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EDITORIAL

EDITORIAL

ABBREVIATIONS

ABPM = ambulatory blood pressure monitoring.
ACE inhibitors = angiotensin-converting enzyme 2 inhibitors.
ACEi = angiotensin-converting enzyme 2 inhibitors.
ACh = acetylcholine.
ACOG = American College of Gynecology and Obstetrics.
Adn = adenosine.
ADR = Adverse drug reactions.
AE = adverse effects.
AHA = American Heart Association.
AMI = acute myocardial infarction.
ARA-II = angiotensin-II receptor antagonists or blockers.
ARBs = angiotensin II receptor blockers.
ART = assisted reproductive therapy.
AT1R antagonist = angiotensin II type 1 receptor antagonists.
AT2R antagonist = angiotensin II type 2 receptor antagonists.
BB = beta-blocker.
BP = blood pressure.
CAS = coronary artery spasm.
CAT = coronary angiotomography.
CT angiography = coronary tomography angiography.
CCTA = coronary computed tomography angiography.
CCB = calcium channel blockers.
CFR = coronary flow reserve.
CHCs = combined hormonal contraceptives.
COCs = combined oral contraceptives.
CKD = chronic kidney disease.
CMD = coronary microvascular dysfunction.
CMR = cardiovascular magnetic resonance.
CV = cardiovascular.
CVD = cardiovascular disease.
STROKE = cerebrovascular event.
RF = risk factors.
CVRF = cardiovascular risk factors.
DASH-like eating = Dietary Approaches to Stop Hypertension-like eating.
DBP = diastolic blood pressure.
DM = diabetes mellitus.
DM1 = type 1 diabetes mellitus.
T2DM = type 2 diabetes mellitus.
DMPA = depot medroxyprogesterone acetate.
ECG = electrocardiogram.
ED = endothelial dysfunction.
ET-1 = endothelin-1.
FFR = fractional flow reserve.
FSH = follicle-stimulating hormone.
GLP-1-RA = glucagon-like peptide-1 receptor agonists.
GnRH = gonadotropin-releasing hormone.
HBP = high blood pressure.
HC = hormonal contraception.
HDP = hypertensive disorders of pregnancy.
HRT = hormone replacement therapy.
IL-6 = interleukin 6.
IMR = index of microcirculatory resistance.
INF-α = interferon alpha.
INOCA = Ischemia with Non-Obstructive Coronary Artery disease.

IUD = intrauterine device.
IVUS = intravascular ultrasound.
LH = luteinizing hormone.
LNG = levonorgestrel.
LNG-IUD = levonorgestrel-releasing intrauterine device.
LVH = left ventricular hypertrophy.
MLC = myosin light chain.
MLCK = MLC kinase.
NNT (NND) = number needed for detection (to treat?) (number needed to diagnose)
NO = nitric oxide.
NTG = nitroglycerin.
OCT = optical coherence tomography.
PCOS = polycystic ovarian syndrome.
PET = positron emission tomography.
PK = pharmacokinetics.
POP = progestin-only pills.
RAAS = renin-angiotensin-aldosterone system.
SAH = systemic arterial hypertension.
SBP = systolic blood pressure.
SCAD = spontaneous coronary artery dissection.
SGLT2i = sodium-glucose cotransporter type 2 inhibitors.
SSD = sex-specific differences.
ST = stress test (stress testing).
TD = thiazide-type diuretics.
TIMI = thrombolysis in myocardial infarction.
TTE = transthoracic echocardiogram.
USA = United States of America.
USMEC = USA medical eligibility criteria for the use of contraceptives.

OTHER ABBREVIATIONS

ACCORD = The Action to Control Cardiovascular Risk in Type 2 Diabetes.
ASCOT = The Anglo-Scandinavian Cardiac Outcomes Trial.
CONVINCE Study = The Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints.
CYP2D6 = Cytochrome P450 2D6.
NVEST Trial = The International Verapamil-Trandolapril Study.
iPOWER Study = Coronary Microvascular Function and Cardiovascular Risk Factors in Women With Angina Pectoris and No Obstructive Coronary Artery Disease.
J-DOIT3 study = Effect of an intensified multifactorial intervention on cardiovascular outcomes and mortality in type 2 diabetes.
NCD risk factor collaboration = non-communicable diseases risk factor collaboration.
NHANES = National Health and Nutrition Examination Survey.
Nifedipine-GITS = Nifedipine gastrointestinal therapeutic system.
NORDIL = The Nordic diltiazem study.
STOP-Hypertension = Dietary Approaches to Stop Hypertension (DASH) Diet and Blood Pressure Reduction in Adults with and without Hypertension.
Syst-Eur = A multicentre trial on the treatment of isolated systolic hypertension in the elderly.

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Editorial

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Systemic arterial hypertension: a public health problem worldwide

Hipertensión arterial: un problema de salud pública a nivel mundial

Gabriela Borrayo-Sánchez,* Arturo Guerra-López‡

INTRODUCTION

Systemic arterial hypertension (SAH) is the most prevalent cardiovascular risk factor in low- and middle-income countries and includes more than 1.13 billion people worldwide. It is considered the main modifiable risk factor for all causes of death, accounting for more than 10 million deaths and 218 million disability-adjusted lives per year.[1]

During 2019, in a campaign that included 92 countries around the world, of 1'508,130 persons examined, 482,273 (32.0%) never had their blood pressure measured, and 513,337 (34.0%) had hypertension, of which 58.7% knew it, and 54.7% received antihypertensive medication.[2] In Latin America,[3] prevalence of 44% (range 17.7% to 52.5%) were found, only 53.3% of them receive treatment and 37.6% reach control levels (< 140/90 mmHg), control is better in urban populations than in rural ones (39.6% vs 32.4%), only 36.4% used two or more antihypertensive drugs.[4] In Mexico, it is estimated that one in three Mexicans over 20 years old have SAH. It has been found in more than 50% of patients with acute coronary syndrome.[5] Although the 2021 National Health and Nutrition Survey (ENSANUT 2021 on COVID-19) identified a reduction in adults who attended for SAH detection, it is recognized that a high percentage of the population is unaware of having the diagnosis and its control is deficient, the total prevalence was 28.2%. It is known that the prevalence increases with aging, being 54.4% at 60 years and 57.0% at 69 years, respectively.[6]

Cardiovascular diseases have been the leading cause of death for over 20 years. In 2021, according to the National Institute of Statistics and Geography (INEGI), there was excess mortality of more than 40%, with more than 226,000 deaths from cardiovascular causes. Which represents 70 thousand more deaths than in 2019, exceeding those caused by COVID-19.[7] One of the main cardiovascular risk factors is SAH. In the Mexican Institute of Social Security (IMSS), SAH has a prevalence of 20.7%, representing a financial risk since it occupies the second place in the most significant financial impact with 52,284 million pesos (3,120 USD) only after diabetes mellitus (96,823 million pesos; 5,779 USD) followed by cancer (19,951 million pesos).[8]

SAH represents a growing public health problem, and cost-effective interventions are necessary, focusing on health promotion, preventing the risk of suffering it, and standardization of treatment protocols based on cardiovascular risk. Of the patient and distribute the tasks in the health team.[9]

PUBLIC POLICIES FOR COMPREHENSIVE CARE FOR SYSTEMIC ARTERIAL HYPERTENSION

Comprehensive public policies are required for the care of SAH; an example of this has occurred in the IMSS (Mexican Institute of Social Security), which, to standardize and systematize the care of its beneficiaries with

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HAS, created the Comprehensive Care Protocol (*del español Protocolo de Atención Integral*, PAI), which contains evidence-based activities on changes in diagnostic criteria, highlighting the importance of proper blood pressure measurement, home measurement, and the use of ambulatory blood pressure monitoring (ABPM), migrating to dual combined therapies, and triples in one pill; without neglecting non-pharmacological treatment.[10] It also seeks to empower the patient, improve self-control and self-care, and promote closer interaction with the health system, including lifestyle changes.[11] The multidisciplinary activities range from the first level of care, with a focus on primary health care, to strengthening it, with the participation of the expanded health team at the first level, with the participation of medical, nursing, nutrition, social work, and psychology personnel. Stomatology and medical assistants help establish health promotion actions and identify the risk of suffering SAH in people aged 20 and over.[12]

CONCLUSIONS

SAH is a public health problem, global policies are required to reduce its prevalence, as well as to address population situations, which include detection, patient education, as well as protocolized and multidisciplinary strategies, with a focus on primary health care to standardize the preventive, diagnostic, and therapeutic approach, especially with emphasis on the preferential use of double and triple fixed-dose combinations, destining monotherapy to low-risk, fragile patients, and pregnant women. Non-pharmacological measures, with an emphasis on patient participation, self-care, and empowerment, are a fundamental part.

