheres.[11,14-16]

1. Education: prevent school dropout in pregnant women. Granting of scholarships and educational policies at all levels with a gender perspective.
2. Health: universal health coverage, quality medical care with a gender perspective.
3. Economic: equal salary, childcare for children of working mothers, economic support, and food subsidy for mothers in vulnerable conditions.
4. Social support: support networks and promotion of social resilience.
5. Environment: safe housing, access to essential services, recreation, and green areas.
6. Sexuality: family planning programs and preventing communicable diseases; promoting content and images free of violence and stereotypes, and avoiding gender discrimination.
7. Culture: avoid language barriers and racism, considering uses and customs.
8. Legal: advice and protection of the victim, maximum penalties for aggressors for physical violence and femicide.
9. Research: greater inclusion in clinical trials and leadership in science.

CONCLUSIONS

Gender violence is considered a cardiovascular risk factor. The conditions in women involve the biological, sociocultural, and economic spectrum, determining common pathophysiological mechanisms. On the

Table 2: Keys to identify violence.

If you feel that…	Reality is that…
It's normal and it only happens to you	What you are going through happens to several women regardless of social, economic, cultural level or nationality
You must feel guilt or shame	You are not to blame; it is not in your hands to change the aggressor's behavior
The situation of violence is temporary, and the situation will improve	The violence will increase. The aggressor does not keep promises or dialogue, he only manipulates and controls
It's better to hold on for your kids	You must get out of this situation as soon as possible because your children are also victims
It is normal to think that only certain types of women suffer	Any woman can suffer from it, but more often, those who have a condition of emotional and socioeconomic vulnerability

other hand, more clinical trials on gender violence are necessary to define the impact on cardiovascular health and consider it within cardiovascular risk scales.

The joint work of all scientific, governmental, and private organizations with actions for preventing and eradicating violence in all its forms is essential.

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Chapter 9

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Mental health and management of emotions: impact on the cardiovascular health of women

Salud mental y gestión de emociones: impacto en la salud cardiovascular de la mujer

Rafaelina Concepción,* Yoloxóchitl García-Jiménez,‡ Alejandra Ávalos-Oddi§

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in women, and this entity has increased in recent decades.

It has been established in recent years that psychological factors are closely related to cardiovascular (CV) disease. The link is bidirectional; psychological factors may be shared in certain CV diseases (CVD), conditioning worse outcomes. On the other hand, psychological conditions may pre-exist and favor the development of CVD. Additionally, treatment for mental health disorders may present CV risk due to side effects or interactions with other drugs.

Evidence shows that patients with significant psychological disorders, such as depression, have higher morbidity and mortality than the general population.[1] A recent meta-analysis of 203 publications from 29 countries on six continents found a relative mortality risk of 2.22 for people with mental disorders. Approximately 8 million deaths worldwide (14.3%) may be associated with mental disorders.[2]

In women, the incidence of mental disorders is more frequent and observed at an earlier age; this trend was exacerbated during the COVID-19 pandemic, where Argentina reached the most significant change in prevalence (36.4%) in Latin America for both depression and anxiety.[3]

In the female group, depression without CVD is a predictor of CV death (relative risk 1.5); in young women, the risk of ischemic heart disease is 15 times higher (14.57 [95% CI, 2.65-80.10]).[4] In the presence of CVD, such as myocardial infarction (MI), depression is two times higher in women than in men, increasing the risk of new CV events, lower therapeutic adherence, and worse prognosis. Anxiety plays a similar role, with a higher prevalence in women, especially when CVD coexists, doubling the risk of new CV events such as reinfarction, *tako-tsubo* cardiomyopathy, or coronary artery dissection with myocardial ischemia induced by mental stress.[5]

The differences between men and women are not limited to the biological sphere. There are also differences at the emotional and sociocultural levels. Women's emotional and psychic worlds are crossed by hormonal variations throughout their lives that affect the central nervous system (CNS) and psychic states. In addition to protecting the CV system, estrogens have an activating action, improving mood through excitatory amino acids such as glutamate and aspartate. Progesterone, for its part, has an effect similar to that of anxiolytics by facilitating GABAergic action. Both hormones remain in balance, and when this is altered, symptoms of the depressive-anxiety spectrum appear. In addition, neurocognitive functions are shaped by the culture of different societies throughout history.[6]

Over the last decade, key findings allowed us to understand the importance of psychological well-being and the social determinants of health in maintaining or improving CV health. Specific characteristics associated with positive

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psychological health, such as optimism, purpose in life, and resilient coping (among others), are related to good CV health. In contrast, higher psychosocial stress and depression are associated with poorer CV condition.

A recent AHA scientific statement (2021) reviewed a large number of studies addressing a wide range of positive (optimism, a sense of purpose, happiness) and negative (stress, depression, anxiety) psychological health factors and their significant associations with CV health and CVD risk.[7]

Poverty and the resulting psychosocial sphere affect women more than men, with a 25% greater probability of having a heart attack than their male peers. This condition is

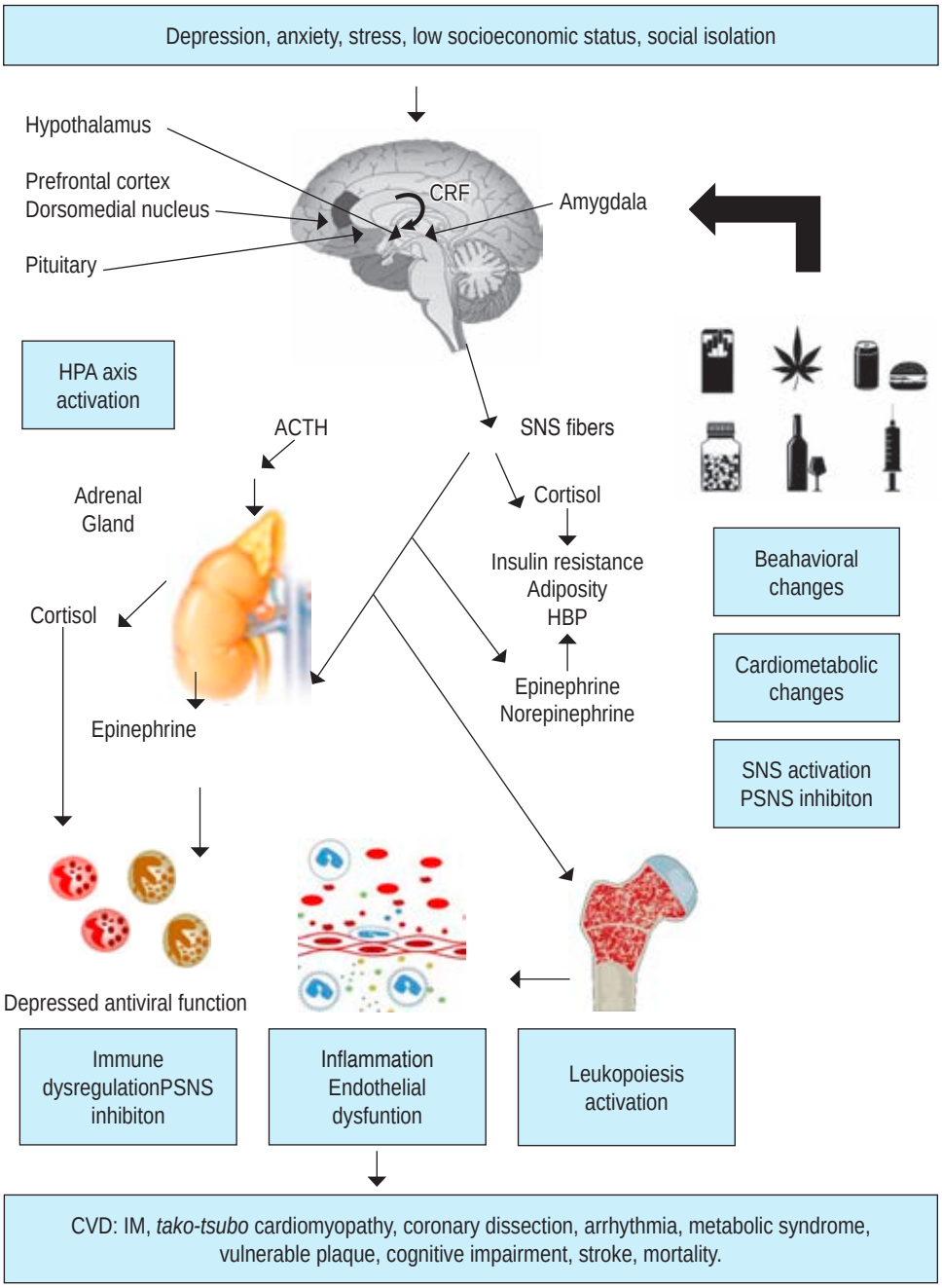

Figure 1:

Pathophysiological and behavioral mechanisms between psychosocial determinants and cardiovascular disease.[9]
CRF = corticotropin-releasing factor. HPA = Hypothalamic-pituitary-adrenal axis. ACTH = adrenocorticotropic hormone. SNS = sympathetic nervous system. PSNS = parasympathetic nervous system. HBP = high blood pressure. CMP = cardiomyopathy. CVD = cardiovascular disease. MI = myocardial infarction.

Table 1: Treatment and recommendations.

Stress and anxiety	I	IIa	IIb	III
Non-pharmacological approach[10-15]				
Refer to programs based on positive psychology		A		
Meditation		B		
Mindfulness		B		
Physical activity and a healthy diet	A			
Pharmacological approach[12,13]				
Benzodiazepines (clonazepam, lorazepam, alprazolam) Examine drug-drug interaction with statins	B			
Depression				
Non-pharmacological approach[10-15]				
Cognitive behavioral therapy, behavioral activation, and interpersonal psychotherapy	B			
Mild-moderate depression: cognitive-behavioral and problem-solving therapy				
Moderate to severe depression: cognitive-behavioral and interpersonal therapy				
MBTC: Mindfulness-based cognitive therapy (relapse prevention)		B		
Physical activity and a healthy diet	A			
Pharmacological approach[12,13]				
CVD patients: use of serotonin reuptake inhibitors: escitalopram, sertraline	B			

CVD = cardiovascular disease.

more prevalent in Latin America than in the rest of the world.

In women, coronary syndromes without obstructive lesions are frequently associated with adverse psychological and sociodemographic profiles with a worst course than expected.

The mechanisms that favor psychosocial factors have two main conditioning factors[8] for the increase in cardiovascular events:

1. Intrinsic: alterations in emotional factors, affective disorders (anxiety/depression), hostility, and tendency to anger.
2. Extrinsic: chronic stressors such as lack of social support, low socioeconomic status, work stress, partner stress, and caregiver stress.

Pathophysiology

The pathophysiological mechanisms involve the biological and behavioral spheres in depression, anxiety, and stress with the activation of various systems such as the hypothalamic-pituitary-adrenal (HPA) axis, the sympathetic nervous system (SNS), and renin-angiotensin-aldosterone. The consequences are inflammation, oxidation, and hemostatic and vascular flow alterations. All this leads to CVD and risk factors such as a sedentary lifestyle, drug use, inadequate diet, and lack of pharmacological adherence *(Figure 1)*.[9]

Diagnosis

The AHA recommends screening all CVD patients with at least the 2-item Patient Health Questionnaire (PHQ-2). Those who test positive on the PHQ-2 should be evaluated with the 9-item PHQ-9 to promptly detect patients with depressive spectrum mood disorders.[10] On the other hand, the WHO has created an application to detect mood disorders, mental, neurological, and substance use for personnel not specialized in mental health that facilitates the diagnosis and management of these patients *(Table 1)*.[11]

CONCLUSIONS

The practice of cardiology medicine imperatively requires gender awareness, given that the evidence shows the impact of psychosocial factors on women's cardiovascular health. Currently, we do not have risk calculators that guide behaviors, so it is necessary to include these factors in the individual risk assessment and implement education campaigns for the general population and the medical community. It depends on this that we can all develop a health system that considers women as part of a whole and not a simple piece of a whole.

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Chapter 10

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Congenital heart disease in women

Cardiopatías congénitas en la mujer

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INTRODUCTION

Advances in diagnosis, anesthesia, intensive care, and surgery have improved the evolution of congenital heart disease (CHD). Sixty years ago, only 25% survived beyond the first year of life. Currently, more than 95% survived to adulthood. It is estimated that 1/150 adults in the United States of America (USA) have different types of CHD, from subclinical forms of the bicuspid aortic valve to severe conditions; there are approximately 10 million adults with CHD in the world.

Khairy et al. analyze mortality in 71,686 patients. They observed that in 2004-2005 mortality was similar to that of the general population, quite different from the observed in 1987-1988, where high mortality was observed in the first year of life.

The estimated number of adults with CHD in the USA was 1,444,500 in 2016, a 63% increase in the estimated population with CHD since 2000. The prevalence in women was 6/1,000 and in men 3.8/1,000.

According to DiNardo, adults with CHD may: 1) have simple or complex lesions that allow survival and are seen for the first time; 2) have previous palliative procedures waiting for a new procedure; 3) be awaiting early reoperation; 4) be awaiting surgery for residual lesions; 5) be awaiting transplant; 6) also acquired heart disease. These heart diseases can be classified anatomically as type I) simple (≈ 45%), II) of moderate complexity (≈ 40%), and III) of great complexity (≈ 15%) *(Figure 1)*.

To facilitate the approach, the AHA/ACC created a functional classification: A, B, C, and D, similar to that of the NYHA for heart failure (HF), but with characteristics typical of adult CHD, indicating that patients in the classifications I B-D; II A-D and III A-D must be explored by a specialist with experience in adult congenital heart disease.

PREGNANCY

Data from the multicenter ROPAC Registry, with 57.4% of pregnant women with CHD, showed maternal mortality of 0.6% in the total group and 0.2% in those with CHD, much higher than expected (0.007% in average pregnant women).

Pre-pregnancy data, such as NYHA HF or CF signs > II, left ventricular ejection fraction < 40%, modified World Health Organization (WHO) class IV, and use of anticoagulation, were cited as predictors of HF or mortality during pregnancy.

In a review of 48 studies performed between 1983 and 2006, including 2,491 pregnant women with CHD, 34.2% have obstetric complications (2.2% embolic events, 8.7% hypertensive disease, 11% early delivery, and 3.9% premature rupture of the membranes), 11.7% of maternal cardiac complications (4.5% of arrhythmia, 4.8% of heart failure and 1.9% of other pathologies such as heart attack, stroke, etc.) and 31.4% of fetal complications among which the most important was preterm birth. CHD recurrence in children was

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3.5%, and infective endocarditis (IE) was a rare event (0.5%).

The number of pregnancies in patients with CHD increases rapidly. Data from the US National Inpatient Sample from 1998-2007 show that the number of deliveries in patients with CHD increased by 34.9%, compared to an increase of 21.3% in the general population.

The care of a pregnant woman with CHD involves:

1. Preconception: women should be assessed before planning a pregnancy using risk stratification scales (ZAHARA, CARPREG, and WHO). The modified WHO risk stratification should be used initially *(Table 1)*.

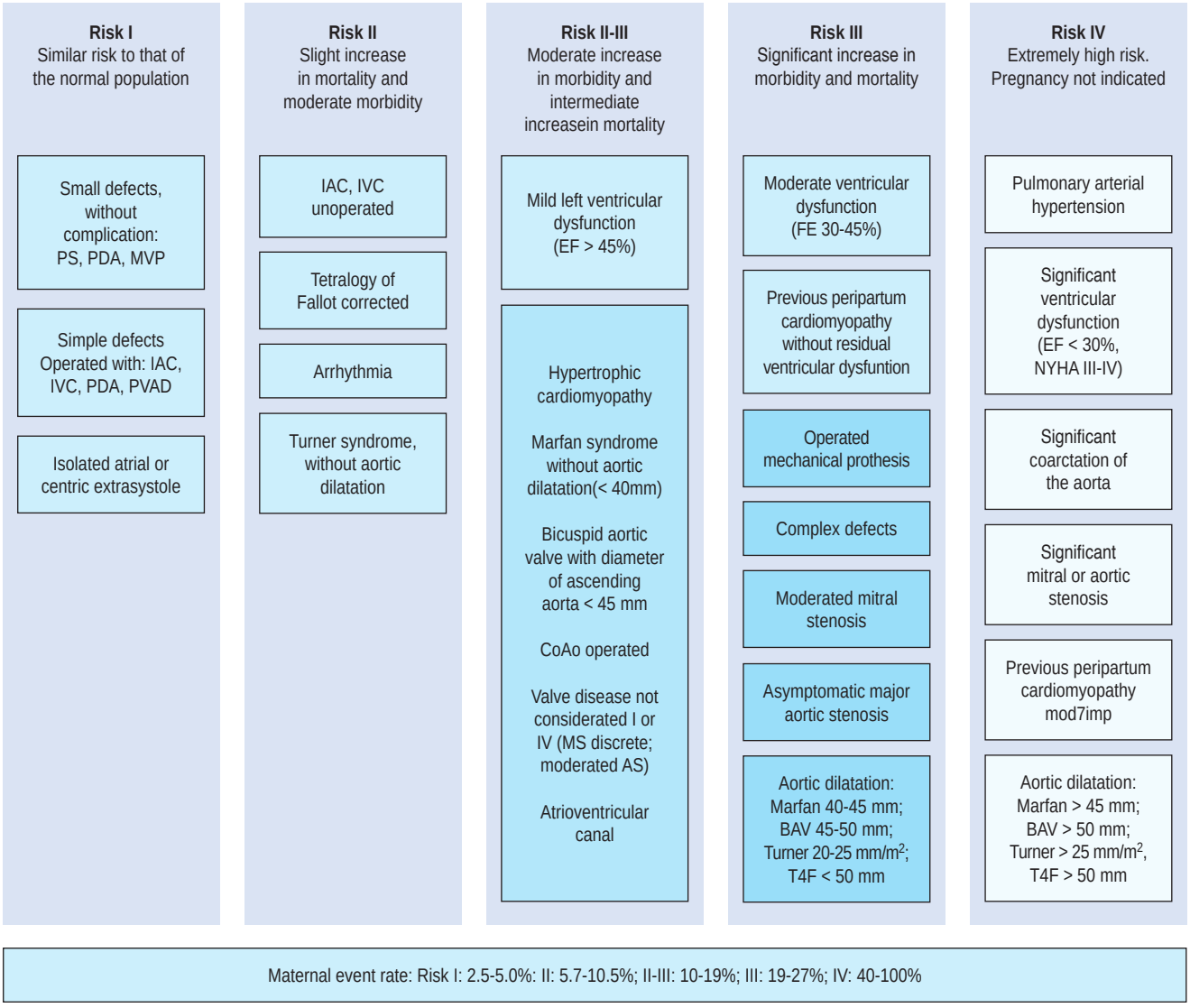

Figure 1: Anatomical classification of congenital heart diseases in adults.
PS = pulmonary stenosis. PDA = patent ductus arteriosus. MVP = mitral valve prolapse. IAC = interauricular communication. IVC = interventricular communication. PVAD = percutaneous ventricular assist devices. CoAo = coarctation of the aorta. MS = mitral stenosis. AS = aortic stenosis. BAV = bicuspid aortic valve; T4F = Tetralogy of Fallot. EF = ejection fraction. NYHA = New York Heart Association Classification.
Modified from: Warnes CA et al.[1], Warnes CA et al.[2], Khairy P et al.[3]

Table 1: Cardiovascular risk according to the WHO in women with congenital heart disease, follow-up strategy, and estimated mortality.

I. Simple congenital heart disease
- Congenital aortic or mitral valve injury isolated (except MV parachute, cleft)
- Isolated small IAC e IVC
- Pulmonar stenosis, small
- Simple defects operated: IAC, IVC, PDA, no residual injury or sequel

II. Congenital heart disease of moderate complexity
- Aortoventricular tunnel
- Abnormal drainage of the pulmonary veins
- AOCA of pulmonary artery or Ao (opposite sinus)
- Atrioventricular septal defects (partial or complete)
- Congenital mitral or aortic stenosis
- Aortic coarctation
- Ebstein anomaly
- Right ventricular outflow tract obstruction
- IAC ostium primum or sinus venosus
- Moderate or significant IAC unoperated
- Moderate or significant ductus arteriosus
- Moderate to severe pulmonary reflux
- Moderate or severe pulmonary stenosis
- Stenosis of peripheral branches of the pulmonary artery
- Sinus of Valsalva aneurysm/fistula
- Sub or supra valvular aortic stenosis (except HMO)
- Atrioventricular valve in straddling corrected Tetralogy of Fallot
- IVC with associated defects and/or mod/imp shunt
- Right ventricle with double chamber
- Marfan syndrome (inheritance of alt Ao), Turner
- Sub, valvar and supra mod/imp pulmonary stenosis
- TGA after switch surgery

III. Congenital heart disease of great complexity
- Cyanotic congenital heart disease (unoperated or palliated)
- Double exit pathway of the ventricles
- Fontan surgery
- Interruption of the aortic arch
- Mitral atresia
- Single ventricle
- Pulmonary Atresia (all forms)
- Transposition of the great arteries (TGA). TGA except patients with previous switch surgery
- Truncus arteriosus
- Others: criss-cross heart; isomerism, heterotaxic syndromes, ventricular inversion
- Congenital heart disease associated with pulmonary hypertension, including Eisenmenger syndrome

MV = mitral valve. IAC = interauricular communication. IVC = interventricular communication. PDA = patent ductus arteriosus. AOCA = anomalous origin of coronary artery. TGA = transposition of great arteries. Ao = aorta.
It is modified from: Drenthen W et al.[8]

2. During pregnancy: Multidisciplinary care to diagnose and treat possible complications. Guide the use of cardiovascular drugs with effects on the fetus.
3. In childbirth: except for some heart diseases, the indication for delivery is obstetric. It is essential to prevent complications related to pain, anxiety, and massive venous return when decompressing the pregnant uterus or using thromboprophylaxis.
4. Puerperium: divided into immediate (24 hours), mediate (7 days), and late (42 days), will be followed up to one year after delivery or interruption of pregnancy. Guiding family planning without interfering with the use of cardiovascular drugs. The physiological changes of pregnancy tend to normalize 45 days after delivery, requiring cardiovascular evaluation at this time.

COMPLICATIONS

Patients with CHD generally use medication for life and require multiple surgeries and hospital admissions; they can present a higher number of complications or mortality during pregnancy, severe arrhythmias and heart failure, and reduced life expectancy. We cannot forget acquired diseases, such as systemic arterial hypertension, acute myocardial infarction, and cerebral vascular accident.

IE is more frequent than in the general population and more severe in prosthetic valves, including those with percutaneous implantation, valve repair with a prosthetic ring, previous IE, any cyanotic CHD or repaired with prosthetic material, up to 6 months after the procedure or permanent if a residual shunt or valvular insufficiency persists.

Antibiotic prophylaxis is recommended in patients at high risk for IE, even during childbirth, without consensus on the preventive use of antibiotics in all women with CHD.

Bleeding diathesis and thrombosis are frequent complications, and their treatment and prophylaxis contribute to survival. Spontaneous bleeding is mild and self-limited (dental, epistaxis, bruising, menorrhagia). Hemoptysis is the external manifestation of intrapulmonary hemorrhage, common in Eisenmenger syndrome.

Concerning thrombosis, the associated risk factors are female gender, oxygen desaturation, senility, biventricular dysfunction, dilatation of pulmonary arteries, and post-surgical complications such as Fontan, in which there may be total or partial thrombotic obstruction of the shunt cavopulmonary. Its treatment includes thrombectomy, percutaneous angioplasty (stent), surgery, and anticoagulant therapy or thrombolysis.

Strokes are frequent and related to thromboembolic events, microcytosis, endothelial dysfunction, and paradoxical emboli due to endocavitary electrodes and catheters. Anticoagulation is not routinely indicated in patients with Pulmonary Hypertension, and its prescription is individualized, as in the case of mechanical valves, vascular prostheses, supraventricular arrhythmias, presence of thrombosis or pulmonary embolism, provided that the bleeding risk is low.

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Chapter 11

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Chronic coronary syndrome

Síndrome coronario crónico

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INTRODUCTION

Coronary heart disease (CHD) is a pathological process with an accumulation of atherosclerotic plaques in the epicardial coronary arteries. It is a chronic, progressive condition that can remain asymptomatic until the occurrence of a plaque event (acute coronary syndrome, ACS.

Chronic coronary syndrome (CCS) encompasses pathological conditions produced by a chronic or repetitive mismatch between supply and demand in myocardial oxygen consumption. The most common cause of ischemia is atherosclerotic obstruction of the coronary arteries. Less frequent are microvascular dysfunction, vasospasm, congenital anomalies, or non-atherosclerotic myocardial injuries.[1,2] The main clinical manifestation of CCS is angina. The reproduction and the duration of the pain with exercise or stress allow this picture to be differentiated from ACS.

FORMS OF PRESENTATION:

Six forms of presentation are distinguished:[1]

1. Patients with chronic stable angina with or without dyspnea with suspected obstructive coronary disease (CAD). The study of these includes evaluation of symptoms, physical examination, comorbidities, and quality of life. It is fundamental to evaluate the pretest probability to choose an appropriate diagnostic method and to establish a prognosis for future CV events.[2]
2. Patients with a recent episode of heart failure or left ventricular (LV) dysfunction. CAD is the leading cause of heart failure.
3. Patients with stable symptoms after < 1 year of an ACS or revascularization.
   They should be followed for the first year after the event, and ventricular function should be evaluated 8 to 12 weeks later.
4. Patients after one year of ACS or revascularization. An annual clinical evaluation is recommended with emphasis on adherence to optimal medical therapy, ECG, and evaluation of ventricular function and silent ischemia every 3 to 5 years.[1,2]
5. Patients with angina and suspected microvascular dysfunction or vasospasm with non-obstructive CHD. They are associated with an unfavorable prognosis. The microvascular disease presents angina without significant obstructive lesions. Vasospastic events occur at rest and usually follow a circadian rhythm with transient ST changes.
6. Asymptomatic patients with CD detection by check-up: a careful assessment of CV risk is suggested.

DIAGNOSIS OF CHRONIC CORONARY SYNDROME

There are six essential steps:[1,2]

1. Take a detailed clinical history for the diagnosis of angina and its classification (typical, atypical, non-anginal chest pain). Then assess symptoms and signs using the Canadian Society of Cardiology classification.[1]

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2. Concomitant diseases, quality of life, presence of anemia, arterial hypertension, valvular disease, hypertrophic cardiomyopathy, heart rhythm disturbances, peripheral vascular disease, thyroid disease, kidney disease, and diabetes must be registered
3. Perform resting ECG, laboratory tests (complete hemogram, kidney function, diabetes screening, lipid profile, thyroid profile), transthoracic echocardiography, and chest X-ray.[1]

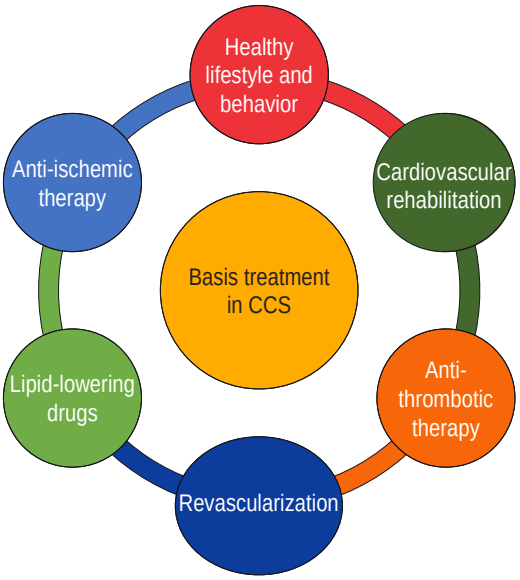

Figure 1: Basis of treatment in chronic coronary syndrome.
CCS = chronic coronary syndrome.

4. Assess the pretest probability (PTP) and the clinical likelihood of ischemic heart disease. When the PPT is < 15%, do not carry out further studies; between 15 and 65%, coronary computed tomography (CTA) is recommended; between 65 and 85%, consider CTA or another ischemia test, and if PTP > 85%, perform coronary angiography.[2,3]
5. The appropriate diagnostic test will depend on the PTP, the patient's comorbidities, and availability. In symptomatic patients in whom obstructive CAD cannot be ruled out, a non-invasive functional imaging test or coronary CT angiography should be performed. The stress test is recommended only in subjects to assess tolerance to exercise, the appearance of symptoms, arrhythmias, pressor response, and the risk of CV events. It can also be considered when non-invasive images are unavailable or in patients already treated to observe symptoms and or signs of ischemia on the ECG. Angio-CT is an alternative to coronary angiography if other non-invasive tests are not diagnostic. Coronary angiography is recommended in patients with high clinical probability, symptoms resistant to therapy, or mild effort angina. Invasive functional assessment should be carried out in cases with doubt about stenosis severity.[3]
6. Risk assessment of CV events based on clinical evaluation and studies performed for diagnosis.

Table 1: Lifestyle recommendations in chronic coronary syndrome.

Intervention	Recommendation ESC 2019	RRR (%)
Physical activity	30-60 minutes of moderate-intensity almost every day	27 mortality
Smoking cessation	Use of the 5As model	36 mortality
Healthy diet	High in vegetables, fruits, and grains. Saturated fats < 10% of total intake Reduce alcohol consumption to < 100 grams per week	31 MACE[10]
Weight loss	Achieve and maintain BMI ≤ 25 kg/m^2	33 MACE[1]

ESC = European Society Cardiology. RRR = relative risk reduction. BMI = body mass index. MACE = major adverse cardiovascular events.

TREATMENT

The main objectives are improving symptoms/quality of life and cardiac event-free survival. The treatment pillars are summarized in *Figure 1*.[1,2]

1. Lifestyle and healthy behavior: *Table 1*.
2. CV rehabilitation: consists in a supervised exercise program. Its benefits are multiple. It has been shown in meta-analyses that it can reduce CV mortality and hospitalizations. However, < 25% of patients are referred to these programs.[4,5]
3. Anti-ischemic therapy: β-blockade and calcium channel blockers are the first lines to reduce angina, but they have not shown an effect on survival. Short-acting nitrates are reserved as a rescue medication, while long-acting nitrates are used as the second line. Ranolazine could be used in patients with refractory symptoms despite therapy.[1,2]
4. Antithrombotic therapy: acetylsalicylic acid (ASA) is the mainstay of treatment for obstructive CAD. Dual antiplatelet therapy is maintained ± 12 months after an ACS. The use after one year of dual treatment therapy a reduction in the risk of CV events ≈ by 25-28%. The addition of the anticoagulant rivaroxaban at a dose of 2.5 mg BID plus ASA reduced the relative risk of events by 24%.[6]
5. Lipid-lowering agents: the LDL goal is < 55 or < 70 mg/dL in Europe and USA, respectively. Management includes lifestyle changes and additive intensive drug therapy with statins, ezetimibe, and PSCK9 inhibitors, in that order.[1,2,7]
6. Revascularization: the ISCHEMIA[8] study, and recently REVIVE,[9] showed equal survival in patients with optimal medical treatment versus coronary revascularization. This last strategy, however, achieves better symptom control.