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Chapter 1

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The impact of arterial hypertension as a cardiovascular risk factor in women: epidemiology and prevalence

Impacto de la hipertensión arterial como factor de riesgo cardiovascular: epidemiología y prevalencia

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Keywords:
arterial hypertension, cardiovascular risk factor, women, epidemiology.

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INTRODUCTION

It is widely known that cardiovascular diseases (CVD) are the leading cause of death worldwide.[1] Systemic arterial hypertension (SAH) is a major public health concern worldwide. It is a significant risk factor for cardiovascular diseases, including heart attacks, strokes, and other vascular complications. While hypertension affects both men and women, there are gender-specific considerations that make its impact on women particularly relevant. In recent years there has been growing recognition of the unique epidemiological and prevalence patterns of arterial hypertension in women.

These CVD have origins in the existence and persistence of risk factors, among which SAH stands out as the leading risk factor for CVD worldwide.[2,3] It has a high global prevalence ranging from 20 to 40%, with a worldwide average of 22% of people affected.[4] In Latin America, it leads to a loss of up to 5.1 years of life,[5] making it the risk factor contributing the most to morbidity and mortality from all causes.[6]

This article aims to explore the epidemiology and prevalence of arterial hypertension in women.

EPIDEMIOLOGY AND PREVALENCE

The prevalence of SAH varies according to regions and population groups, but it is generally considered one of the main chronic conditions worldwide. Prevalence estimates may change over time due to various factors such as changes in lifestyle, population aging, and early disease detection.

Here is an overview of the prevalence of SAH worldwide, in Mexico, and especially in women:

Global prevalence of arterial hypertension: according to the World Health Organization (WHO):

1. 1.28 billion adults aged 30–79 years worldwide have hypertension, most (two-thirds) living in low- and middle-income countries.
2. An estimated 46% of adults with hypertension are unaware that they have the condition.
3. Less than half of adults (42%) with hypertension are diagnosed and treated.
4. Approximately one in five adults (21%) with hypertension have it under control.[7]

Prevalence in Mexico: SAH is a significant public health issue in Mexico. According to the National Health and Nutrition Survey (ENSANUT) 2020, the prevalence of hypertension in adults aged over 20 years in Mexico is 30.2% (> 140/90 mmHg criteria) or 49.4% (> 130/80 mmHg criteria), the prevalence was 44.0% in women and 55.3% in men.[8]

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It is essential to highlight that these figures may vary according to the source and criteria used to define SAH in each study. Additionally, prevalence can be influenced by socioeconomic, cultural, and healthcare access factors in different regions of the world and in Mexico. Early detection, appropriate treatment, and the promotion of healthy lifestyles are crucial to prevent, and control SAH and its consequences in the population, especially in women.

In general, the prevalence of SAH tends to increase with age in both sexes, but it is less common in women than in men before menopause. It is still unclear whether this difference is related to the protective effect of estrogens or other yet-to-be-determined biological factors, including differences in many biological and psychosocial variables. Prevalence increases after menopause, equaling that of men.[9] However, other reports indicate that prevalence in women after menopause slightly exceeds that of men.[10] Factors contributing to SAH in women after age 60 are related to differences in cardiovascular risks and life expectancy between men and women and a possible survival effect in older men. A recent global analysis in 2019, showed that 59% of women and 49% of men with hypertension reported a previous diagnosis, and 47% of women and 38% of men received treatment. The rates of control among those individuals were 23% for women and 18% for men.[11]

Hypertensive disorders of pregnancy, such as gestational hypertension and preeclampsia, affect up to 10% of all pregnancies. These women have, on average, twice the risk of developing cardiovascular disease later in life compared to women with normotensive pregnancies. This increased risk may be the result of an underlying predisposition. Women with hypertension during or after pregnancy show more classic cardiovascular risk factors, including chronic hypertension, renal dysfunction, dyslipidemia, diabetes, and subclinical atherosclerosis.[12]

RISK FACTORS FOR THE DEVELOPMENT OF ARTERIAL HYPERTENSION IN WOMEN

Several common factors can contribute to the onset of arterial hypertension in both women and men, such as family history, age, sedentary lifestyle, obesity, high salt intake, stress, alcohol, etc. However, specifically in women, having polycystic ovaries, early menarche, history of contraceptive use, hormonal changes during the menstrual cycle, pregnancy, and menopause can influence the onset of this disease.[13,14] Additionally, autoimmune, or rheumatic diseases associated with inflammation, endothelial dysfunction, and accelerated atherosclerosis can play a role.[15]

HYPERTENSION AS A CARDIOVASCULAR RISK FACTOR IN THE CONTEXT OF GYNECOLOGICAL-OBSTETRIC GLOBAL CARDIOVASCULAR RISK

Arterial hypertension is a well-known risk factor for the development of cerebrovascular disease, cognitive impairment, heart failure, coronary artery disease, chronic kidney disease, and peripheral arterial disease, among others. Therefore, assessing and managing hypertension from the overall cardiovascular risk control perspective is important, considering other risk factors such as diabetes, dyslipidemia, smoking,

Table 1: Factors that increase cardiovascular risk in women at different stages of life.

Childhood	Adolescence	Pregnancy	Older women
Unhealthy diet	Early or late menarche	Gestational diabetes	Menopause
Sedentary lifestyle	Polycystic ovary syndrome	Gestational hypertension	Hormone replacement therapy
Overweight and obesity	Contraceptives	Preeclampsia	
	Premature menopause	Premature birth	
	Primary ovarian insufficiency	Fertility therapy	

sedentary lifestyle, obesity, etc. Additionally, specific risk enhancers should be regarded during the gynecological-obstetric medical history, such as early menarche, contraceptive use, gestational hypertension, and gestational diabetes *(Table 1)*.[13,14]

CONCLUSION

The prevalence of arterial hypertension in women is lower than in men before menopause, but it becomes equal or even higher after reaching menopause. Given the significant impact of arterial hypertension as a cardiovascular risk factor in women, it is crucial to undergo frequent blood pressure checks, adopt healthy lifestyle habits, and follow medical recommendations to prevent and control arterial hypertension. Additionally, women should receive comprehensive medical care considering their gynecological-obstetric medical history, identifying, and treating autoimmune or rheumatic diseases, investigating their specific needs, and estimating their cardiovascular risk profile. This includes early detection of additional risk factors related to reproductive health, such as early menarche, contraceptive use, gestational hypertension, and gestational diabetes. Addressing these risk factors comprehensively promotes women's cardiovascular health, and potential long-term complications can be prevented.

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Chapter 2

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Hypertension and diabetes mellitus in women: a high-risk combination

Hipertensión y diabetes mellitus en la mujer: una combinación de alto riesgo

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Keywords:
hypertension, diabetes mellitus, estrogens, cardiovascular disease.

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INTRODUCTION

Mortality in women due to cardiovascular disease is a national and global problem. The relationship between type 2 diabetes mellitus (T2DM) and systemic arterial hypertension (SAH) is complex and bidirectional. In T2DM, different conditions lead to SAH, while some mechanisms in the latter contribute to a more significant alteration in insulin resistance and the development of T2DM. Both pathologies act synergistically at the micro and macrovascular levels, which can lead to higher mortality.

Risk factors related to gender have not been fully clarified. The coincident pathophysiological mechanisms of SAH and T2DM in women are also differentially affected by the stages of their lives and hormonal variations. Treatment recommendations are similar for women and men; however, the reproductive stage, risk assessment, and possible adverse effects must be considered in women.

In this review, mechanisms and factors that favor SAH in patients with T2DM are pointed out, aspects of the treatment of both conditions are also reviewed, and the differences in some therapeutic responses are related to gender.

Diabetes mellitus (DM) and systemic arterial hypertension (SAH) are two entities that coincide for a long time in their evolution. SAH is a significant risk factor for cardiovascular disease (CVD), chronic kidney disease (CKD), and stroke, frequently affecting DM patients. In turn, DM is more common among patients with SAH. The latter occurs in 50 to 70% of patients with type 2 diabetes mellitus (T2DM) and 30% among patients with type 1 diabetes mellitus (T1DM).[1,2] Evidence suggests that insulin resistance contributes to the pathogenesis of SAH, which is a factor that frequently precedes the development of T2DM.[1-3] Pathophysiological mechanisms and overlapping risk factors are fundamental in the coexistence of SAH and DM, increasing mortality risk and micro and macrovascular complications. Shared pathophysiological mechanisms contributing to the co-occurrence of both diseases include insulin resistance, endothelial dysfunction, inflammation, dysautonomia, and inappropriate activation of the renin-angiotensin-aldosterone system (RAAS) and atherosclerosis *(Figure 1)*. These mechanisms can increase sodium absorption, sympathetic activity, vasoconstriction, inflammation, and oxidative stress.[4] Other associated mechanisms include activation of epithelial sodium channels, alteration of extracellular vesicles and their microRNAs, alteration of the intestinal microbiota, and increased activity of the renal sodium-glucose cotransporter.

Angiotensin II can lead to insulin resistance at the skeletal muscle level by decreasing blood flow, inhibiting intracellular insulin-triggered signaling pathways, and impairing insulin secretion from pancreatic beta cells. Estrogens present variability in their concentration, producing different responses in the mentioned mechanisms. Estradiol is a determining hormone in controlling several mechanisms that affect

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insulin resistance and the vascular system, in addition to the RAAS. Estradiol deficiency leads to changes in immune function, dysregulation of the RAAS, and modification of the anti-inflammatory response.[5]

The differences between women and men in systolic blood pressure are more accentuated in patients with DM than in non-diabetics, and the difference is more apparent after 55.[1,4] On the other hand, the SAH control rate is 33.6% in men and 30.6% in women, and it is lower in the population with diabetes compared to non-diabetic patients.[1] The factors and conditions that mark the differences between men and women in SAH and DM are diverse *(Figure 2)*.

TREATMENT

The goals of treatment with changes in lifestyle and drugs must be individualized, considering cardiovascular risk, possible adverse drug reactions (ADR) to antihypertensives, and the patient's characteristics.[6-8]

In patients with T2DM and blood pressure (BP) levels greater than 130/80 mmHg, it is recommended to start antihypertensive drug treatment. The recommended goal is < 130/80 mmHg.[7,8] In pregnant women with diabetes and arterial hypertension, a blood pressure threshold of 140/90 mmHg for initiation and treatment adjustment is associated with better pregnancy and neonatal outcomes.[8]

Hygienic-dietary measures. Lifestyle modifications are the initial steps for treating hypertension in patients with diabetes and should always be recommended for patients with BP > 120/80 mmHg.[7,8]

These generally include reducing body weight, a DASH-like eating pattern [consumption of fruits and vegetables (8-10 servings per day) and low-fat dairy products], moderate-aerobic physical activity (> 150 minutes/week), restriction in sodium intake (< 2,300 mg/day) and avoiding excessive alcohol consumption (no more than one serving per day in women).[8]

These measures improve the efficacy of some antihypertensives, favoring metabolic and vascular health and reducing ADR.[7,8]

Pharmacotherapy. Drug treatment should be started or adjusted in patients with diabetes and BP ≥ 130/80 mmHg, establishing a regimen of two or more drugs in those with BP > 160/100 mmHg.[7,8] The choice of antihypertensive is similar in men and women, but the reproductive stage and adverse effects must also be considered in women.[3]

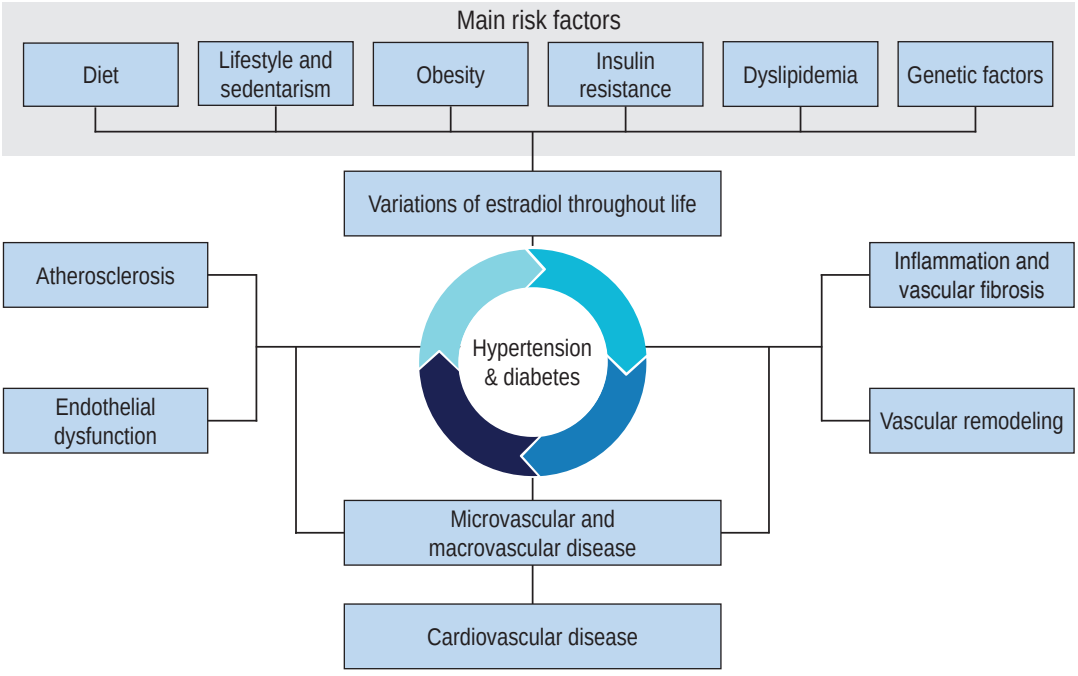

Figure 1:

The pathophysiological mechanisms that arterial hypertension and diabetes mellitus share include insulin resistance, obesity, dyslipidemia, genetic factors, and lifestyle, and they are affected by estrogen concentration, which presents variations in the different stages of women.