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Chapter 12

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Non ST elevation acute coronary syndrome in women: unstable angina and non ST elevation acute myocardial infarction

Síndrome coronario agudo sin elevación del ST en la mujer: angina inestable e infarto agudo de miocardio sin elevación del segmento ST

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INTRODUCTION

Non-ST-segment elevation acute coronary ischemic syndrome (NSTEACS), in its form of unstable angina or infarction, is a frequent reason for medical care in the emergency room and hospitalization. According to the Global Burden of Disease study in 2019, it was estimated that there were 275.2 million cases of cardiovascular disease (CVD) in women around the world, and even when a reduction in the global prevalence standardized by age in women of 5.8% was seen between 1990 and 2010, the trend seems to increase again after 2010.[1] Hospital admissions for young women with acute myocardial infarction (AMI) increased from 27% in 1995-1999 to 32% in 2010-2014.[1,2]

The immediate and mediate hospital morbidity, and mortality of NSTEACS are lower than in the case of ST-segment elevation acute coronary syndrome (STEACS). However, in the medium-long term, it may be higher. Globally, it was estimated that there were 6.10 million deaths from CVD in women in 1990; while in 2019, they increased to 8.94 million, and the highest mortality rates occurred in low- and middle-income countries.[1,2]

In general, the diagnostic, prognostic, and therapeutic approach to NSTEACS in women should be the same as in men; however, it is crucial to take into account the following gender-specific considerations:

Clinical presentation

In women, it can vary from dyspnea to sudden death or cardiogenic shock, but the most frequent manifestation is pain or pressure/discomfort in the chest or precordium (angina). They are more likely to have accompanying symptoms such as dyspnea, nausea, weakness, and fatigue; the location is different, with less intensity or nonspecific, which generates difficulty and delay in diagnosis. Patients with obstructive coronary artery disease more commonly manifest «typical» angina events, while ischemic heart disease without obstructive coronary lesions (INOCA or MINOCA) and vasomotor disorders present microvascular angina, characterized by a crescendo-decrescendo pattern that changes over time, appearing hours after physical exercise, at rest or associated with stressful situations. They frequently present extreme tiredness that interferes with their daily activities and work capacity.[3-5] Women attend later to receive medical care, compared to men.[4,5]

1. **Electrocardiogram.** They are the same, but women tend to present more frequent

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changes in the T wave and fewer alterations in intraventricular conduction, such as left or right bundle branch block.[3,5]

2. **Biomarkers.** Different studies have reported lower concentrations of ultrasensitive troponins (troponin T or I hs-cTn) in women compared to men. These gender differences could contribute to underdiagnosis and inequality in the treatment of the acute coronary syndrome. The upper level or reference limit for the infarction diagnosis could be twice as high in men. Sex hormones seem to alter the differential expression of hs-cTn. Estrogens appear to exert a protective role on the myocardium; their antioxidant properties and ability to eliminate reactive oxygen species may help to limit cardiomyocyte injury.[6] However, even though the use of sex-specific hs-cTn cut-off points increased the detection of acute infarction in women, it has no impact on short- or long-term prognosis; in contrast, the standard troponin levels criteria misdiagnose one in five heart attacks, and associate with high mortality rate.[7]

   Another biomarker showing gender differences is a brain-type natriuretic peptide (BNP or proBNP). Levels are significantly higher in both healthy and diseased women than in men.[3,4] Women receiving hormone replacement therapy may have higher levels of BNP, suggesting that its production may be sensitive to regulation by estrogens.[8]

3. **Imaging studies.** There is consensus that women tend to receive cardiac catheterization with the intention of revascularization in very high-risk

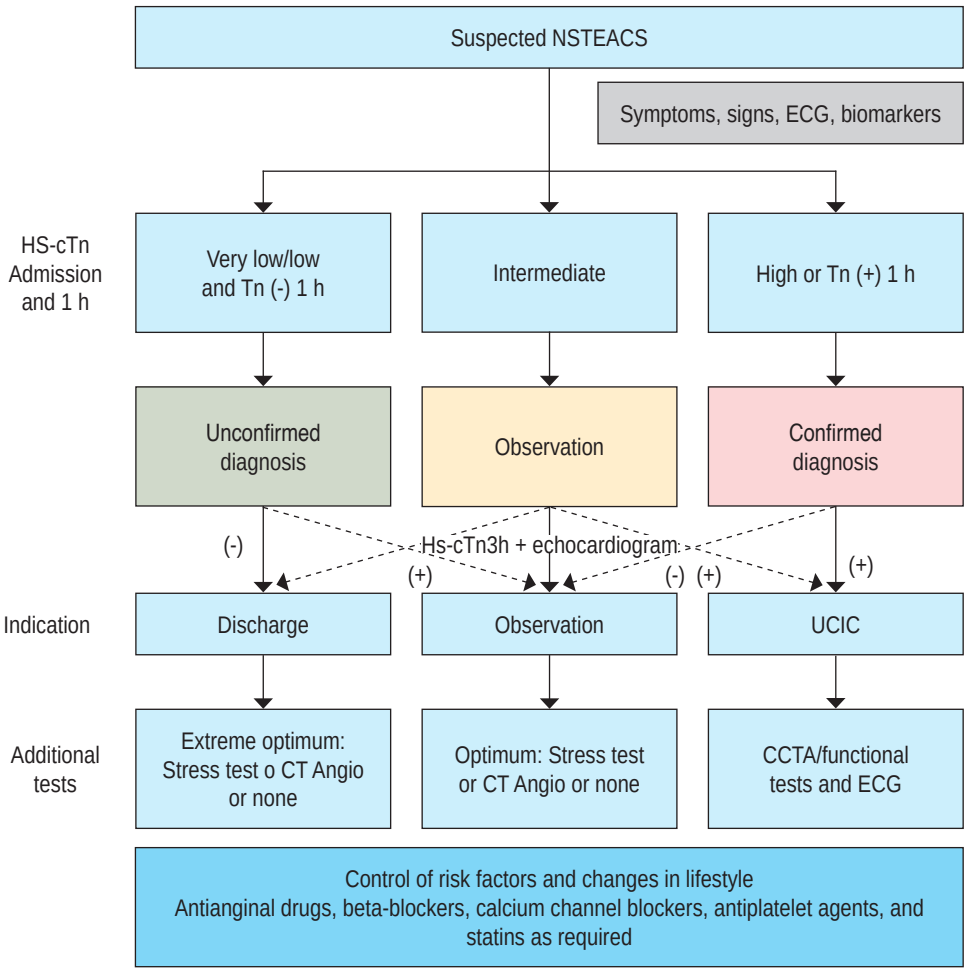

Figure 1:

Algorithm for diagnosis and treatment of patients with SICAsEST.
Adapted from: Collet JP et al.[4]

patients with NSTEACS less frequently. Because they present coronary arteries without significant lesions, microvascular dysfunction, endothelial erosion, non-obstructive lesions, or coronary spasm as the cause of myocardial ischemia more frequently, their evaluation should be completed by intravascular ultrasound with a pharmacological challenge (acetylcholine or adenosine) or coherence tomography optical, to assess coronary vasomotor function.[4,5,9]

Compared to other functional tests, multicenter imaging studies demonstrated the non-inferiority of coronary computed tomography angiography (CCTA). In addition, it allows calculating the functional impact of coronary stenosis by evaluating the fractional flow reserve, non-calcified, non-obstructive plaque characteristics, external remodeling, and coronary dissection or myocardial bridging. Current technology has managed to reduce radiation exposure by up to 80%, which is essential to consider in young women. Its use in the emergency room can accurately identify low-risk patients for safe, cost-effective, and accelerated discharge.[8,9]

4. **Treatment.** In women with NSTEACS, there is less adherence to the guidelines for medical treatment recommendations: aspirin 93.4% vs 94.7%, P2Y12 inhibitors 79.3% vs 86.1% and statins 73.7% vs 77.5%; and revascularization (angiography [adjusted OR 0.71), percutaneous coronary intervention (OR 0.73).[2-4,9] Even when women are underrepresented in clinical trials (less than 39%), no scientific evidence shows that using these recommendations is ineffective. In the case of coronary microvascular dysfunction, it is suggested to include β-blockers, short-acting nitrates, calcium channel blockers, and angiotensin-converting enzyme inhibitors for symptom relief.

It must be recognized that NSTEACS presents differently in women, symptomatically, biochemically, and pathophysiologically, establishing the need to develop clinical studies focused on the identification and better understanding of these differences, as well as the development of guidelines for diagnosis, prognosis, and optimal sex-specific treatment *(Figure 1)*.

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Chapter 13

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Acute ST elevation myocardial infarction in women

Infarto agudo de miocardio con elevación del ST en la mujer

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INTRODUCTION

ST-Elevation myocardial infarction (STEMI) manifests later in women than in men. The prevalence of myocardial infarction in the United States between 2015 and 2018 was lower in women than in men (2.1 vs 4.3%). Still, in-hospital mortality (7.4 vs 4.6%) and in the long term, has remained higher in women, varying according to age range.[1]

The INTERHEART study showed that although the risk factors (RFs) for having a myocardial infarction (MI) affect both sexes, some generate a higher relative risk (RR) in women: diabetes (4.3 vs 2.8), hypertension (3.0 vs 2.3), ratio ApoB/ApoA1 (4.4 vs 3.8) and psychosocial factors (3.5 vs 2.6).[2] Smoking is the most important preventable cause of MI in women.[3]

The randomized, multicenter VIRGO and GENESIS-PRAXI studies of STEMI in young women (< 55 years) showed that they are associated with multiple traditional and non-traditional RFs, a family history of early coronary disease and comorbidities, with psychosocial RFs having a great impact.[4,5]

There are pathophysiological differences in STEMI between women and men.[3,4] Plaque destabilization is the most common cause in both sexes, with 55% of plaque rupture and 25-30% of plaque erosion observed in women. Infarction in the absence of obstructive coronary disease follows in frequency (5-25%). Its treatment and prognosis will depend on the mechanism.[6] Spontaneous coronary artery dissection (1-4%) is associated with female gender, pregnancy, and fibromuscular dysplasia and is generated by emotional and physical stress.[4,7]

The most common symptom in both sexes is precordial pain. Compared with men, women are more likely to have high-risk clinical presentations, less likely to manifest central chest pain, and have a more significant number of non-anginal symptoms (atypical pain).[4,6] Canto et al. observed in a study of the National Registry of Myocardial Infarction of Acute Myocardial Infarction (NRMI registry of AMI, 1994-2006) that women without angina had a delay in diagnosis, a significant decrease in reperfusion treatment, an increase in reperfusion time, and the risk of in-hospital mortality.[8]

Despite the proven benefit in mortality, women are referred less frequently for reperfusion treatment. The strategy of choice should be primary transluminal coronary angioplasty (PTCA) because it has fewer serious bleeding complications and mortality. Regardless of the method used (fibrinolytics [FT] or PTCA), women have worse results than men, which is often due to confounding factors: age, RF, previous heart failure (HF), and comorbidities.[3]

The first analysis by gender in acute coronary syndrome (ACS) was presented at the XXVII Inter-American Congress of Cardiology in 2019 and is part of the National Registry of Acute Coronary Syndrome (RENASCA IMSS).[9] From 2014 to 2018, 37,168 patients were included, 73.8% men (27,419) and 26.2% women (9,749); the average age was 66 ± 11 in women compared to 62 ± 11 years ($p < 0.0001$). Risk factors were significantly more frequent in women *(Figure 1)*. In men,

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STEMI was more frequent (75.1 vs 64.9%, p < 0.0001), and in women, non-ST-segment elevation acute coronary syndrome (NSTE-ACS) (24.9 vs 35.1%, p < 0.0001).

In patients with STEMI with the IMSS Infarction Code strategy,[10] improvement in reperfusion strategies was observed after the implementation of the care protocol. However, there was a significantly higher frequency of non-reperfusion in women (33.3 vs 28.9%, p < 0.0001) *(Figure 2)*. Women had significantly more early hospital complications such as angina/re-infarction (16.4 vs 20.1%, p < 0.0001), HF (9.4 vs 15.5%, p = 0.001), cardiogenic shock (7.7 vs 10.6%, p < 0.0001), kidney failure (6.8 vs 8.1%, p < 0.0001) and death (11.0 vs 15.6% OR 1.49 95% CI 1.40-1.60, p < 0.0001).

Women are significantly less likely to be discharged according to international optimal medical treatment guidelines and less likely to adhere to long-term treatment.[4]

Everything analyzed above leads to women having worse prognoses in the short, medium, and long term. It is necessary to continue with public health messages and interventions to reduce the gender gap in results.

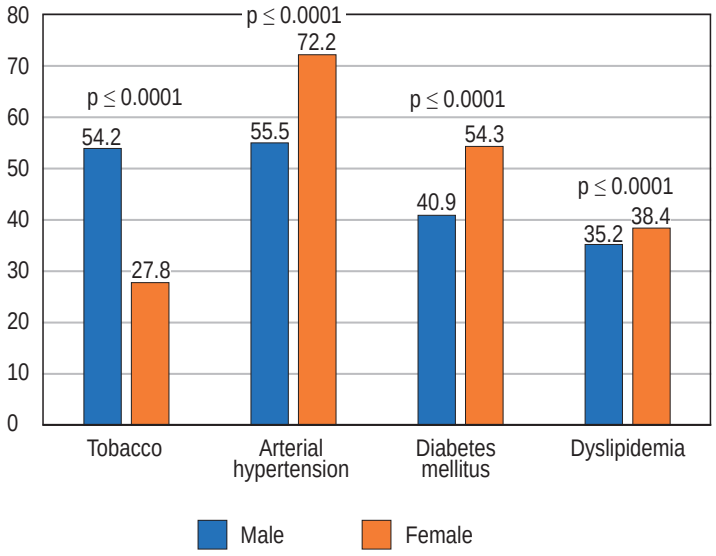
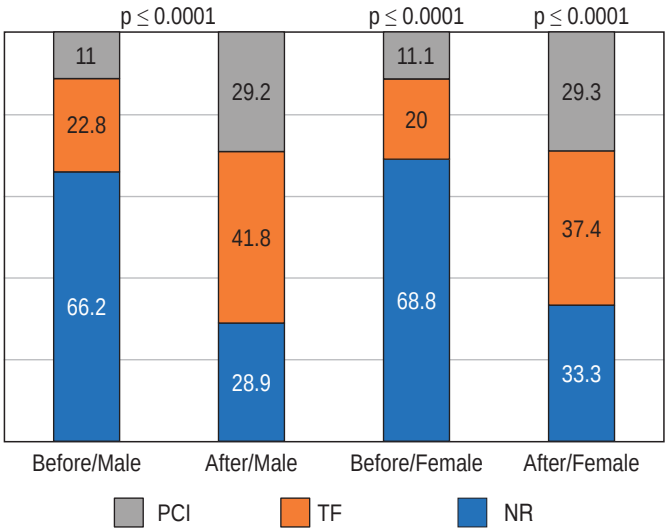


Figure 1: Differences by sex of risk factors in the RENASCA IMSS (National Registry of Acute Coronary Syndromes).



PCI = percutaneous coronary intervention. TF = fibrinolytic therapy. NR = no-reflow.

Figure 2: Differences by sex in reperfusion strategies, before and after code infarction.

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Chapter 14

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INOCA and MINOCA: are they invisible to the eyes?

INOCA y MINOCA: ¿son invisibles a los ojos?

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Keywords:
INOCA, MINOCA, woman.

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ABSTRACT

Coronary ischemic phenomena without obstructive arteries (INOCA-MINOCA) remain enigmatic clinical entities characterized by evidence of myocardial injury without obstructive coronary atherothrombotic etiology. Although it is attributed to multiple possible mechanisms, in recent years, significant advances in the underlying pathophysiological understanding have made it possible to get a better guide for treatment. Although it is more benign than infarcts with obstructive arteries, its prognosis is not very predictable and is being evaluated by ongoing studies. This article presents an updated view of these pathologies.

INTRODUCTION

Angiographically, one in four coronary angiographies (CCG) performed for myocardial ischemia present epicardial coronary atheromatous disease (EAD) with occlusion < 50%. This paper summarizes a current approach for a diagnostic algorithm and treatment of patients admitted with angina with or without high-sensitivity troponin T increase (TrIUS).[1]

These conditions have recently become relevant due to the diagnostic and therapeutic challenge, impact on quality of life, and not insignificant mortality.

According to their clinical presentation, clinical syndromes characterized by angina with coronary arteries without significant angiographic lesions encompass ischemic pathologies known by their acronyms INOCA and MINOCA.[1]

Operational definitions

INOCA (ischemia and non-obstructive coronary artery disease) relates to heterogeneous disorders characterized by signs and symptoms of chronic myocardial ischemia in the absence of EAD > 50% in CAG.

MINOCA (myocardial infarction with non-obstructed coronary arteries) is the set of diseases associated with myocardial damage meeting the criteria of the 4th Universal Definition of Acute Myocardial Infarction (MI): MI type 1 or 2 with elevated TrIUS > 99th percentile, in the absence of angiographic EAD > 50%, and the subtypes: normal, mild (< 30%) and moderate (> 30% < 50%), with or without electrocardiogram (ECG) abnormalities. The exclusion criterion of any other manifest cause for acute presentation than MI is added to the definition.[2,3]

INOCA

Up to 70% of patients undergoing CAG for angina do not have obstructive (> 50%) EAD but have demonstrable ischemia, which is more commonly seen in women.[4] These patients present a broad clinical spectrum, often misdiagnosed as non-cardiac, leading

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to inappropriate diagnosis, evaluation, and treatment.[1]

Heterogeneous pathophysiological mechanisms of coronary microvascular dysfunction (CMD) and epicardial vascular dysfunction are responsible for the angina. CMD and vasospastic angina (VSA) isolated or combined with EAD should be evaluated and confirmed with CAG imaging studies, coronary CT angiography, PetScan, and pharmacological tests (acetylcholine-adenosine) to assess vascular reactivation / coronary flow reserve (FFR)/CMR during CAG, necessary to elucidate INOCA endotypes for therapeutic purposes.[1,2,4]

Microvascular angina (MVA): clinical manifestation of myocardial ischemia caused by CMD due to structural microvasculature remodeling or vasomotor disorders that affect the coronary arterioles. Both mechanisms of vascular dysfunction can coexist and contribute to MVA.