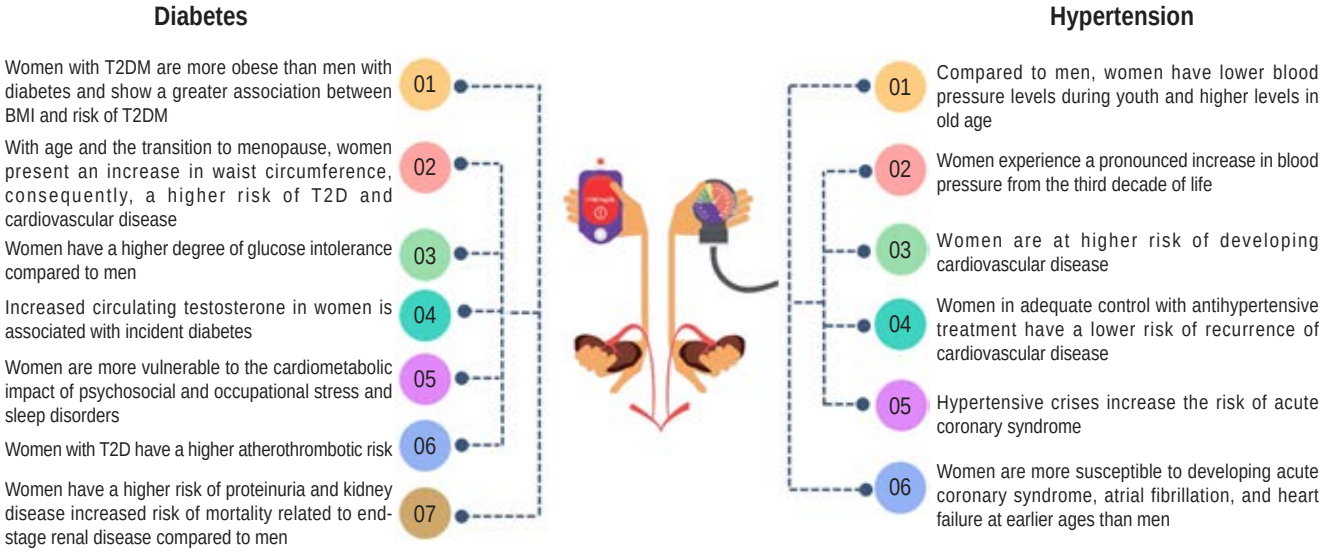

Figure 2: The pathogenesis and clinical presentation of arterial hypertension and diabetes mellitus present differences according to sex and gender.

Angiotensin-converting enzyme 2 inhibitors (ACE inhibitors) or angiotensin II receptor blockers (ARB) are the recommended first-line treatment in patients with DM.[8] In patients with diabetes, arterial hypertension, and urinary albumin/creatinine ratio of > 30-299 mg/g, especially > 300 mg/g, ACE inhibitors or ARB are recommended at the maximum tolerated dose.[8] In patients with diabetes and hypertension who do not achieve blood pressure goals using three classes of antihypertensives (including a diuretic), treatment with mineralocorticoid receptor antagonists such as spironolactone should be considered.[7,8]

Hypoglycemic agents with cardiovascular benefit. Sodium-glucose cotransporter type 2 (SGLT2i) inhibitors and GLP-1 receptor agonists (aGLP-1) have been shown to have beneficial cardiovascular effects, partly attributed to BP reduction.[7] SGLT2i are associated with a mild diuretic effect and a reduction in systolic/diastolic BP of 3-6/1-2 mmHg.[9,10] In contrast, aGLP-1 produces a decrease in BP of 2-3/0-1 mmHg.[11]

Complications. SAH in patients with DM conditions is a greater risk of cardiovascular events, heart failure, deterioration of microvascular complications (nephropathy and retinopathy), and mortality.[7,8] According to the ACCORD study[12,13] and J-DOIT3,[14] an optimal BP control reduces these complications. Regarding gender, women have more adequate rates of hypertensive control; however, their therapeutic adherence is lower. The BP threshold associated with cardiovascular risk is lower in women than men; likewise, target organ damage[15,16] and treatment-resistant hypertension is more common.[17] To date, no significant differences in the efficacy of antihypertensives have been confirmed according to gender; however, a higher prevalence of ADR has been reported in women.[15,16]

CONCLUSION

Relationship between type 2 diabetes mellitus (T2DM) and systemic arterial hypertension (SAH) in women is complex and involves many pathophysiological mechanisms that lead to endothelial dysfunction, micro and macro vascular disease, that increase their cardiovascular risk. Pharmacological treatment must be optimized to achieve therapeutic goals and reduce cardiovascular complications.

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Chapter 3

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Dyslipidemia as an associated risk factor in hypertensive women

Dislipidemia como factor de riesgo asociado en mujeres hipertensas

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Keywords:
hypertension, dyslipidemia, women, Mexico.

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INTRODUCTION

The current prevalence of arterial hypertension in Mexico has been estimated at 30.05%.[1] Its relationship with age, dyslipidemia, obesity, and carbohydrate metabolism disorders is recognized.[2]

An increase in total circulating cholesterol, on the other hand, represents another important marker of cardiovascular risk.[3-6] Cardiovascular disease (CVD) is the leading cause of death in most middle-income and developed countries and has recently increased in low-income countries. In Mexico, as worldwide, the leading cause of death is cardiovascular disease for both women and men.[7]

Approximately 80% of CVD are preventable. Atherosclerotic cardiovascular disease (ASCVD) prevention and risk reduction benefit individuals and society, which is why it represents a challenge. The expenditures associated with these diseases are catastrophic and capable of slowing down the social development of a country. Many patients cannot access preventive cardiology.[8,9]

Hypertension and dyslipidemia are important risk factors for CVD. The coexistence of hypertension and dyslipidemia is often observed in daily clinical practice. Epidemiological studies have also reported that gradual increases in blood pressure (BP) or the prevalence of hypertension are associated with increases in circulating lipid levels. One possible explanation for this relationship is that hypertension and dyslipidemia share common pathophysiological mechanisms, such as obesity and the resulting dysregulation of adipokine release. Dyslipidemia, however, adversely affects functional and structural arterial characteristics and promotes atherosclerosis. These changes may affect BP regulation, which, in turn, predisposes people with dyslipidemia to the development of hypertension.[10,11]

From an epidemiological perspective, several cohort studies have indicated a causal relationship between dyslipidemia and future risk of developing hypertension.[8] However, with one exception, these studies have been conducted in non-Asian populations.[8,12-15]

Hypertension is a modifiable risk factor to avoid premature death. Evidence supports that effective treatment of hypertension results in a significant reduction in CVD.[6] The may measurement month (MMM) initiative of the International Society of Hypertension and epidemiological studies such as PURE have concluded that at least a quarter of the Latin American population suffers from hypertension. However, only 20-30% of them are within the BP control goals, according to the recommendations of the current guidelines.[3,4,12]

These data align with the Global Blood Pressure Screening Campaign of the International Society of Hypertension (MMM).[4] Of 1'508,130 subjects examined, 32% had never previously undergone BP measurement, only 58.7% of patients with hypertension

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knew their diagnosis, and 54.7% were taking antihypertensive drugs.[4] In patients taking antihypertensives, only 57.8% were controlled with BP < 140/90 mmHg and 28.9% with lower values. Those values mean that only 31.7% of all those with hypertension were controlled with BP < 140/90 mmHg and 23.3% of participants had untreated or inadequately treated hypertension.

The urgent need to implement innovative strategies to reverse this alarming health situation is evident in this context. In recent years, physicians have noted that an increased frequency of out-of-office BP measurements may be helpful to keep patients and physicians in touch and promote better medication adherence and BP control.[11,16,17] Many systematic reviews and meta-analyses confirm the validity and usefulness of home self-measurements that patients can share with physicians via telemedicine. In a study in a Mexican population that included more than 120,000 patients, the prevalence of hypertension was 30.2% in adults aged 20 or over. Interestingly, hypercholesterolemia with cholesterol levels greater than 200 mg/dL was more prevalent in the hypertensive population than the non-hypertensive population (57.8% vs 39.8%, respectively, p < 0.05).

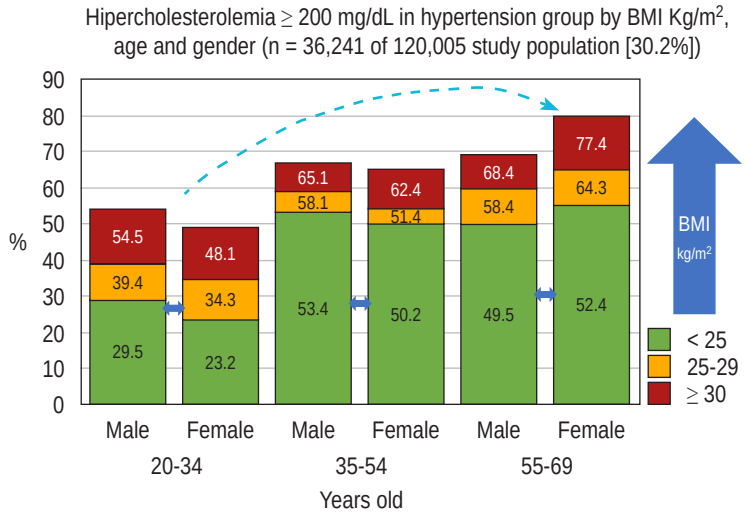

Figure 1: Distribution of total cholesterol level (mg/dL) by age group and gender. The red box corresponds to total cholesterol > 240 mg/dL, the yellow box to total cholesterol 200-240 mg/dL, and the green box to cholesterol less than < 200 mg/dL. BMI = body mass index.