Vasospastic angina (VSA): clinical manifestation of myocardial ischemia caused by dynamic epicardial coronary artery disease associated with a spastic vasomotor disorder characterized in invasive tests with >90% luminal reduction of the associated vessel with ST electrical changes.

The coexistence of these phenomena is associated with a worse prognosis. Age, diabetes, arterial hypertension (HBP), and dyslipidemia are associated with altered CMD. However, the link between traditional cardiovascular risk factors (TCVRF) and INOCA is not well established, except for smoking, which strongly correlates with DMC altered.[4] A very outstanding aspect is the presence of proinflammatory markers in women with INOCA. Contemporary studies evaluate the potential role of inflammation in the modulation of the coronary microvascular response.[4]

MINOCA

Diagnostic criteria have recently been outlined to define MINOCA to exclude non-ischemic causes of myocardial injury (Takotsubo, myocarditis, heart failure (HF), pulmonary thromboembolism, cerebrovascular events (stroke), renal failure, etc.) due to overlapping of the different spectra of myocardial injury in the real world.[5]

Diagnostic algorithm

A miscellany of etiologies underlies the etiopathogenesis of MINOCA: atheromatous coronary causes (rupture, plaque erosion), non-atheromatous (coronary spasm (CAS), spontaneous coronary artery dissection (SCAD), thromboembolism), CMD, oxygen supply/demand mismatch. It is therapeutically relevant to follow a specific diagnostic/etiological protocol with complementary studies to the CAG as a) invasive coronary imaging: intravascular ultrasound (IVUS), optical coherence tomography (OCT), b) functional: provocation test (VEC, FFR, and measurement of microvascular resistance dysfunction), and c) Non-invasive: ECG, transesophageal/transthoracic echocardiography, Holter ECG and Cardiac MRI to confirm the diagnosis of true MINOCA and rule out other causes of myocardial injury.[5]

Etiologies and prevalence

It represents 4-10% of myocardial infarctions, is more frequent in women (> 50%) with less TCVRF, but is commonly associated with hypertension, dyslipidemia, and smocking, in a younger population than patients with obstructive thrombotic EAD.

Among atherosclerotic causes, plaque rupture accounts for 60-70% of type 1 and 2 MI, common in MINOCA (13-40%) with or without visible thrombus on OCT. IVUS better identifies plaque erosion but is less frequent.[5,6]

Among non-atherosclerotic causes, CD (epicardial luminal obstruction > 90%) is more common in young subjects (5-15%) and is associated with the use of illicit drugs (e.g., cocaine) and drugs (pseudoephedrine, anti-migraine). CMD documented by positive functional tests related to vasospasm explains up to 30% of MINOCA and 3% isolated. Endocardial defect (ECD) is a common cause between 40 and 62 years of age; commonly in women with fibrodysplasia disease or those related to collagen, autoimmune, pregnancy and puerperium diseases, CAG is usually

sufficient for diagnosis in these cases. Embolic etiologies (intracardiac thrombi, paradoxical embolisms, tumors) and thrombotic etiologies associated with thrombophilia represent 1-4% of MINOCA causes and are difficult to diagnose in practice.[5-7]

Use of cardiac magnetic resonance in MINOCA

This non-invasive diagnostic method is highly relevant to confirm the diagnosis of MINOCA; an early evaluation is recommended, in a period of 7 to 14 days after the onset of symptoms, being helpful to exclude non-ischemic myocardial injury conditions such as Takotsubo and myocarditis. The cardiac magnetic resonance (CMR) imaging protocols allow the evaluation of anatomy and function, the detection of myocardial edema, acute cell membrane damage, and chronic myocardial fibrosis with patterns that will enable differentiation between MI and myocarditis.[5]

However, in some patients with MINOCA criteria, it will not be possible to demonstrate the area of infarction by this technique.

Prognosis

The mortality of MINOCA ranges between 2-4%, being lower than that of infarcts with atherothrombotic EAD (6.7%), but with increased costs due to morbidity associated with new events that increase hospitalizations, HF, stroke, and deterioration of quality of life.[6,7]

Therapeutic approach

Current treatment guidelines for both entities recommend general measures such as changes in lifestyle and control of TCVRF.

INOCA treatment is a challenge, depending on endotypes for appropriate treatment. VSA and MVA benefit from both treatments with calcium antagonists (CA) and beta-blockers such as carvedilol or nebivolol, associated with inhibitors of the renin-angiotensin-aldosterone system due to their beneficial effect by improving coronary reserve flow (CRF) and decreasing periarteriolar fibrosis, reducing symptoms and cardiovascular events.[1,2,8]

Drugs such as trimetazidine (myocardial metabolism modifier) and nicorandil (coronary microvasculature vasodilator) could help improve symptoms in patients with INOCA.[1]

Sublingual nitrates remain a therapeutic option for acute episodes of VSA, being ineffective in prolonged use.[2] The first pharmacological line in these patients is non-dihydropyridines CAs such as diltiazem. The association with amlodipine (CA dihydropyridines) could synergize to reduce symptoms in refractory cases.

Ranolazine can be used in MVA to improve the altered CRF, increasing the myocardial perfusion index.

Statins are indicated in INOCA and MINOCA with proven atherosclerotic etiology due to the regression and stabilization of plaques responsible for the pathology, improving endothelial dysfunction, and directly impacting the reduction of morbidity and mortality.[1] It is considered that there is a class effect, so that no one can be recommended.

A systematic review has shown the benefit of cardiovascular rehabilitation in these patients: improvement in symptoms, documented ischemia, with improvement in functional capacity and quality of life.[4,5]

Antiplatelet therapy (single or dual) does not differ from the initial MI recommendations. However, there is no evidence of benefit from its prolonged use.

In patients with SCAD, low-dose aspirin is recommended for long-term use for secondary prevention. Neither endovascular treatment (coronary angioplasty) nor myocardial revascularization (bypass) is a therapeutic option. These are reserved for hemodynamic instability due to plaque rupture with thrombi or severe TIMI flow impairment due to anatomical location and extension of compromised myocardial mass.

CONCLUSION

INOCA and MINOCA are associated with a higher incidence of cardiovascular events, repeat hospital admissions, unnecessary CCGs, impaired quality of life, adverse short-term and long-term cardiovascular outcomes, and increased healthcare costs.

The available evidence on the treatment of INOCA and MINOCA is still limited, with most recommendations based on expert opinion.

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Chapter 15

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Heart failure in women

Insuficiencia cardiaca en la mujer

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INTRODUCTION

Heart failure (HF) is a global pandemic, affecting 26 million people in 2017.[1] In 2019, about 6.5 million were diagnosed with HF in the United States, 3.6 million (55.4%) were women.[2] Despite advances in treatment, morbidity and mortality remain high.

In Latin America, the incidence of HF is 199/100,000 person-years; it is the leading cause of hospitalization and re-hospitalization after three months.[1,2]

It is a clinical syndrome with cardinal symptoms (dyspnea, fatigue) accompanied by signs (pulmonary crackling rales, systemic edema). It is due to a structural and/or functional abnormality of the heart that causes elevated intracardiac pressures and or inadequate cardiac output at rest and or during exercise.[3-5] It is due to myocardial dysfunction (systolic, diastolic, or both), and the pathology of valves, pericardium, endocardium, alterations of cardiac rhythm, and conduction abnormalities can cause or contribute to its occurrence.[3-5]

Identification of the etiology of the underlying cardiac dysfunction is mandatory in the diagnosis of HF since the specific pathology may determine subsequent treatment.[3-5]

It presents in different phenotypes, depending on the measurement of the left ventricular ejection fraction (LVEF): a) with reduced LVEF (HFrEF) ≤ 40%; b) with mid-range LVEF (HFmEF) 41-49%; c) with preserved LVEF (HFpEF) 40-50%.[3-5]

Due to geographic, economic, and cultural diversity and different health protocols, the causes of HF are heterogeneous between countries. In South America, Chagas disease and rheumatic valve disease are frequent causes.[1,2]

Differences at the cellular level that impact the phenotype in men and women have recently been identified. Women have estrogen-dependent changes in the transcription of messenger RNA, which means that the mitochondria behave differently from men, more resistant to changes in pressure overload and oxidative processes.[6]

HF is more prevalent in men and determines higher mortality in women. Phenotypically, men have more HFrEF, while the incidence of HFpEF is almost three times higher in women. Women may have HFrEF from specific causes such as peripartum cardiomyopathy, cardiotoxicity, or *tako-tsubo*.[7,8]

PATHOPHYSIOLOGY OF HEART FAILURE IN WOMEN

The pathophysiology of HF in women is complex and is related to many intrinsic and extrinsic factors.[7,8]

Women usually have a smaller, stiffer ventricle, and under stress conditions, they develop concentric hypertrophy, and to maintain the filling volume, they need a higher heart rate at rest.[6] Despite this, and thanks to the estrogenic effect, it has less fibrosis, and the myocytes have a lower tendency to apoptosis, so the presentation of symptoms due to HF is later.[6] When women reach menopause, the protective estrogenic effect is lost. Because of the hypertrophy induced by pressure overload and a more significant increase in

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end-diastolic pressure, they can develop HF symptoms[6] *(Figure 1)*.

When the level of estrogens falls, occur greater activation of the renin-angiotensin-aldosterone system, more arterial stiffness, and added to specific biological factors and risk factors such as high blood pressure (HBP), endothelial dysfunction appears, with less availability of nitric oxide, increased collagen synthesis, microvascular dysfunction, and fibrosis. Therefore, LV diastolic dysfunction and HF symptoms develop. More than 50% of patients have five or more comorbidities. In women, HBP, obesity, and diabetes occupy a relevant role.[6-8]

DIAGNOSIS

HF is diagnosed as a syndrome with symptoms and signs corroborated by elevated concentrations of natriuretic peptide, NTproBNP.[3-5] Laboratory tests and an electrocardiogram should be added. Transthoracic echocardiography (TTE) remains the gold standard for determining structural changes and LVEF. LVEF stratification is necessary due to different prognoses and therapeutic responses.[3-5]

The NYHA classification is used to characterize symptoms and functional capacity along with a 6-minute walk. The Kansas test is necessary for follow-up, evaluating the quality of life, and prognosis. Cardiac MRI, computed tomography, and radionuclide imaging also assesses LVEF.[3-5]

Noninvasive stress imaging (stress echocardiography, single photon emission computed tomography, and positron emission tomography for detecting myocardial ischemia) is used to guide invasive investigation and coronary revascularization.[3-5]

Coronary angiography and hemodynamics, with the measure of filling pressures or end-diastolic pressures of the LV, pulmonary artery pressures, systolic volumes, and cardiac output, can contribute to the etiological diagnosis.[3-5]

TREATMENT

Several recent clinical trials have provided treatments with better results for patients with HF, introducing inhibitors of the sodium-glucose cotransporter 2 (iSGLT2) and angiotensin receptor-neprilysin inhibitors (ARNI).[3-5]

Therapeutics in HFrEF include four classes of drugs: a) iSGLT2; b) ARNI, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor antagonists (AIIRAs); c) beta-blockers (BB) and d) mineralocorticoid receptor antagonists (MRA), all with indication

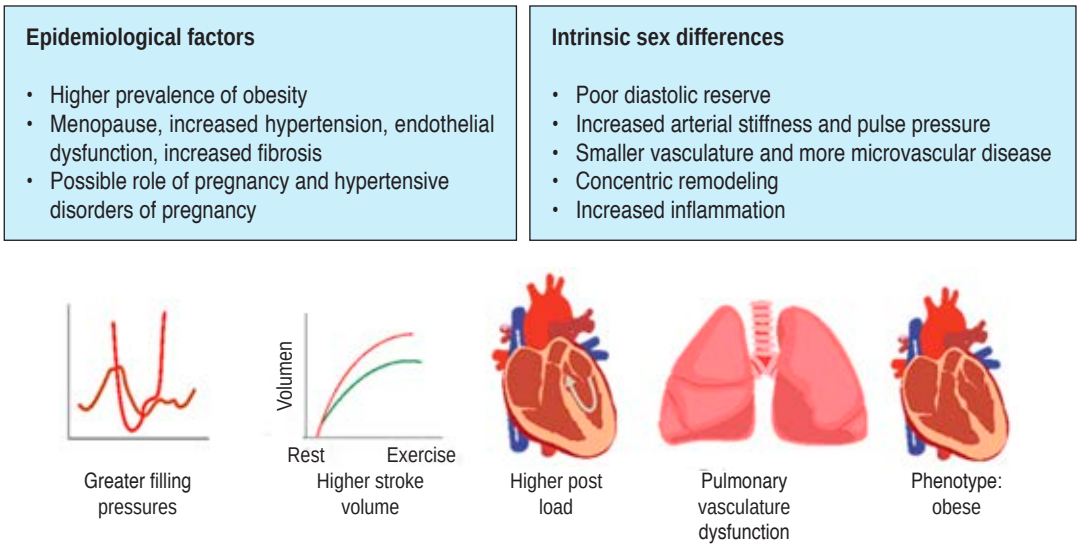

Figure 1: Epidemiological factors and by sex in heart failure.
Adapted: Lam CS et al.[6]

I-A.[3-5] Patients with improved HFrEF should maintain drug treatment.[3-5]

In patients with HFrEF, SGLT2 inhibitors have IIa recommendation, and those used in HFrEF (ACEI-ARB-ARNI; MRA and BB) have IIb indication.[3-5]

In patients with HFpEF, iSGLT2 have IIa indication; MRA and ARNI have IIb indication; BBs are not indicated in these patients.[3-5]

Women have been underrepresented in cardiovascular clinical trials, including those for HF, and there are no specific guidelines on treating HF in women.[3-5,9,10]

Thus, it is necessary to expand the involvement of women in clinical trials on HF so that the treatments with the best results in them become part of the specific guidelines.

CONCLUSION

HF mortality rates are higher in women, and the prevalence is higher in men. In addition, men have more modalities of HFrEF, while women have more HFpEF than the former. HBP is the most common cause of HF in women and ischemic heart disease in men. Therefore, sex-specific studies (risk factors, pathophysiology, treatment) are necessary to allow even better results in patients with HF.

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Chapter 16

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Frequent cardiac arrhythmias in women

Arritmias cardiacas más frecuentes en la mujer

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INTRODUCTION

Gender is a determining factor in arrhythmias' incidence, etiology, and clinical presentation.[1] These cover a broad spectrum of clinical manifestations, ranging from benign extrasystoles on the electrocardiogram (ECG) to arrhythmias that can represent a significant clinical threat. The predominant factors that determine the differences in women are sex hormones.[2]

Epidemiology of the most frequent arrhythmias in women

The general population's prevalence of supraventricular tachycardia (SVT) is 2.25/1,000 persons, and the incidence is 35/100,000 persons/year. Women have twice the risk of SVT than men. Atrioventricular node reentrant tachycardia (AVNRT) is the most treated type of SVT after atrial fibrillation (AF), followed by atrial flutter and atrioventricular reentrant tachycardia (AVRT). Women are more likely to suffer from AVNRT than men (70:30). It has been suggested that there is a relationship between the menstrual cycle and that the episodes are more frequent during pregnancy, especially in women with pre-existing SVT.[3]

Inappropriate sinus tachycardia (IST)

It generally affects women between the ages of 15 and 45, with a prevalence four times higher than men. The demographics of patients affected by IST can be confused by its association with psychological disorders; therefore, this syndrome is not well recognized. Some evidence links IST to hormonal changes associated with age, pregnancy, and menstruation in women.[4]

Acquired long QT syndrome (LQTS)

The female sex has been associated with a higher risk of torsade de pointes (TdP).