DYSLIPIDEMIA IN HYPERTENSIVE WOMEN IN MEXICO

Thus, it is clear that chronic noncommunicable diseases frequently coexist, and the presence of one enhances the existence of the others.[17,18] The prevalence of hypercholesterolemia > 200 mg/dL in the population aged 20-34 without arterial hypertension was 27.2% vs 36.5% in the group with hypertension of the same age.[16,19]

Interestingly, the prevalence increases in the 35-54 age group to 44.9% in participants with normal BP and 62.3% in patients with hypertension, without significant differences between both sexes.[16] However, in the 55-69 age group, the prevalence increases to 47.3% in subjects with normal BP vs 68.6% in the population with hypertension. The differences by gender are notable, observing an increase of more than ten percentage points in women with hypertension *(Figure 1)*. Of the total population of this study, 36,257 (30.2%) were hypertensive; however, 60% were unaware of it.[16] The prevalence of hypercholesterolemia in the population with hypertension was 52.5%; however, the prevalence was not only associated with the type of hypertension (55.6% systolic vs 53.2% diastolic) but also with the stage. Thus, the prevalence of hypercholesterolemia in stage one patients was 52.3%, while in stage 2, the prevalence was 56.1%.[16]

CONCLUSIONS

Chronic noncommunicable diseases frequently coexist and enhance their prevalence among them. In this sense, there is a synergy between hypertension and hypercholesterolemia. The female gender shows a peculiar association according to age and body weight, and a higher prevalence of hypercholesterolemia is observed in women with hypertension. Dyslipidemia is a prevalent cardiovascular risk factor, and in women with hypertension, it presents a prevalence of more than 50%, particularly after age 55.

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Chapter 4

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Sex differences in the treatment of arterial hypertension

Diferencias de sexo en el tratamiento de la hipertensión arterial

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Keywords:
arterial hypertension, differences by sex, treatment, adverse events.

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INTRODUCTION

Although systemic arterial hypertension (SAH) guidelines do not make specific recommendations by sex (except pregnancy), a substantial body of evidence shows sexual dimorphism in various aspects. This chapter summarizes the main sex-specific differences (SSD) in the treatment of hypertension.

PHARMACOKINETICS

SSD in body composition and organ physiology may influence the pharmacokinetics (PK) (absorption, distribution, metabolism, and excretion) of antihypertensive drugs closely linked to sex hormones.[1-3] These differences are shown in *Figure 1*.

DIFFERENCES IN DRUGS FOR THE TREATMENT OF HYPERTENSION

Diuretics: thiazide and thiazide-type diuretics (TD) are widely indicated in women, and the female sex is a predictor of response to TDs, affecting the reduction of systolic and diastolic blood pressure.[4] In the Women's Health Initiative, a project that recruited 98,705 women between the ages of 50 and 79 with hypertension and no history of cardiovascular disease (CVD), treatment with TD as monotherapy was associated with better blood pressure (BP) control than other drugs used as monotherapy.[5] In middle-aged women, the reduction in systolic blood pressure produced by indapamide was significantly more significant than in men.[6] In another study with SSD analysis including 51% of women, TD presented similar benefits in reducing all cardiovascular events, but a more significant reduction in stroke was observed in women.[7]

There are no gender differences concerning urinary flow rate and excretion rate of sodium and potassium. In older women, although thiazides reduce the risk of bone loss and fractures, becoming an attractive option for this population, the deterioration of glomerular filtration is more pronounced; this fact needs to be considered at the time of its indication since it can lead to more significant adverse drug reactions (ADR).[8] Electrolyte disturbances (hyponatremia and hypokalemia) and arrhythmic events are more common in women. Another possible ADR to consider, is sexual dysfunction, as thiazides decrease vaginal lubrication.[8]

Renin-angiotensin-aldosterone system inhibitors: sex hormones interact with the RAAS at multiple levels; estrogens inhibit it, while androgens increase their activity. However, how sex hormones modulate the efficacy and safety of these drugs remains uncertain.

SSD has not been described in the pharmacokinetics of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), aliskiren, or spironolactone. However, some data on SSD on the efficacy of ACE inhibitors or ARB exists. In a review that included 13 studies with 74,105 patients (39% women), SSD data were reported in

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only nine studies, and in seven of them, both ACE inhibitors and ARB demonstrated slightly greater efficacy in men.[9] Regarding adverse effects, they are also higher in women, having up to three times more incidence of cough with ACE inhibitors. On the other hand, they decrease vaginal lubrication just like TDs (frequent association).[8]

Pharmacokinetic differences	Clinical consequences and specific examples in some drugs
Bioavailability	
• ↓ secretion of gastric acid with slower gastric emptying • Slower intestinal transit • No consistent changes in intestinal metabolism	• ↓ oral availability of drugs that require an acidic environment for their absorption • Delayed/decreased absorption of enteric-coated drugs (captopril, metoprolol, verapamil, aspirin)
Distribution	
Body composition • ↓ body surface area • ↓ body water content and plasma volume • ↑ body fat	• ↑ of Vd and longer half-life of lipophilic drugs • ↑ of the Vd of lipophilic drugs reached a higher Cmax with more AED (amlodipine)
Binding to plasma proteins • ↓ albumin and α1 acid glycoprotein • ↑ globulins	• Contraceptives ↓ decrease plasmatic albumin and α1-acid glycoprotein and may ↑ free drug levels • Estrogens ↓ α1-acid glycoprotein and ↑ plasmatic binding globulins
Metabolism	
Phase I • ↓ CYP1A2, 2C9, 2D6, 2C19 and 2E1 activity • ↑ CYP2A6, 2B6, 2D6 and 3A4 activity	• ↑ biotransformation of CYP3A4 substrates (CCB, losartan) • ↓ biotransformation of CYP2D6 substrates (metoprolol, propranolol) - higher exposure in women • CYP1A2 and 2C19 are inhibited by contraceptives and during pregnancy, therefore, their activity is ↓. Contraceptives and estrogens ↑ CYP2A6 and 2B6 activity
Phase II • ↓ uridine diphosphate glucuronosyltransferase activity (UGTs 1/2) • ↓ N-acetyltransferase and alcohol dehydrogenase activity • ↑ xanthine oxidase activity	
Transport • ↓ P-glycoproteins, OCT2, OATP 1B1 and OATP 1B3	• ↑ exposure to substrates of P-glycoproteins (colchicine, dabigatran, digoxin) • Estrogens ↓ the regulation of OCT2 but ↑ the activity of P-glycoproteins
Excretion	
↓ renal blood flow, GFR rate, tubular secretion and/or reabsorption	• ↓ renal chloride with a slower mean elimination time in the excretion of drugs: ACE (atenolol, bisoprolol, nadolol, diuretics) • Differences are reduced when doses are adjusted for weight or creatinine Cl

Vd = volume of distribution. Cmax = maximum concentration. ACE = angiotensin-converting enzyme inhibitors. AED = adverse effects of drugs. CCB = calcium channel blockers. GFR = glomerular filtration rate. OCT2 = organic cation transporter 2. OATP = organic anion transporting polypeptides.

Figure 1: Sex-specific differences in pharmacokinetics (modified from 1-3).

Calcium channel blockers: calcium channel blockers (CCB) are a pharmacological group widely used in women. There are PK differences between verapamil and amlodipine *(Figure 1)*. A multicenter study (35% of women) showed that amlodipine was more effective in women older than 65. However, other extensive studies (ASCOT, CONVINCE, INVEST, Nifedipine-GITS, NORDIL, Syst-Eur, STOP-Hypertension) did not find SSD.[10] However, CCB have a more significant effect on reducing stroke than other antihypertensives in women.[11] Peripheral edema is the most common adverse effect and is even more common in older women.[1]

Beta-blockers (BB): propranolol and metoprolol are mainly metabolized by CYP2D6, which is more active in men, so women experience greater exposure with more possibility of adverse effects. There are no differences between carvedilol, atenolol, nebivolol, and nadolol.[8] BBs remain the drug of first choice in women with ischemic heart disease, heart failure with reduced ejection fraction, or atrial fibrillation. In addition, labetalol is the drug of choice in pregnant women with SAH.[11]

DIFFERENCES IN THE TREATMENT, ADHERENCE, AND CONTROL OF SAH

In a recent NCD risk factor collaboration[12] analysis of 1,201 populations analyzed in 2019, with 104 million participants, 59% of women reported a previous diagnosis of SAH vs. 49% of men. Women presented higher rates of treatment and control than men, and a similar behavior was observed in Latin America and the Caribbean, with even more marked differences *(Figure 2)*.

When age groups were analyzed, the behavior was opposite in older women with lower control rates than men and young and middle-aged women. In a Canadian study that examined the rates of treatment and control of SAH in women over ten years, a decline in diagnosis, treatment, and control rates was observed in the period analyzed, a fact that did not occur among men.[13] In the NHANES (2017-2020), the proportion of hypertensive adults with controlled BP is lower in women and only 23% vs. 38% of men older than 80 who presented controlled BP.[14] Whether this is due to biological factors, inappropriate

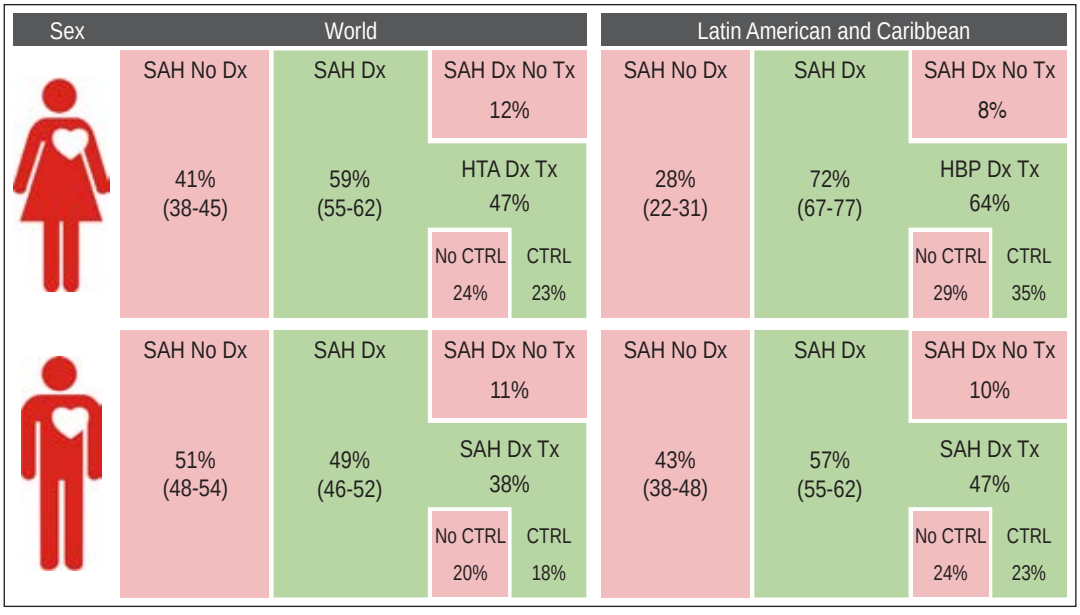

Figure 2: Diagnosis, treatment, and control of hypertension in men and women worldwide and in Latin American and Caribbean regions. Adapted from Zhou B et al.[12]

SAH = systemic arterial hypertension. Dx = diagnosis or diagnosed patient. No Dx = no diagnosis or undiagnosed patient. Tx = treatment or treated patient. No Tx = no treatment or untreated patient. CTRL = control or controlled patient, No CTRL = no control or uncontrol patient.

treatment (medical inertia, wrong choice of drug), lack of adherence, or a higher prevalence of comorbidities is unknown.

Regarding whether one family of antihypertensive drugs is better than another in treating hypertension in women, it is essential to mention that, despite many clinical studies, the specific data for women are limited and sometimes controversial. Until 2000, most studies were conducted mainly in middle-aged people and almost exclusively in men. They were not designed to have the statistical power to assess differences between the sexes. However, the results of these studies greatly influenced the recommendations of the leading clinical practice guidelines. Neverthless, there is a greater enrollment of women in recent studies, and under-representation persists, especially in women over 70, the age group where hypertension is more prevalent.

Furthermore, most SSD information comes from post-hoc analysis, which has limitations. On the other hand, SSD is usually analyzed dichotomously (men vs. women). Still, data on different sub-populations are unavailable, such as women of reproductive age, advanced age, or menopause-treated hormone replacement therapy.

Due to these limitations, more data is necessary to rule out the presence of SSD in the efficacy of antihypertensive agents in controlling SAH. This possibility exists and deserves further investigation.[1] In the guidelines for the primary prevention of CVD in women of the Inter-American Society of Cardiology, taking into account the pathophysiological mechanisms of hypertension in menopause, inhibition of the RAAS with ACE inhibitors or ARA II is suggested, with a grade of recommendation IIa and level of evidence C, since there is still no certainty from studies that more strongly support this recommendation.[15]

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Chapter 5

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Arterial hypertension throughout the life cycle of women: what factors influence it?

Hipertensión a través del ciclo de vida de la mujer: ¿qué factores influyen?

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Keywords:
arterial hypertension, woman, risk factors, life cycle.

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INTRODUCTION

Detection and timely managing cardiovascular risk factors (CVRF) reduce cardiovascular (CV) morbidity and mortality. Systemic arterial hypertension (SAH) is the main modifiable CVRF contributing to the global cardiovascular disease (CVD) burden due to ischemic heart disease being a leading cause of disability. Women represent ~51% of the hypertensive population and are at greater risk than men for acute myocardial infarction (AMI) and stroke.[1]

During the life cycle, women experience sex-linked changes, which increase the risk of SAH. They manifest from adolescence, early adulthood, reproductive stage, and menopause until late adulthood *(Figure 1)*. The prevalence of SAH is low in women during adolescence, youth, and young adulthood (20%), it increases towards the third decade of life and in perimenopause (40%). This increase is more notable at menopause or in the fifth decade of life (75%), when it exceeds men, being even more frequent after 75 years (85%). The impact on CVD is greater in women, since an increase of 10 mmHg in SBP increases the risk of CVD by 25%, compared to 15% in men.[2,3]

ADOLESCENCE AND EARLY ADULTHOOD

Women have lower blood pressure (BP) levels than men because of the effect of female sex hormones. Estrogens regulate the renin-angiotensin-aldosterone system (RAAS), reduce the activity of the angiotensin-converting enzyme (ACE), levels of angiotensin-2, endothelin, and the expression of its A and B types of receptors; 17β-estradiol increases nitric oxide synthase and decreases angiotensin 2 production, which leads to vasodilatation and decreased BP. The maximum estrogen peak in the luteal phase of the menstrual cycle coincides with a decrease in BP and should be considered in BP measurements.[2] Polycystic ovarian syndrome (PCOS) is a common cause of SAH in young women. Metabolic alterations and SAH, are related to a state of insulin resistance and overstimulation of the RAAS. Elevated levels of testosterone and hypothalamic hypoestrogenism, decrease vasodilation and increase BP levels. The prevalence of SAH in women with PCOS is 65%.[4,5] SAH in adolescents (12-18 years) and young adults (19-39 years) can be secondary to other etiologies such as fibromuscular dysplasia, rheumatological diseases (rheumatoid arthritis, vasculitis, Takayasu, systemic lupus erythematosus) and to the use of combined oral contraceptives (COC). The use of COC, mainly those containing medroxyprogesterone acetate or ethinylestradiol), can increase BP levels and may condition SAH by 5-10%; their use is not recommended in patients with uncontrolled BP (> 140/90 mmHg). Once therapy is installed, ambulatory BP measurements at least four times per week are recommended, with follow-up visits with their physician every four to six months. If there is an increase in BP, COC should be suspended and continued