Acquired LQTS is clinically more common than congenital LQTS, associated with female gender, other anomalies, and the use of drugs that prolong the QT interval (QTI). Therefore, class IA and III antiarrhythmic drugs have a higher risk of TdP in women than in men.[1]

Ventricular arrhythmias of the right ventricular outflow tract (VA RVOT)

RVOT occurs more frequently in women. Men have a higher incidence of ventricular arrhythmias of the LV outflow tract, of the tricuspid and mitral rings, and of the ventricular septum compared to women.[5]

Sex-specific triggers were described in a short report of 47 RVOT patients. In 20 of 34 (59%) female patients reported initiation of RVOT with recognized states of hormonal flux (premenstrual, gestational, perimenopausal, and coincident with the administration of contraceptive pills).[1]

Conduction system diseases

Sex differences have been described in various bradyarrhythmia. Women have a higher incidence of sinus node dysfunction, and men

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have a higher incidence of atrioventricular node dysfunction. Women, on average, are older at the time of permanent pacemaker implantation, receive more single-chamber pacemakers, and have higher complication rates (higher incidence of pocket hematoma and pneumothorax), regardless of age and type of device implanted.[5]

Mechanisms and pathophysiology

Two mechanisms explaining the differences between the sexes in the incidence and mechanisms of different types of cardiac arrhythmias have been proposed: 1) differences in autonomic tone and 2) hormonal effects on the expression or function of ion channels or a combination of both.

Mechanisms

Autonomous regulation: it plays a relevant role in arrhythmogenesis. Premenopausal adult women have faster heart rates (HR) than men. Spectral analyses of HR variability in women have reported an increase in high-frequency components associated with vagal modulation of the sinoatrial node. The ratio between the low-frequency and high-frequency components, which expresses the sympathovagal balance, is consequently lower in women.

Effects of sex hormones: differences in the expression of ion channel subunits and the modulation of their function between the sexes have been described with longer duration of the action potential of female myocytes and differences in ventricular repolarization. Progesterone and testosterone shorten the ventricular action potential, while estrogens lengthen the action potential and have a proarrhythmic effect.[2] More dispersion of Ca^{+2} currents and, therefore, greater susceptibility to early post-depolarizations have been reported. Activity triggered by the increased risk of drug induced TdP and sudden death in patients with congenital LQTS has also been reported.[1]

This combined effect translates into a more pronounced parasympathetic activity in women, with gonadal steroids determining the differences, due to their different effects on the cell membrane's ion channels.[6]

These differences may be why AVNRT and acquired LQTS are more frequent in women and why women with ischemia experience less ventricular tachyarrhythmia than men.

TREATMENT

Vagal maneuvers can be performed safely in women with SVT. Adenosine is recommended as a first-line drug when vagal activation fails to stop SVT. Synchronized cardioversion is recommended in hemodynamically unstable arrhythmias or when drug therapy is ineffective.[6]

A diagnostic electrophysiological study (EPS) may be offered in women with symptoms suggestive of SVT even before the arrhythmia is documented. In documented SVT, the same access to catheter ablation should be provided. In women with a previous electrophysiology study without inducible arrhythmias, a second electrophysiology study scheduled in the first few days of the menstrual cycle may be recommended to render the arrhythmia inducible. Catheter ablation should be offered equally to women and men with symptomatic ventricular arrhythmias.[1]

Beta-blocker therapy is recommended as class I in all women with LQTS. Women treated with class IA or class III antiarrhythmic drugs (AADs) should be aware of the risk and symptoms associated with TdP. ECG monitoring should be considered at the onset of AAF to monitor HR and QTI. It should be contraindicated in women with prolonged QTI (> 500 ms) or significant SA or AV node disease without a permanent pacemaker. Amiodarone should be considered in the setting of life-threatening arrhythmias or when other therapies with better safety profiles have failed.[5]

Women who meet guideline indications for pacemaker, defibrillator, or cardiac resynchronization therapy (CRT) therapy should receive it; however, they may have a lower all-cause mortality benefit from defibrillation as primary prevention, sex-specific differences in therapy benefits should not be considered for risk stratification. Women have a high probability of responding to CRT.[1]

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Chapter 17

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From the pathophysiology to the treatment of atrial fibrillation in women

De la fisiopatología al tratamiento de la fibrilación auricular en la mujer

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Isabel Cristina Cárdenas,§ Jennifer Escobar,¶ Carina Hardy‖

EPIDEMIOLOGY AND PARTICULARITIES

Atrial fibrillation (AF) is the most common sustained arrhythmia, with a growing impact on global public health.[1] It is associated with developing dilated cardiomyopathy (with heart failure), stroke, and high mortality.[2]

Although it affects men and women, however, several studies show differences between the two genders related to biological characteristics (concerning sex) and gender (concerning the social role of individuals observed in epidemiology, risk factors (RF), clinical presentation, interventions, and prognosis.[1,2]

The cumulative risk of developing AF in life is similar for men and women. In women, AF appears later (men from 40 and women from 50 years of age).[1] The incidence and prevalence are higher in men in all age groups. In both genders, the prevalence increases with age.[1] Epidemiological studies show that mortality from AF is more elevated in women.[1,2]

In addition, women are underrepresented in clinical trials evaluating therapeutic interventions (drugs, electrical cardioversion, and catheter ablation) for AF.[2] In *Figure 1*, the particularities of AF in women are listed.

PATHOPHYSIOLOGY AND RISK FACTORS

Several mechanisms, including stretch fibrosis, hypocontractility, fatty infiltration, inflammation, vascular remodeling, ischemia, ion channel dysfunction, and calcium instability, contribute to complex atrial changes that increase the propensity to develop/maintain AF and facilitate a hypercoagulable state in both genders.[2,3]

Aging is a prominent RF for the development of AF; however, other comorbidities play an essential role in its mechanisms: high blood pressure (HBP), diabetes mellitus (DM), heart failure (HF), coronary artery disease (CHD), kidney disease (CKD), obesity and obstructive sleep apnea (OSA).[3] In addition, other modifiable factors (excessive alcohol consumption, smoking, physical inactivity, extreme exercise) have also been proposed as potential contributors to the development and progression of AF.[3] Thus, women with AF are older, have a higher prevalence of hypertension, valve disease, HF with preserved ejection fraction, and have a lower prevalence of CAD than men.[3]

RHYTHM CONTROL AND RATE CONTROL

Treatment of AF includes anticoagulation (AC), control of symptoms through strategies to control heart rate and rhythm, and therapy of RF and comorbidities.[2]

Meta-analyses on rhythm vs. rate control therapies have not shown a significant difference in reducing the risk of stroke and all-cause mortality. Thus, rate control remains an option to improve symptoms in patients with AF.[2]

Recent evidence from the EAST-AFNET4 study supports the use of early rhythm control

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(antiarrhythmics and or catheter ablation) to decrease cardiovascular events.[4] There are gender differences in the clinical presentation of AF: women have atypical, more severe symptoms and more significant deterioration in the quality of life. Despite this, they tend to receive fewer rhythm control therapies. In the ORBIT-AF registry (42% of women), the use of antiarrhythmic drugs (AD) was similar in men and women; however, electrical cardioversion and catheter ablation (ABL) were less frequent in women; the use of digoxin was more significant, and in symptomatic cases, they only received drugs to control heart rate.[5]

A subanalysis of outcomes by sex from the CABANA study (included 37% women; (ABL vs AD) showed that the benefits of ABL are similar in men and women; Adverse drug events were rare in both.[6] Rhythm control therapy is effective in patients with AF, regardless of gender.

ANTICOAGULATION

In patients with AF and a high risk of thrombus formation, identified using specific scores (the most used is the CHA2DS2-VASc), AC reduces the risk of stroke by 60%. Direct oral anticoagulants (DOAs) are currently recommended over warfarin in patients with AF.[7,8]

The representation of women in the different clinical studies with DOAs was 37%, and in subgroup analysis, no significant differences were found in the clinical outcomes between men and women.[9]

Data on gender differences in CA in patients with AF are not consistent. In the Euro Heart Survey, a cohort of 5,000 patients (42% women) showed no difference in CA rates. Another cohort study (6,000 patients) showed a significant difference in the AC of women and men, 76.8% and 82.5%, respectively; one of the possible explanations for this difference in AC between women and men over 75 years of age was perhaps the perception of more significant bleeding in older women. The CODE-AF registry showed no significant difference in the prescription of AC between women and men, although women were more likely to receive subtherapeutic doses of AODs. The

Risk factors
- Hypertension
- Obesity
- Valve disease
- Depression

Rate & rhythm
- More treatment for heart rate control
- Minus probability or electrical cardioversion
- Minus probability of ablation
- More extopic foci no pulmonary veins

Structural differences
- Small left atrium
- More atrial fibrosis
- More inflammation

Prognosis
- More serious cerebrovascular events (CVE)
- Greater limitation after CVE
- Higher mortality
- Less therapeutic anticoagulation

Epidemiology
- Lower prevalence, but similar absolute number with AF
- Later age of onset (to 10 years)

Clinical presentation
- More symptomatic
- More atypical symptoms
- Worse quality of life

Representation in studios
- Less presentation in anticoagulant and ablations

Figure 1: Peculiarities of atrial fibrillation in women. CVE = cerebrovascular event. CVE = electrical cardioversion. AF = atrial fibrillation. HR = heart rate. HBP = high blood pressure. BMI = body mass index. PV = pulmonary veins. Modified from: Linde C et al.[7]

PINNACLE Registry (2008-2014) showed that women were less likely to receive oral AC across all CHA_2DS^2-VASc scores.[9]

CATHETER ABLATION

Catheter ABL offers an effective option to maintain sinus rhythm and improve symptoms, exercise capacity, and quality of life when ADs have been ineffective, contraindicated, or not tolerated.[2,7]

Compared to men, women receive more AD treatment for rhythm control and are referred less for ABL. They are also older, have a longer duration of AF, a lower proportion of paroxysmal AF, more comorbidities, more dilated left atria and more extrapulmonary venous triggers.[9]

The ablation success rate is comparable to that of men; however, the FIRE AND ICE[10] study, which evaluated cryoablation vs. radiofrequency ablation for paroxysmal AF, showed that women had a 36% higher rate of recurrence and a 37% higher rate of cardiovascular re-hospitalization after ablation.

Recognition of differences based on sex/gender offers a good opportunity to improve treatment outcomes (including ablation) in women with AF.

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Chapter 18

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Valve disease in women

Valvulopatías en la mujer

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INTRODUCTION

Valvular disease (VD) has a prevalence of 2.5% in the population, with an increase in degenerative etiologies and in older adults.[1] Women and men are equally likely to develop VD, with some sex-specific differences. In general, women suffer more mitral valve diseases, especially mitral valve prolapse (MVP) and rheumatic valve disease (RVD), and men have more aortic valve diseases, such as aortic insufficiency (AI) and aortic stenosis (AS).

AORTIC VALVE DISEASE (AVD)

Men are at higher risk of developing AS; it is more common in the elderly, mostly women. Women have less valvular calcium but more fibrosis. At presentation, they are older, hypertensive, with worse functional class but better left ventricular ejection fraction (LVEF) with hypertrophic ventricles. Greater low-flow, low-gradient paradoxical AS and less amyloidosis.[1,2] Aortic insufficiency is more frequent in men associated with bicuspids (BAV), with a 2% male/female ratio of 3:1. Women will develop more AS and men AI aneurysms, aortic dissection, and endocarditis.[2]

MITRAL VALVE DISEASE (MVD)

RVD is responsible for the most significant global burden of VMD and is more common among women in all age groups.[1] New mechanisms for the pathogenesis of VRD suggest that Prothymosin alpha, associated with Estrogen Receptor alpha activity, would have a role in the sexual predisposition of RVD, perhaps explaining the higher incidence of rheumatic valve disease in women.[3]

Mitral valve insufficiency (MVI) is women's most common valve pathology. It can be primary: rheumatic, valve prolapse (myxomatous degeneration, thickening of the leaflets), or secondary: due to alteration in the geometry of the left ventricle, due to ischemic heart disease, or other dilated heart diseases. Women have more symptoms of heart failure (CHF), their condition is underestimated, and fewer are referred for intervention.[1,2]

Mitral stenosis (MS) is more common in women; its etiology is rheumatic or degenerative, associated with calcification of the mitral annulus at an advanced age. Some cases are related to chest radiation, carcinoid heart disease, or inherited metabolic disorders. It is classified as severe when the mitral valve area is ≤ 1.5 cm^2.[1,3]

TRICUSPID VALVE DISEASE (TVD)

Tricuspid regurgitation (TR) can be due to primary causes (congenital, genetic, endocarditis, rheumatic compromise, or device-related anomalies) or secondary causes (right ventricular dilatation and dysfunction). TR is more common in women/men in a 1.6:1 ratio. Once it develops in them, it progresses more rapidly, possibly due to anatomical differences in the annulus more elastic, cellular, and smaller[1] than in men, that have myocardium fibers in the annulus.

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In women, secondary TR occurs at an older age than in men (72 [62-79] years vs 70 [61-77] years; p = 0.003) and is more symptomatic. The most common etiology in women is isolated TR or is related to left-sided valvular disease.[1] In the imaging evaluation of the severity of TR, the quantification of the size of the cardiac cavities, according to sex and body surface, must be considered. Sex-specific dimension data now exist for different cardiac imaging modalities.[4,5]

VALVE INTERVENTIONISM

AVD. Women treated with surgical aortic valve replacement (SAVR) are older than men, with more advanced disease and higher operative

Table 1: Valvular disease in pregnancy.

Physiological changes
Increased blood volume and preload, increased cardiac output and rate
Decreased vascular and pulmonary resistance. Decreased blood pressure
Hypercoagulability. Cavity dilation

Valve stenosis	Poorly tolerated when severe First-line beta-blockers and diuretics Consider valvuloplasty if medical therapy fails. If surgery is required, preferably in the 2nd trimester Fetal adverse events are increased (especially mortality) with surgery with the fetus *in utero* Gradients rise throughout pregnancy	**Aortic stenosis**	**Severe symptomatic aortic stenosis** **WHO class IV (pregnancy is contraindicated)**
			Congenital > AVB High risk in the 2nd and 3rd trimesters Adverse fetal events
		Mitral stenosis	**Severe mitral stenosis** **mWHO class IV (pregnancy is contraindicated)**
			Congenital, rheumatic High risk of supraventricular arrhythmias (atrial fibrillation) Adverse fetal events
		Pulmonary stenosis	Congenital Generally better tolerated The right ventricle should be monitored, and the appearance of symptoms
Valvular insufficiency	Better tolerated except when accompanied by severe ventricular dysfunction Symptoms of dyspnea and heart failure in advanced stages They tend to be more symptomatic at the end of pregnancy or postpartum (close monitoring for signs of overload in the early postpartum period)	**Aortic/mitral valve insufficiency**	Ideally, surgical management before pregnancy Avoid pregnancy if severe aortic/mitral regurgitation and LVEF < 30% Diuretic management, if required. Avoid surgery during pregnancy
		Pulmonary insufficiency	Congenital. Late postoperative of ROSS or tetralogy of Fallot Evaluate failure of the right ventricle

Table 1 continues: Valvular disease in pregnancy.

Prosthetic valves	Maternal and fetal adverse events (mainly with mechanical valves) Ideally, pregnancies with biological prostheses Preconception couple and family counseling consultation and clarify the risks Analyze time in therapeutic range adherence to Warfarin Weekly monitoring of defined anticoagulant therapy	**Biological valves**	Use of aspirin in pregnancy. Fewer complications than mechanical valves but higher than other cardiac pathologies in pregnancy. Fewer complications as long as the Bioprosthesis is functioning normally. Fewer complications as long as the Bioprosthesis is functioning normally
		Mechanical valves	**WHO class III mechanical valve (significant mortality and morbidity)**
			Warfarin associated with teratogenic effects but dose-dependent in the 1st trimester: **First trimester:** warfarin, if the dose is ≤ 5 mg/day, is the choice, or LMWH as an alternative, but always with measurement of activated anti-factor Xa levels* **Second trimester:** warfarin independent of dose **Third trimester:** dose-independent warfarin with the transition at 36 weeks to UFH by nomogram or LMWH based on activated anti-factor Xa levels* Vaginal delivery if at least two weeks of discontinuation of Warfarin and bridging suspension with UFH 4-6 hours before delivery

mWHO = modified obstetric risk classification World Health Organization. BAV = bicuspid aortic valve.
LMWH = low molecular weight heparin. UFH = unfractionated heparin.
* Recommended activated anti-factor X levels of 0.8 to 1 U/mL for the aortic valve and 1 to 1.2 U/mL for the mitral or tricuspid valve.

mortality. Female gender is considered an independent predictor of post-SAVR operative mortality and morbidity.[6] Transcatheter aortic valve implantation (TAVI) results by gender show no differences in implant success; the female sex was associated with increased vascular complications and major bleeding but a lower incidence of paravalvular leak, pacemaker, and better medium-term survival.[7]

MVD. The registries show that the women were taken significantly less or later to mitral surgery (repair/replacement). In degenerative MI, women are less frequently taken to repair (44 vs 31.9%, p = 0.001), with slightly lower long-term survival.[1]

In percutaneous therapy in severe functional MR with TEER (Transcatheter Edge-to-Edge Repair) with more MitraClip evidence, women represented only 36% of patients in the COAPT study and 25% in MITRA-FR, being younger, but with worse quality of life and functional capacity. TEER resulted in better clinical outcomes vs. medical therapy, regardless of gender; the reduction in CHF hospitalizations was less pronounced in women. Female gender was independently associated with a lower adjusted risk of death at two years (HR, 0.64; 95% CI, 0.46-0.90; p = 0.011).[1]

In RVD, the treatment of choice is mitral valvuloplasty with a catheter and a balloon, followed by valve surgery.[8]

TVD. Regarding the surgical results in tricuspid insufficiency (TI), the repair has higher survival, and there is no difference by sex in terms of results.[1]

PREGNANCY AND STROKE

Moderate or severe EV in pregnancy is complex and requires an experienced cardio-obstetric

multidisciplinary team. Significant MS and symptomatic severe AS are poorly tolerated. Percutaneous commissurotomy should be considered in MS with severe symptoms (NYHA III-IV) or pulmonary artery systolic pressure > 50 mmHg and unresponsive to medical treatment. Aortic balloon valvuloplasty can be regarded as salvage therapy in AS with severe symptoms despite medical treatment, and definitive interventions will be defined after delivery. Valvular insufficiencies are usually better tolerated, except when there is associated ventricular dysfunction.[9]

If valve surgery is required and the fetus is viable, a cesarean section will be performed, followed by valve surgery. Valve surgery with extracorporeal circulation with a fetus in utero has fetal mortality of 15-56%. Therefore, it should be restricted to situations with life-threatening risk for the mother and no percutaneous management option.