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with non-hormonal contraception (condoms, spermicide, intrauterine device (IUD). The relative risk of SAH (RR 1.5) with COC has a reversible cumulative effect, wich increases by 13% for every five years of use; in most cases, BP returns to previous values three months after cessation. The increase in BP is related to a rise in hepatic production of angiotensinogen, activation of the RAAS, an increase in vascular resistance, and a decrease in circulating nitric oxide (NO).[2,6]

REPRODUCTIVE AGE

Hypertensive disorders of pregnancy (HDP) are characterized by systolic blood pressure (SBP) ≥ 140 mmHg and diastolic blood pressure (DBP) ≥ 90 mmHg and include chronic SAH, gestational SAH, preeclampsia/eclampsia, and chronic SAH with superimposed preeclampsia/eclampsia. They have an annual incidence of 5-10% and cause complications in the mother and the child. Endothelial dysfunction may persist after delivery. Women with a history of HDP, especially preeclampsia, have a higher risk of CV events and mortality (RR 2.0) during the subsequent ten years. BP generally subsides within two weeks of delivery and resolves in 12 weeks. If hypertension persists, the diagnosis of chronic hypertension should be considered.[7,8]

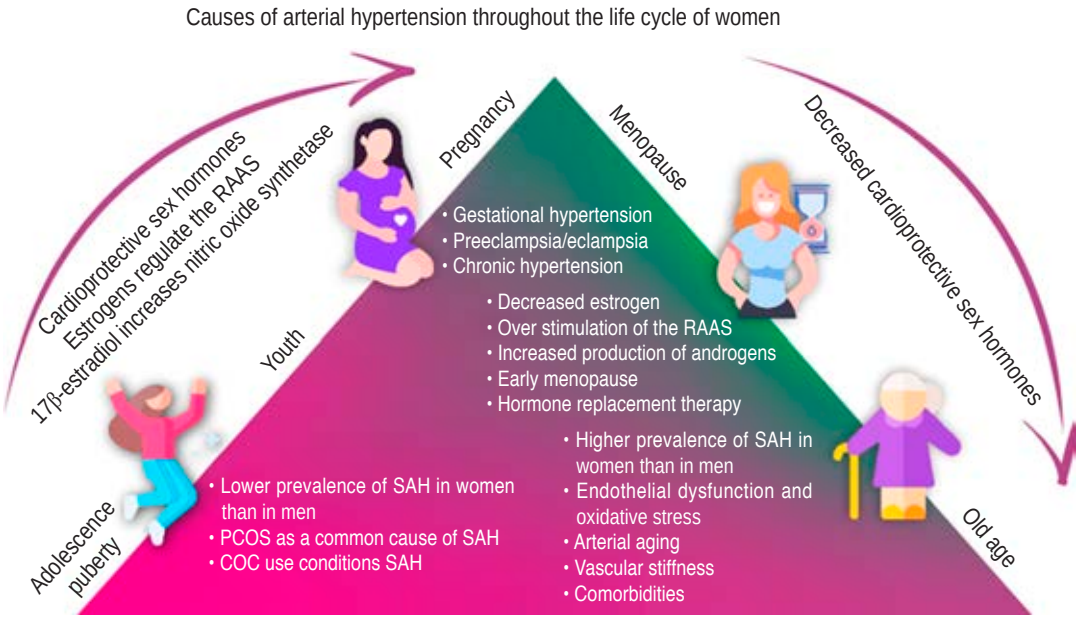
Women with assisted reproductive therapy have a greater susceptibility to presenting HDP (30.6%); the probability increases with twin or multiple pregnancies (13%) vs single pregnancy (6%). Compared with spontaneous conception, they have a higher risk of HDP and preeclampsia (RR 1.7 and 1.34, respectively), so, they must be followed up throughout their lives and estimated their CV risk.[2,9,10]

MENOPAUSE

In post-menopause, women have a higher prevalence of hypertension than same-age men. In addition to the hormonal factor (decrease in estrogen), genetics and other CVRF influence the elevation of BP. Likewise, there is overstimulation of the RAAS, vasoconstriction, and increased sensitivity to salt. Androgen production conditions increased arterial stiffness, vascular inflammation, and endothelial dysfunction. All these factors are related to increasing BP levels during this stage.[11] The testosterone/estradiol ratio increase is associated with an increased incidence of CVD (RR 2.0) and cardiovascular events.[12] Women with early menopause (< 45 years), whether natural or induced, have a higher risk of SAH compared to those with menopause at an expected age (> 45 years, RR 1.20, p = 0.03).[13]

Figure 1:

Causes of arterial hypertension throughout the life cycle of women. Different conditions influence the increase in blood pressure at different stages of life. SAH = systemic arterial hypertension. PCOS = polycystic ovary syndrome. COC = conjugated oral contraceptives. RAAS = renin-angiotensin-aldosterone system.



The effect of hormone replacement therapy (HRT) on BP elevation is controversial. There is evidence reporting an increase in SBP levels with the use of combined therapies (estrogens/progestins); however, other authors refer that the use of HRT does not modify BP.[12,14]

OLDER ADULTHOOD

The prevalence of SAH after age 65 is higher in women than men, 80-85% of women > 75 years are hypertensive. The associated factors are multiple: endothelial dysfunction, oxidative stress, vascular age, arterial stiffness, and other comorbidities. BP elevation is more severe and difficult to control, so management must be strict to avoid CV complications.[2,11]

CONCLUSIONS

SAH can be present throughout the different stages of a woman's life. The increase in BP is conditioned by sex-specific risk factors and other comorbidities, which vary according to age. These must be recognized and considered for proper management and control of BP to reduce CV complications and mortality.

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Chapter 6

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Polycystic ovaries as a cardiometabolic risk factor for arterial hypertension

Ovarios poliquísticos como factor de riesgo cardiometabólico para hipertensión arterial

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Keywords:
arterial hypertension, polycystic ovary syndrome, cardiovascular risk.

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INTRODUCTION

Polycystic ovarian syndrome (PCOS) is an endocrinopathy that affects women of reproductive age and is diagnosed when at least two of the following criteria are present: oligo or anovulation, hyperandrogenism, and ultrasound imaging of polycystic ovaries.[1]

PCOS has a prevalence of 4-8% worldwide; however, this may vary depending on the diagnostic criteria used (National Institutes of Health, Rotterdam, among others). In Mexico, PCOS has an estimated prevalence of 6% (95% CI 1.9-10.1).[2]

PCOS is frequently associated with obesity due to increased visceral fat, insulin resistance, type 2 diabetes (T2DM), systemic arterial hypertension (SAH), and metabolic syndrome, which lead to an increased cardiometabolic risk.[3]

Women with PCOS have a higher prevalence of SAH, reaching 5.5% vs. 2.0% of their peers without the disease.[4] Some studies have reported a prevalence of SAH of up to 30% in specific groups of women aged 20-34.[5]

The pathophysiology of PCOS includes epigenetic, environmental, and inflammatory factors, insulin resistance, oxidative stress, and obesity, which together may be associated with increased risk of SAH in women.[6]

PATHOPHYSIOLOGY

Women with PCOS present endocrine disorders characterized by an increase in the frequency of pulsatile secretion of luteinizing hormone (LH), follicle-stimulating hormone (FSH), hyperandrogenism, and increased secretion of gonadotropin-releasing hormone (GnRH), which consequently produces an absence of the late luteal and early follicular phase.[7]

On the other hand, androgens exert a negative feedback loop towards the pituitary, reducing the sensitivity to estrogens and progestogens and the frequency of pulsatile release of GnRH and inducing aromatization to estrogens.[7]