Pregnant women with mechanical prostheses are very complex since there is no ideal anticoagulant regimen, so it is necessary to weigh the risks for the mother and the fetus (Warfarin according to the dose or low molecular weight heparin but always with monitoring of antifactory Xa levels)[9,10] *(Table 1)*.

Women with VD have been underrepresented in studies and tend to be diagnosed and referred for interventions later, leading to adverse outcomes[1,2] summarizes the complex relationship between pregnancy and valvular heart disease.

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Chapter 19

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Impact of cancer in cardiovascular risk

Cáncer y su impacto en el riesgo cardiovascular

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INTRODUCTION

Cardiovascular diseases (CVD) and cancer are the leading causes of mortality worldwide. Cancer survivors experience a higher risk of CVD morbidity and mortality than the general population.[1] Cardiovascular risk factors are associated with more significant cardiotoxicity (CTOX) and lower long-term survival.

Epidemiological studies have reported that adherence to heart-healthy lifestyle habits could prevent the development of cancer and CVD, improving the survival of the general population.[1]

Determining cardiovascular risk (CVR) and early detection of myocardial damage from the therapies used are the cornerstone of CVD prognosis in cancer patients.[2]

Mechanisms of cardiotoxicity. Myocardial injury.

Cardiotoxicity includes the development of ventricular dysfunction, myocardial ischemia, arterial hypertension, arrhythmias, pulmonary thromboembolism, pulmonary hypertension, pericardial complications, peripheral vascular disease, and stroke, among others.

The myocardial injury occurs through 2 types of mechanisms

Type 1 cardiotoxicity is dose-dependent and irreversible; the damage occurs on the enzyme Topoisomerase II, with the generation of free radicals, the classic example being the anthracyclines.

Type 2 cardiotoxicity, generally reversible, is caused by the blockage of cell repair pathways that occur by inhibiting the HER2 receptor, ultimately leading to an acceleration of the myocyte death process and decreased functional recovery, mainly caused by trastuzumab.[3,4]

Tyrosine kinase inhibitors produce cardiotoxicity through other mechanisms characterized by mitochondrial dysfunction,[3] loss of membrane potential, cytochrome C release, and decreased ATP levels, ultimately leading to myocyte death.[5]

Radiation-induced CVD is characterized by endothelial dysfunction, considered a risk factor in the pathogenesis of accelerated atherosclerosis and heart failure, usually associated with preserved ejection fraction. For each dose of radiation measured in gray (Gy), the probability of the appearance of a significant CVD increases by 7.4%.

Chemotherapy cardiotoxicity: How to diagnose it? Prevention

Cardiotoxicity is defined as alterations at the level of the heart, vessels, and conduction system derived from antitumor treatment (chemotherapy and or radiotherapy); according to the European Society of Cardiology (ESC), ventricular dysfunction is the decrease in the fraction of left ventricular ejection (LVEF) > 10% compared to baseline LVEF, with the average cut-off point being 50%. The Spanish Image Society (ASE) and The Spanish Association of Cardiac

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Imaging (AEIC) suggest an average LVEF cut-off point of 53%.

The objective of monitoring patients is to make an early diagnosis of myocardial damage considering the following studies:

Biomarkers

1. Ultrasensitive troponin I baseline quantification is recommended, and after each cycle of treatment, it has a high negative predictive value; persistent elevation suggests a worse prognosis. The use of NT proBNP is not yet well defined.[6]

Multimodal image

1. The transthoracic echocardiogram is the most common method used for patients with antitumor treatment, it suggests serial evaluation of the LVEF, and in 2D, the biplanar method is preferred (intra and interobserver variability is 7.4%), whenever possible, the 3D (intra and interobserver variability Interobserver is 4%)[6,7] is preferred. LVEF is not considered a marker of myocardial function for subclinical diagnosis since it is altered once DV is established, which is generally irreversible.[3] The Global Longitudinal Strain (GLS) of the LV is the best predictor of cardiotoxicity, mainly with the use of anthracyclines; it is a robust measure for the subclinical diagnosis of DV,[8] a decrease between 10 and 15% is associated with symptomatic and asymptomatic CTOX. In some studies, GLS < 19% at the end of treatment is associated with the late development of CTOX.[7,8] Radial and circumferential strain have not been associated with the diagnosis of CTOX, and reproducibility is not as robust as GLS.[8,9] Studies show that for every 1% reduction in initial GLS, it is associated with a 1.48% chance for the development of CTOX.
2. The American College of Cardiology (ACC) recognizes cardiac magnetic resonance Imaging as a powerful imaging study for the detection of CTOX; its use is not recommended routinely unless discontinuation of CTOX treatment is considered and verification of LVEF is required. CT angiography is not used as a first-line image to assess LVEF.

Post-radiotherapy cardiovascular damage

Radiation therapy affects cardiac structures primarily when the heart is at the radiation site. Risk factors for post-radiotherapy heart damage: high doses of radiation (more than 30-35 Gy), adjuvant treatment with chemotherapy (mainly anthracyclines), irradiation in the left hemithorax, atherosclerotic risk factors (smoking, high blood pressure, hyperlipidemia and diabetes), cardiovascular disease (CVD) pre-existing.[10]

Radiation can cause pericardial, coronary artery, noncoronary atherosclerotic disease, myocarditis, cardiomyopathy, valvular heart disease, arrhythmias, and conduction disturbances, months to more than 20 years after radiation therapy.

There are no universally accepted clinical guidelines for post-radiotherapy damage stratification. Follow-up should begin five years after radiotherapy in high-risk patients and ten years in the rest, with subsequent evaluation every five years.

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Chapter 20

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Autoimmune and inflammatory diseases

Enfermedades autoinmunes e inflamatorias

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INTRODUCTION

The prevalence of autoimmune diseases (AI) is around 4%. It is more common in women (78-80%), with a higher incidence of cardiovascular disease (CVD), which is considered an emerging or gender-specific cardiovascular risk factor (CVRF). There is an increased immune and inflammatory response, suggesting an involvement of the sex chromosome and sex hormones. Risk factors (RF) and poor lifestyles, immune system disorders, chronic systemic inflammation, endothelial dysfunction, increased oxidative stress, and accelerated atherosclerosis (atherosclerotic cardiovascular disease - ACVD) at the coronary artery level and microvessels. The risk of developing ACVD shows a linear relationship with the activity and severity of AI, higher in women < 40 and with SLE. The risk of ACVD in rheumatoid arthritis (RA) is 1.5 to 2, psoriatic arthritis (PSA) 1.5 to 1.7, systemic lupus erythematosus (SLE) 2 to 3, and 2 to 12 in vasculitis. They can present valvular, pericardial disease, myocarditis, fibrosis, heart failure (HF), and arrhythmias. RA and SLE are more likely to develop left ventricular hypertrophy (LVH) (RR 6.5 and 4, respectively).[1-3] Nonsteroidal anti-inflammatory drugs (NSAID) and corticosteroids reduce inflammation and cause dyslipidemia, hyperglycemia, obesity, and hypertension. Biological immunosuppressants as anti-TNF (adalimumab, etanercept, infliximab) and non-TNF (abatacept, anakinra, and rituximab) reduce CVR (< 30%) (suppress inflammatory state and improve endothelial function), the same as disease-modifying drugs (DMD) (hydroxychloroquine, methotrexate, and sulfasalazine).[1,4]

In women with intermediate CVR (according to the risk calculator for CVD of the American Heart College), the existence of AI should be considered a «risk increaser or potentiator». The available tools underestimate the existing CVR by 12 to 20%.[1,4] The Interamerican Society of Cardiology (SIAC),[4] in the guide on primary prevention of cardiovascular disease in women, recommends:

1. Calculation of CVR and controlling CVRF (recommendation class IIb, evidence level A).
2. Healthy lifestyles (recommendation class I, evidence level B).
3. Apply in RA a correction factor of 1.5 on the risk calculation score and search for subclinical atherosclerosis (recommendation class IIa, evidence level B).
4. Regular blood pressure measurement is recommended, and if necessary, implement treatment (recommendation class I, evidence level B).

TREATMENT, MONITORING, AND PREVENTION OF CARDIOVASCULAR DISORDERS

The drugs used in AI pose a high risk of complications and systemic and CV adverse effects[1,5,6] *(Table 1)*.

NON-INVASIVE CARDIOVASCULAR IMAGING

Noninvasive imaging methods assess disease activity, treatment effects, and complications.[7]

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Table 1: Pharmacological therapy, secondary and adverse effects.

Drug	Indications	Mechanisms of injury	Alterations and metabolic and cardiovascular risks
Nonsteroidal anti-inflammatory drugs	All inflammatory diseases	Direct endothelial damage, decreased nitric oxide and bleeding	Arterial hypertension MI, CVE, AF, HF
Glucocorticoids		Inhibition of the hypothalamic-pituitary-adrenal axis, premature atherosclerosis, water retention, insulin resistance	Osteoporosis, obesity, high blood pressure, MI, CVE, HF, arrhythmias (AF, flutter), DVT, PE
Antimalarials drugs (hydroxychloroquine)	SLE, RA, SS	QT prolongation, electrolyte imbalances	Arrhythmias (torque de pointes, ventricular tachycardia), cardiotoxicity
Cyclophosphamide	SLE, SSc	Direct drug toxicity	Cardiotoxicity, premature ovarian failure, cytopenias
Metotrexato	RA, myopathies SS, SLE, TA	Increased LDL, hyperhomocysteinemia, folate inhibitor	Elevated liver enzymes, exacerbation of rheumatic nodules, nephropathy, hypercholesterolemia
Anti-CD20 (rituximab)	SLE, SS	Ventricular remodeling	HF
JAK inhibitors (baricitinib, tofacitinib)	SLE, RA	Hypercoagulability	MI, CVE, DVT, PE, hypercholesterolemia
Anti-TNF alfa (etanercept, infliximab)	RA, TA	Left ventricular dysfunction	HF worsening

MI = myocardial infarct. CVE = cerebral vascular event. AF = atrial fibrillation. DVT = deep vein thrombosis. PE = pulmonary thromboembolism. SLE = systemic lupus erythematosus. RA = rheumatoid arthritis. SS = Sjogren's syndrome. SSc = systemic sclerosis. TA = Takayasu arthritis. HF = heart failure.

Echocardiography shows valvular involvement (30-70%), pulmonary arterial hypertension (20-30%), pericardial effusion (30%), mobility alterations, and subclinical systolic/diastolic dysfunction (30%).[3,7-9] Single photon emission tomography (SPECT) and positron emission tomography (PET), nuclear magnetic resonance (NMR), and computed tomography (CT) allow an anatomical assessment of the coronary tree and great vessels (inflammation) and functional (ischemia).[10]

CONCLUSIONS

Autoimmune diseases confer high cardiovascular risk in women. The calculation of the CVR and intensification of the CVRF are essential. CV imaging is helpful in the diagnosis of complications and follow-up. Management requires multidisciplinary intervention to reduce cardiovascular morbidity and mortality.

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Chapter 21

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COVID-19 and cardiovascular disease in women

COVID-19 y enfermedad cardiovascular en la mujer

Silvina Brienza*

INTRODUCTION

On March 11, 2020, the WHO defined COVID-19 as a global pandemic. A year later, as of January 31, 2021, the numbers were staggering, close to 102 million cases of COVID-19 and more than 2.2 million deaths.

The pandemic accelerated in the Americas when the epicenter shifted from Europe around May 2020. As of October 9, 2022, more than 621,366,370 million positive cases and 6,557,231 million deaths have been reported; more than 68.3% of the world population is fully vaccinated for COVID-19.[1]

In the first meta-analysis with available data, it was found that men could have a higher risk of suffering from a severe condition of COVID-19; the number of men hospitalized was 50% more than women.[2,3] When examining the greater likelihood that men would have more severe manifestations of COVID-19, the differences in biological pathways between men and women in their immune response to the virus were assessed. It was found that women produced more effective immune responses and better adapted to viruses, resulting in less severe cases of COVID-19.[4] There are currently several hypotheses by which patients with cardiovascular risk factors (CVRF) with atherosclerosis and with established cardiovascular disease have been associated with worse outcomes in people with COVID-19. Among them are the uncontrolled inflammatory state, the immunological alteration, and the viral properties currently under study.[5]

As with other infections by different pathogens, COVID-19 affects differently according to existing gender norms. Women were also affected by other factors, such as sociodemographic, physiological, genetic, immunological, and cultural. Many of them had to have more than three roles simultaneously. It was observed that the age group between 40-50 years presented a higher % risk for suffering from Long COVID, that is, a longer duration of symptoms or long-term effects. This would be because of sex hormones, which correspond to fatigue, myalgia, palpitations, cognitive impairment, sleep disorders, and perimenopausal and menopausal symptoms.[6,7] According to the WHO, today it is known that the most frequent cardiovascular conditions due to COVID-19 infection and long COVID are: myocarditis, pericarditis, pericardial effusion, arrhythmias, venous thromboembolism, heart failure and heart attacks (pathologies that increase the probability to trigger sudden death).

Most of the reports of women who presented with COVID-19 (85%) were cardiovascular symptoms such as chest pain, palpitations, exercise intolerance, and tachycardia. The proposed causative mechanisms were inflammation, immune system activation, viral persistence, endothelial dysfunction, metabolic changes during exercise, and nonspecific cardiac abnormalities after acute infection.[8]

Recent studies published by the American Heart Association (AHA) affirm that among patients who suffered from COVID-19 and presented a poor evolution of the disease, there was a direct relationship between the possibility of giving underlying cardiovascular disease (CVD) and a previous myocardial injury. These findings did not depend on the

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severity of the acute infection. The pre-existing cardiovascular pathologies identified that exposed the patient to a higher risk of suffering from COVID-19 are heart failure, ejection fraction deteriorated, dilated and hypertrophic cardiomyopathy, coronary and valvular disease (angina, infarction, previous angioplasty, cardiac surgery) and arrhythmogenic dysplasia of the right ventricle.

Regarding clinical studies of COVID-19, as in most other pathologies, the number of women participating was lower than that of men. The evidence demonstrates the need to incorporate more women in all clinical studies. More cardiovascular follow-up should be carried out about this disease in all patients with acute illness, those with symptoms compatible with long COVID, and those who have recovered.

Reassessing this history of disease in patients remains a pending issue, depending on a complete history and complementary studies to better understand these cardiovascular findings in the future.

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Chapter 22

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Current impact of traditional risk factors in women

Impacto actual de los factores de riesgo tradicionales en la mujer

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INTRODUCTION

Traditional cardiovascular risk factors (CVRFs) play a crucial role in developing cardiovascular disease (CVD), the leading cause of death in women. Among these, arterial hypertension (HBP) stands out as the primary contributor to cardiovascular mortality (CV mort) standardized by age in women worldwide, followed by high LDL cholesterol and diabetes mellitus (DM), factors analyzed in this review *(Figure 1 and Table 1)*.[1,2]

HBP in childbearing age

Endogenous estrogens maintain vasodilation, contributing to blood pressure (BP) control; therefore, hypertension appears a decade later than in men. However, hypertension in women is less controlled. The risk of long-term hypertension increases four times in patients with hypertensive disorders of pregnancy.[3-5]

Mediterranean-style diet or DASH (low in salt, saturated fat, and alcohol; rich in potassium, whole grains, vegetables, and fruits), moderate physical activity, weight control within a healthy range, control of BP values since childhood, and absence of active or passive smoking, are essential in the prevention and initial treatment of hypertension.[3-5]

Pharmacological treatment is started with objective BP (blood pressure) values > 140/90 mmHg. It is necessary to discard secondary hypertension, mainly in adolescence and young adulthood. Antihypertensive drugs allowed during pregnancy are preferred, given the possibility of an unplanned one: alpha methyldopa, labetalol, and long acting nifedipine. Angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARB) are not recommended.[3-5]

Hypertension in menopause

The incidence of HBP is higher in menopausal women than in men, reaching a prevalence of up to 80% in older adults. Aging and estrogen decline production may trigger a decrease in endothelial nitric oxide and activation of the renin-angiotensin-aldosterone system (RAAS), endothelin, and the sympathetic autonomic nervous system, as vasoconstrictor mechanisms that generate endothelial dysfunction.[3-5]

Hypertensive women develop more isolated systolic hypertension, white coat hypertension, left ventricular hypertrophy (LVH), diastolic dysfunction, heart failure (HF) with preserved ejection fraction, increased arterial stiffness, and chronic kidney disease.[3-5]

The diagnosis, management, and proposed goals in postmenopausal hypertensive women are similar between the genders. For treatment, ACE inhibitors and ARBs are an acceptable option, given the excessive activity of the RAAS in menopause. It must be consider the pharmacodynamic and pharmacokinetic differences that cause more cough with ACE inhibitors, more cramps with thiazide diuretics, and more edema in the lower limbs with calcium blockers.[3-5]

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Dyslipidemias

Various studies demonstrate the correlation between alterations in lipid levels and cardiovascular risk (CVR) in women. Despite this, many women are not aware of their lipid values. This risk factor must be recognized, particularly in postmenopausal women, since it modifies the lipid profile, raising the low-density lipoprotein (LDL-C) concentration by 10-15%. Total cholesterol (TC), triglycerides, and lipoprotein (a) also increase, with a significant decrease in high-density lipoproteins (HDL-C) being observed. The increased atherogenic lipid fractions increment the risk of CVD. Screening for hypothyroidism, a frequent cause of secondary dyslipidemia, is advisable.[6-8]

In pre-menopause, women are protected by endogenous estrogens through their vasodilator action, but the protective effect only delays the onset of CVD for a decade. Even more alarming is that a smaller proportion reaches the established goals of the main current guidelines since they are treated less vigorously than men and have less pharmacological adherence.[6-8] The reduction of CVD in primary and secondary prevention, with statins, has been demonstrated; although the impact is less

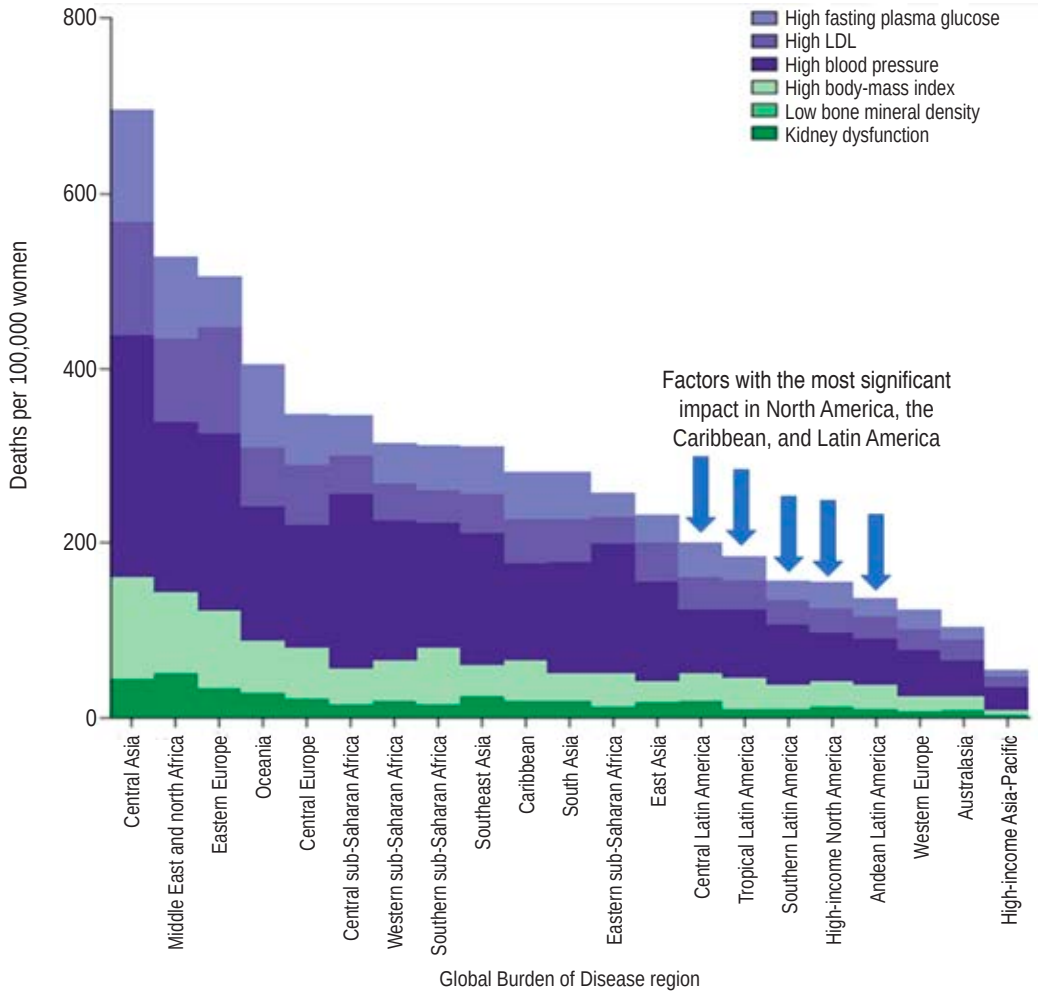

Figure 1: Metabolic risk factors contributing to age-standardized deaths from cardiovascular disease per 100,000 women across all global burden of disease regions in 2019.
Adapted from: Institute for Health Metrics and Evaluation. GBD 2019. Deaths per 100,000-females, age-standardized, 2019. http://ihmeuw.org/5g2x (accessed April 1, 2021).

Table 1: Desirable target goals for cardiovascular risk factors in women.

CVRF	Goal	Considerations in women
Hypertension	Optimal: < 120/80 mmHg Normal: 120-129/80-84 mmHg High normal: 130-139/85-89 mmHg Grade 1 hypertension: 140-159/90-99 mmHg	Rule out secondaries in young people of childbearing age: renal parenchymal disease renovascular (muscular fibrodysplasia), hyperaldosteronism, hypothyroidism, oral contraceptives, illicit drugs, herbal products, pheochromocytoma, coarctation of the aorta, Turner syndrome, Takayasu's arteritis, systemic lupus erythematosus, rheumatic diseases, preeclampsia predisposes to the development of hypertension in the long term. Higher prevalence in postmenopausal women More isolated systolic hypertension More white coat hypertension More left ventricular hypertrophy More adverse effects with some antihypertensives Different drug bioavailability
Dyslipidemia	Primary objective LDL- Very high risk < 55 mg/dL High risk < 70 mg/dL Moderate risk < 100 mg/dL Low risk < 115 mg/dL Secondary objective is non-HDL-C+ Very high risk < 85 mg/dL High risk < 100 mg/dL Moderate risk < 130 mg/dL Low risk not established + non-HDL cholesterol, can be the primary target when the triglyceride level is > 400 mg/dL Serum triglycerides are not a control target	Determination of the lipid profile, particularly in menopause, due to the increased cardiovascular risk Integrate the determination of the thyroid profile (the most frequent cause of secondary dyslipidemia) The scope of goals is lower in women, and also the prescription of lipid-lowering therapies Female gender is a possible risk factor for more side effects Hypolipidemic therapy is not recommended during pregnancy and lactation
Diabetes mellitus	ADA HgA1c < 7% ASA DM who are at increased risk of CVD CAC/AHA HgA1c < 7% ASA There are no specific recommendations for DM CES HgA1c < 7% and < 6.5%, if it can be achieved without hypoglycemia (less stringent in elderly patients) ASA only in very high risk/high risk	Increased CVD risk in women and increased risk of CVD mortality Screening for CV risk 3 months after delivery. Vigilance: in weight changes every 6 to 12 months. Girls have higher rates of DM In youth: increased insulin resistance early childhood to puberty; increases incidence of congestive heart failure and mortality

in women, in primary prevention (16% versus 22% in men), the benefit is significant. However, one problem is the underrepresentation of women in controlled trials, leading to poor statistical power in the results.[6-8]

The guidelines establish that women should receive statins at the maximum tolerated dose; if the goal set by the risk category is not reached, considering the combination with ezetimibe and, in specific scenarios, monoclonal antibodies.[6-8]

It is essential to adopt healthy habits, especially in menopause, dietary-nutritional management, avoiding saturated fats, and having moderate physical activity.[6-8]

The female sex is described as a condition that favors myopathies, but this should not limit exercise prescription.[6-8]

Diabetes mellitus (DM)

DM is one of the causes of the highest morbidity and mortality in the world. The International Diabetes Federation estimates that 1 in 11 adults have diabetes, while 1 in three have glucose intolerance, with type 2 DM (DM2) being the most common. There are differences throughout the life of women, with high rates in youth; men have it more in middle age, and it is similar for both sexes in older ages. There is an increased risk of CV mort in women with DM compared to men. In addition to atherosclerotic events, there is an increased incidence of congestive HF. Early onset of DM in young women translates into a longer duration of the disease throughout their lives and significantly increased mortality in women under 40 years of age.[7-9]

The basis of the treatment is an intervention towards a healthy lifestyle focused on weight loss, physical activity, and pharmacological treatment. Meta-analysis (2019) shows diabetic women with higher CV mort due to coronary heart disease and stroke due to insulin resistance, which begins after birth.[7-9]

Some sex-specific effects in pharmacotherapy for DM: GLP1, similar to glucagon, have lower glycemic control in women but more significant weight loss; thiazolidinediones have a better glycemic reduction in obese women.[7-9]

The EMPA-REG study showed a reduction in CV mort in patients with DM treated with empagliflozin. All patients with DM require aggressive RF reduction. There are no specific recommendations in the guidelines for preventing or treating DM related to sex; they recommend aggressive control of lipids and anti-aggregators only in patients with high CVR.[7-9]

CONCLUSIONS

The recognition, control, and treatment of CVRFs in women are still poor, and they are not treated aggressively enough. Therefore, an individualized approach to these CVRFs is necessary to reduce the excessive burden of CVD in women.[10]

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Chapter 23

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Cerebrovascular disease in women

Enfermedad cerebrovascular en la mujer

Dulce Bonifacio-Delgadillo*

INTRODUCTION

The cerebrovascular event or stroke definition is based on the sudden onset of focal neurological dysfunction due to infarction or hemorrhage in the brain, retina, or spinal cord. It is currently defined as an acute episode of the brain, retina, or spinal cord dysfunction lasting more than 24 hours or of any duration if it demonstrates infarction or hemorrhage on imaging studies or autopsy.[1] Of them, 87% are ischemic, and 10% are hemorrhagic.[2] In the ResISSSTE brain stroke network, the percentages were 80.8% ischemic, 14.0% hemorrhagic, and 5.2% transient ischemic attacks.

In 2010, an estimated 16.9 million strokes occurred, and 102 million disability-adjusted life years were lost.[1,2]

GENDER DIFFERENCES IN THE EPIDEMIOLOGY OF STROKE

Incidence, prevalence, and mortality due to CVD are higher in men in almost all the world, except in Arab countries in the Middle East, North Africa, Israel, and Western Europe, where mortality is higher in women.[3] In Mexico, PREMIER registered 55.2% of women, with a mean age of 63 years (IQR 48.5-75).[4]

NON-MODIFIABLE GENDER-INDEPENDENT RISK FACTORS

In ResISSSTE brain, 55.7% were women, with a mean age of 71 years versus 66 years in men. At the time of the stroke, women are older, and the higher prevalence is attributable to the fact that women live longer and confer a higher risk (17% versus 15% after 50 years).[5] Survival of low-income patients is reduced by 30% (relative risk, 0.70, 95% confidence interval, 0.65-0.74) *(Table 1)*.[6]

MODIFIABLE GENDER-INDEPENDENT RISK FACTORS

INTERSTROKE described the impact of modifiable risk factors for cerebral infarction that are summarized in *Table 2*.[7]

RISK FACTORS ATTRIBUTABLE TO THE FEMALE GENDER

Early menarche

There are controversial data, but it has been found that early and late menarche (< 10 or > 17) have a higher cardiovascular risk, but the association to a stroke is weak.

The risk of stroke is 1.7 times higher with oral contraceptives that contain estrogens; it varies depending on the dose of estradiol. In the risk of a stroke, it is recommended to avoid hormonal contraception with estrogens. Contraception with progestogens does not confer a more significant risk.

Pregnancy

In pregnancy and postpartum, the risk of stroke is three times higher than in other young adults. The crude incidence is 30.0 per 100,000 pregnancies, including ischemic, venous thrombosis, and hemorrhage. Hypertensive

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disorders of pregnancy (preeclampsia, eclampsia, and gestational hypertension) confer a fivefold increased risk of stroke. It also increases if congenital heart disease, atrial fibrillation, primary thrombocytopenia, or migraine occurs. Risk factors for a specific type of stroke as arteriovenous malformations and aneurysms, predispose to brain hemorrhage, while other factors predispose to both hemorrhage and thrombosis. *Table 3* lists the risk factors for ischemic and those associated with both.[3]

Diagnosis

Neuroimaging should be performed before any reperfusion therapy.[8] Computed tomography without contrast is acceptable during all trimesters because the risk of delaying the diagnosis of a time-dependent disease outweighs the risk of radiation, contrasting with iodine for angio-tomography and perfusion is acceptable if they are essential to decide treatment. Magnetic resonance does not produce radiation; therefore, it is the choice for pregnant women if it does not delay the time to diagnosis.

Alteplase intravenous is reasonable in pregnant women with disabling ischemic stroke who meet the criteria for thrombolysis, do not cross the placenta, and are not expected to increase the risk of bleeding in the fetus; the decision is based on the risk of maternal bleeding, especially early postpartum.

Endovascular thrombectomy with abdominal protection and limited use of X-rays is reasonable in pregnant women with large vessel occlusions (LVO). Thrombectomy may not be associated with thrombolysis in LVO because it can increase the risk of bleeding.[9]

Menopause

Due to the protective effect of estrogens on the vessels, the age of onset of menopause is a risk factor for stroke (relative risk of 1.25 in those under 40 versus 0.99 in those under 45). Vasomotor symptoms are interrelated with anxiety, depression, panic attacks, and lack of sleep which could increase the risk associated with hypertension and hyperlipidemia.

Late introduction of estrogen hormone replacement (> 10 years) increases the risk

Table 1: Comparison of risk factors between men and women treated for stroke in the ResISSSTE brain network.

Risk factors	Men (N = 102) n (%)	Women (N = 134) n (%)
Arterial hypertension	74 (72.6)	100 (74.6)
Diabetes mellitus	38 (37.3)	43 (32.1)
Smoking	9 (8.8)	4 (3.0)
Obesity	19 (18.6)	22 (16.4)
Chronic kidney disease	5 (4.9)	8 (6.0)
Epilepsy	2 (2.0)	2 (1.5)
Heart failure	4 (3.9)	4 (3.0)
Dyslipidemia	7 (6.9)	3 (2.2)
Cancer	6 (5.9)	13 (9.7)
Myocardial infarction	13 (12.7)	4 (3.0)
Valvulopathy	6 (5.9)	8 (6.0)
Arrhythmia	8 (7.8)	16 (11.9)
Previous heart attack	8 (7.8)	21 (15.7)

Source: personal communication, Bonifacio Delgadillo D.

Table 2: Magnitude of the impact of modifiable risk factors for cerebral infarction.

Risk factor	OR	Population attributable risk (RAP)
Arterial hypertension	2.98, IC 99% (2.72-3.28)	47.9%, IC 99%, 45.1-50.6%
Regular physical activity	0.60, 0.52-0.70	35.8%, 27.7-44.7%
Waist-hip ratio	1.44, 1.27-1.64	18.6%, 13.3-25.3%
Diabetes mellitus	1.16, 1.05-1.30	3.9%, 1.9-7.6%

Table 3: Risk factors for stroke during pregnancy.

Predisposing of ischemic stroke	Predisposing of ischemic and hemorrhagic stroke
Amniotic fluid embolism	Chronic kidney disease
Antiphospholipid antibody syndrome	Reversible cerebral vasoconstriction syndrome
Atrial fibrillation	Hypertensive disorders of pregnancy
Cardioembolism	Migraine
Cervical artery dissection	Older
Choriocarcinoma	Peripartum infection
Congestive heart failure	Primary thrombocytopenia
Diabetes mellitus	Coagulopathy
Congenital heart disease	
HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count)	Posterior Reversible Encephalopathy Syndrome (PRES)
Peripartum cardiomyopathy	
Systemic lupus erythematosus	

of thromboembolic events; early introduction confers little or no risk.[3]

Thrombosis of veins or cerebral venous sinuses

It represents 0.5 to 1 of all strokes; in women, it is three times more frequent than in men. Predisposing factors are genetic (thrombophilia) and acquired, which can be transitory (pregnancy, puerperium, surgery, trauma, or exogenous hormones) or permanent (cancer or antiphospholipid syndrome). The most common presentation is a headache. Treatment includes parenteral anticoagulation, regardless of bleeding, low molecular weight heparin, and oral anticoagulation with vitamin K antagonists or dabigatran. In pregnancy, therapeutic doses of low molecular weight heparin.[10]

Symptoms and simulators of infarction

Presenting symptoms are similar in women and men; however, women are less likely to be diagnosed with CVD (67.8 versus 76.8) and less likely to investigate etiology but have a similar risk of recurrence (2.3 versus 2.6), which may be due to characterization bias.[11] In the ResISSSTE brain, 22.6 of stroke mimics were presented in men and 29.9 in women.

TREATMENT AND PROGNOSIS OF ISCHEMIC STROKE IN WOMEN

Women may benefit from intravenous thrombolysis even more than men but are less likely to receive it.[12] There is no gender difference in the benefit of mechanical thrombectomy.[13] *Figure 1* shows the cases of a 95-year-old woman in whom successful

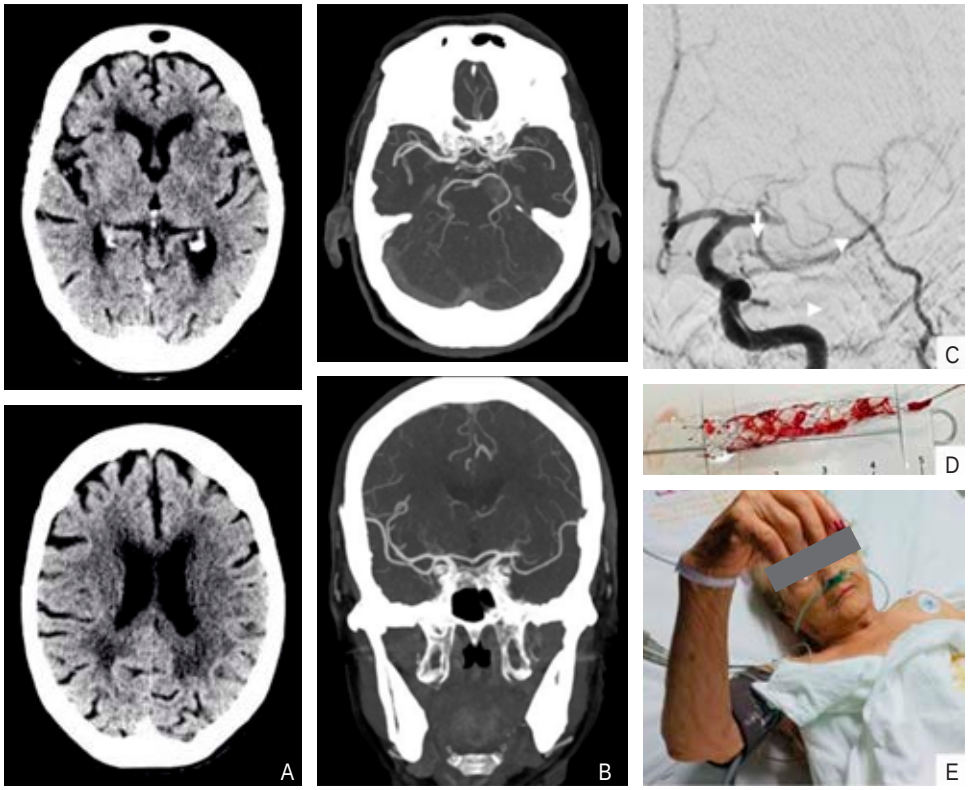

Figure 1:

See text.

recanalization was achieved with mechanical thrombectomy 6 hours after the onset of symptoms. Women have a worse prognosis due to age, functional status before the event, and comorbidities.[8]

CONCLUSION

There are significant differences in epidemiological characteristics, risk factors, and access to treatment in women; strategies are needed to avoid gender disparities in terms of access to prevention, treatment, and research of cerebrovascular disease in women.

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Chapter 24

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Climateric and menopause

Climaterio y menopausia

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MENOPAUSE AND RISK OF CARDIOVASCULAR DISEASE. IMPORTANCE OF EARLY PREVENTION

Natural menopause is defined as the permanent absence of menstrual periods, determined retrospectively. Thus, the transition to menopause or perimenopause (PM) begins, on average, four years before the last menstrual period with irregular cycles and metabolic changes with implications for long-term health.[1]

The SWAN study (3,000 women, 42-52 years old, 15-year follow-up) showed changes in the lipid profile from PM, a slight elevation of 6% on average in low-density lipoproteins, and minimal changes in the levels in high-density lipoproteins and its antiatherogenic function.[2,3]

At the end of 2020, the American Heart Association included PM as a sex-specific condition with cardiometabolic impact in the future; PM is considered a transcendental moment to generate lifestyle changes that impact cardiovascular (CV) prognosis in women.[4]

The protective effect of estrogen helps prevent atherosclerosis, that protection is lost after menopause, and it is associated with body changes, increasing visceral fat and decreasing lean mass. Furthermore, visceral adipose tissue secretes proinflammatory substances, determining a chronic proinflammatory state, favoring atherosclerosis, and increasing the risk of cardiovascular disease (CVD). Therefore, a higher incidence of ischemic heart disease (IHD) is observed compared to young women, and it can manifest as acute coronary syndromes (ACS) with or without angiographically significant coronary lesions, coronary dysfunction (coronary spasm or microvascular dysfunction) or nonspecific chest pain.[1] Also, at the cardiac level, a more significant diastolic dysfunction of the left ventricle (LV) is observed, as well as an increase in the concentric remodeling of the LV, which could make PM women susceptible to heart failure (HF) with preserved ejection fraction.[5]

PSYCHOLOGICAL CHANGES IN CLIMACTERIC AND MENOPAUSE

Psychological changes in the climacteric, such as stress and its complex management, result in a higher risk of depression and anxiety that can worsen according to personality and low self-esteem. This can add irritability, which is the most frequent problem and the one that most affects social activities.[6,7]

Vasomotor symptoms: hot flashes and night sweats constitute the most characteristic clinical manifestations of the climacteric, affecting the quality of life, even decreasing libido, causing irritability, fatigue, an embarrassment in public, anxiety, and depression.

Sleep and memory disorders may appear, such as Alzheimer's or dementia.[8] These occur with different intensities and frequencies, affecting alertness with decreased mental activity and productivity.

In addition to fatigue and irritability, these changes affect family and social relationships.

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IMPORTANCE OF TREATING CARDIOVASCULAR DISEASE IN WOMEN

CVD is the leading cause of mortality in women; among these, coronary heart disease stands out. Both sexes do not respond equally to different *noxa*, the different prevalence of risk factors (RF) for CVD are associated, and their evolution can differ in acute or chronic entities.

The RF associated with CVD are hypertension (HBP), diabetes, obesity, dyslipidemia, sedentary lifestyle, and smoking, among the most important. These cardiovascular risk factors (CVRF) are common to both sexes, but their impact may differ; hence, recognizing these differences is essential for their correct treatment.[9]

Women are underrepresented in clinical trials, this leads in part to a lack of knowledge of the treatment. However, it is assumed that the treatment of CVRF is similar in both sexes without significant evidence of differences in doses, additional benefits, or side effects. There is evidence of converting enzyme inhibitors (ACEI) and Angiotensin Receptor Antagonists (ARA II) in pregnancy, platelet antiaggregant in primary prevention, and thrombolytic therapy in some cases. Women have more adverse effects to ACE inhibitors (cough), calcium antagonists (edema), and diuretics (cramps).[10] It is time to involve gender from the beginning of research for better medical practice.

HORMONE TREATMENT IN CLIMACTERIC: RISK OR BENEFIT?

Estrogens regulate blood pressure (BP), endothelial function, and cardiac remodeling. Alterations in estrogen levels affect the immune system, related to vascular function and aging. After menopause, there is a tendency for increased BP, central adiposity, insulin resistance, and dyslipidemia.[1,2]

Cohort or case-control studies have shown that hormone therapy (HT) reduces the incidence of coronary heart disease and CV mortality after menopause by 30-50%, especially if administered to younger women. This is due to multiple protective mechanisms of the estrogens, such as nitric oxide-mediated vasodilation, increased flow, and decreased vascular resistance. Other factors involved are increased cardiac output, facilitation of angiogenesis and an anti-apoptotic effect on cardiomyocytes, antioxidant and anti-inflammatory actions, beneficial changes in the lipid profile, increased sensitivity to insulin, attenuation of the weight gain typical of menopause, and less abdominal adiposity.[2]

The Women's Health Initiative[3] study (27,000 women, average age 63 years) showed no benefit. In this study, the CV risk of coronary heart disease, stroke, and venous thromboembolism was only increased in the combined arm with oral estrogens and progestins. This study had some methodological flaws to consider: advanced age, associated comorbidities, and inappropriate dose schedule. The latest studies show that in younger women, there is a window of opportunity for the use of HT in the first ten years of menopause since they have a healthier arterial system, and it favors cardioprotection due to the mechanisms described.

CONCLUSION

Hormone therapy could be associated with increased cardiovascular risk in women who start or continue treatment after ten years of menopause and could be neutral or protective in younger women for a limited period.

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Chapter 25

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Cardiac rehabilitation in women

Rehabilitación cardiaca en la mujer

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DEFINITION, INDICATIONS, BENEFITS, AND CHARACTERISTICS OF WOMEN

Cardiac rehabilitation (CR) is the set of activities aimed at achieving the best physical, mental, and social level for the cardiovascular patient based on comprehensive management, an interdisciplinary team, patient evaluation, supervised exercise, management of risk factors, and education.[1]

Its recommendation is Class IA for patients after an acute coronary event, percutaneous or surgical myocardial revascularization, and heart failure; for the known benefits for both men and women, in improved functional capacity, quality of life, lower risk of hospitalizations and decreased morbidity and mortality.[1,2]

Women have specific differences in the presentation, diagnosis, and treatment of coronary heart disease related to biological, psychosocial, and socioeconomic aspects, older age, comorbidities, worse quality of life, more significant depression, and worse prognosis.[1,3]

INCORPORATION

The average reference to CR around the world ranges from 30 to 50% for men and 15 to 30% for women.[4,5] There are different factors for not referring to CR: a) Clinical factors: older age, comorbidities, anxiety, and depression; b) Psychosocial: absence of a support network, educational and socioeconomic level c) From the health system: access to CR centers. Of all the factors described, the independent prognostic predictor for referral to CR is the doctor's order, which makes it a determining factor in the incorporation route.[1,4,5] After the referral and incorporation, it is vital to achieve the participation, adherence, and completion of the patients in the program, since benefits such as decreasing the risk of death and the risk of a new heart attack are related to the number of sessions performed, with its most significant impact by completing 36 sessions.[6]

BENEFITS FOR WOMEN OVER 75 YEARS OF AGE

Life expectancy increases every time we have a larger population older than 75. Cardiovascular disease occurs later in women, with the characteristics previously exposed. There is no age limit for women's participation in CR programs; studies have shown benefits in quality of life and functional capacity.[1,2]

CARDIAC REHABILITATION MODELS

Implementing new cardiac rehabilitation models that improve patient engagement while maintaining core components, safety, and benefits have evolved over the past two years. In addition to the Center-Based Cardiac Rehabilitation (CCR) model, the Home-Based Cardiac Rehabilitation (HBCR) model and the Hybrid-CR model. The home-based model includes possibilities, such as community centers and parks, which define itself as a community-based model (CBR).

The HBCR and the hybrid-CR models use information and telecommunications

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technologies (smartphones, internet, portable sensors, etc.) according to availability, the environment, and the patient's and their caregivers' characteristics. They include the components of exercise and education. Some advantages: low cost, greater privacy, independence and flexibility, less travel time, individual time planning, and integration into daily routines. Disadvantages; lack of direct contact and social interaction for patients, feeling of insufficient security. Lack of published standards, regulations, and economic recognition for the programs.[7,8]

SECURITY

Serious events in a CCR rarely occur (one per 50,000 patient hours). No cardiovascular complications or death have been reported in HBCR in low- and moderate-risk patients. Several studies have shown that, with proper evaluation, detection, and monitoring in higher-risk patients, out-of-center CR may be safe and doable.[1,2,7]

EFFECTIVITY COST

CR programs with a multidisciplinary approach have proven to be cost-effective in caring for patients with chronic cardiovascular diseases. The evaluation of this relationship is based on costs and indicators such as reduction of re-hospitalizations, years of life gained, and rate back to work. CR programs reduced re-hospitalizations from 16 to 11 days, return to work increased from 38 to 53%, and years of life increased from 2.4 to 20.8. 12-week participation in CR reduces medical costs by approximately $700 per patient, considering direct and indirect costs, after 21 months of follow-up.[1,2,9]

EXERCISE PRESCRIPTION IN CR

Exercise prescription should be individualized and follow physical training principles. A comprehensive evaluation is required through a multidisciplinary team, including a cardiac rehabilitative cardiologist, physiotherapist, nurse, psychologist, and nutritionist. And risk stratification through a review of the clinical history, disease evolution, laboratory tests, and test of effort. In a hemodynamically stable patient, admission to the outpatient CR program can be initiated two weeks after uncomplicated myocardial infarction and 4 to 6 weeks after uncomplicated cardiac surgery.[2]

Exercise is recommended according to individual limitations or comorbidities. It is based on FITT-VP (frequency, intensity, time, type, volume, and progression). Two exercise modalities: moderate-intensity continuous aerobic exercise (MICE), high-intensity interval training (HIIT), and resistance exercise (strength is evaluated with maximum voluntary resistance 1RM) *(Table 1)*. Coordination, balance, and elasticity exercises should be included. Each session should consist of a warm-up period of 5-10 minutes, a primary (training) phase of between 20-45 minutes, and a cool-down period of at least 5 minutes, for 30-60 minutes per session.[2,10]

Table 1: Prescription of physical training.

	Aerobic exercise	Resistance exercise
Frequency	3-5 days/week	2-3 non-consecutive days/week
Intensity	40 to 80% RHR, VO_2max, Max HR in CPET or ST; borg rating 12-14 (6-20 scale)	10 to 15 reps, Borg 11 to 13, 40 to 60% MR
Duration	10-20 to 60 min/session	1 to 3 sets, 8 to 10 exercises (for larger muscle groups) 30 min
Equipment	Treadmill, cycle ergometer, arm ergometer. To walk	Use safe and comfortable equipment. (Weights, leagues, balls)

RHR = reserve heart rate. VO_2max = maximal oxygen uptake. Max HR = maximun heart rate. CPET = cardiopulmonary exercise test. ST = cardiopulmonary stress test. MR = maximum resistance.

FINAL MESSAGES

1. All women should be referred to CR after an acute coronary event, percutaneous or surgical myocardial revascularization, or heart failure.
2. The implementation of the automatic referral to CR before hospital discharge improves the rate of incorporation to CR.
3. There is no age limit to participate in RC.
4. CR models outside the center (home, community, hybrid) are safe and favor the participation and adherence of women to CR programs.

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