These endocrine disorders lead women to have impaired fertility, hyperandrogenism, obesity, insulin resistance, T2DM, dyslipidemia, endothelial dysfunction leading to peripheral vasoconstriction, increased peripheral resistance, and SAH.[8]

The etiology of SAH in women with PCOS is multifactorial, and various mechanisms have been proposed through which these hemodynamic changes are explained, such as obesity, alteration of the renin-angiotensin-aldosterone system (RAAS), proteinuria, and hyperandrogenism, among others *(Figure 1)*.[7-9]

Obesity is a common finding in women with PCOS and has a predominantly visceral distribution that exacerbates SAH and is associated with components of metabolic syndrome. Weight loss as the first line of treatment in these patients reduces hyperinsulinemia, insulin resistance, and hyperandrogenism.[8]

Regarding the renin-angiotensin-aldosterone system (RAAS) alteration, it

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has been shown that women with PCOS have elevated renin, angiotensin-converting enzyme (ACE), and angiotensin II levels. Visceral fat adipocytes produce high levels of angiotensinogen and contain high levels of androgens, causing RAAS overactivation. Evidence shows that angiotensin II type 1 receptor (AT1R) antagonists and type 2 receptor (AT2R) activation normalizes androgen levels by a not yet discovered mechanism.[8]

There is evidence in the literature suggesting elevated androgen levels also produce alterations in the cellular immune response and cytokine levels in association with a proinflammatory phenomenon such as occurs in cardiometabolic syndrome; these pathophysiological changes lead to endothelial dysfunction, oxidative stress, increased peripheral resistance, and kidney damage, all of which are factors that contribute to the pathophysiology of SAH.[9]

The role of the immune response and T lymphocytes in the pathogenesis of SAH and target organ damage has been established in clinical studies. In the case of women with PCOS, the combination of the inflammatory phenomenon induced by hyperandrogenism, immune activation, infiltration of T lymphocytes at the vascular level, and the imbalance of Th17/Treg cells can lead to vascular damage and nephropathy.[10]

Among the molecules involved in the pathophysiology of inflammation and immunity are reactive oxygen species, metalloproteinases, cytokines such as interleukin 6 (IL-6), interferon alpha (INF-α), and antibodies that lead to vascular damage (increased endothelial permeability, vasoconstriction, remodeling, and rarefaction) and renal (activation of sodium transporters, interstitial fibrosis, and glomerular damage).[10]

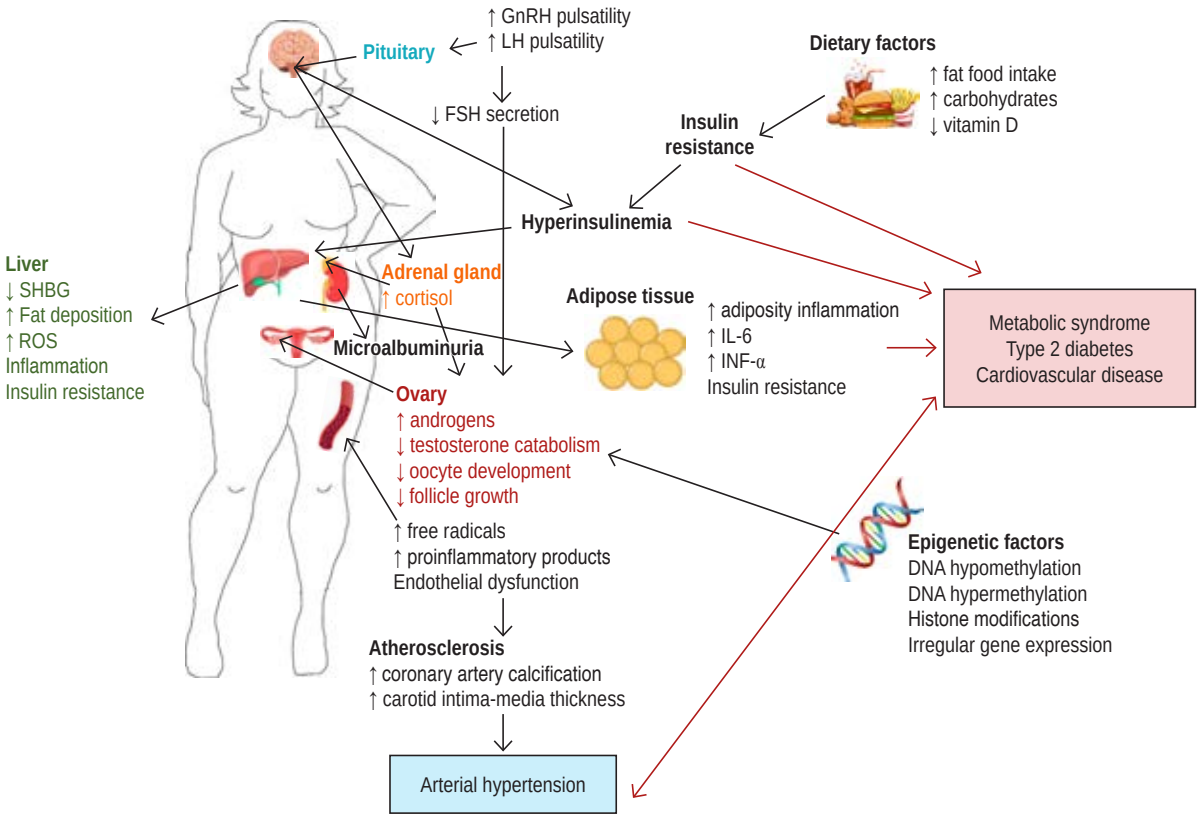

Figure 1: Pathophysiology of arterial hypertension in women with polycystic ovarian syndrome.
GnRH = gonadotropin-releasing hormone. LH = luteinizing hormone. FSH = follicle-stimulating hormone. SHBG = sex hormone binding globulin. ROS = reactive oxygen species. IL-6 = interleukin 6. INF-α = alpha Interferon.

CARDIOVASCULAR RISK

According to a meta-analysis, Anderson et al. demonstrate that young women with PCOS tend to have an increased risk of non-fatal stroke (OR 1.61; 95% CI 0.82-3.15) and coronary heart disease (OR 1.63; 95% CI 0.96-2.78). The higher prevalence of SAH, obesity, dyslipidemia, and cardiometabolic syndrome in women with PCOS explains this tendency.[11]

In postmenopause, the cardiovascular risk in women with PCOS and hypertension is practically the same compared to healthy women matched by age. In contrast, in premenopausal, the risk is higher (RR 1.7).[12]

Meta-analysis studies also confirm an increased risk of SAH in women with PCOS, but only in women of reproductive age; after menopause, having a history of PCOS may not be a significant predisposing factor for developing SAH.[12]

CONCLUSIONS

Early detection of cardiovascular risk factors in women with PCOS is essential for the prevention of cardiovascular outcomes (myocardial infarction, stroke, heart failure, cardiovascular death) because these women present chronic inflammation, endothelial dysfunction, oxidative stress, immune system disorders, kidney damage, hypertension, insulin resistance, and cardiometabolic syndrome.

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Chapter 7

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Hormonal contraception in women with hypertension

Anticoncepción hormonal en mujeres con hipertensión

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Keywords: hormonal contraception, arterial hypertension, cardiovascular disease, estrogen, progestin.

INTRODUCTION

Hormonal contraception (HC) is the method most used by women of reproductive age to avoid unplanned pregnancies.[1] Since its introduction in the decade of 1960, it is considered that 80% of women in the United States of America (USA) have used combined hormonal contraceptives (CHC) at some stage of their lives, more frequently those of oral administration, since their efficacy and relative safety allowed their widespread use.[2,3] CHCs increase blood pressure (BP) by 2 to 5% in previously normotensive women. With the use of second-generation CHCs, the observed increase in BP was 7-8 mmHg. Currently, the trend is towards using preparations with lower doses of estrogens and developing new progestin-only pills (POP) with a more significant margin of safety that can even decrease systolic BP in hypertensive women.[4,5]

HORMONAL CONTRACEPTION OVERVIEW

CHCs are estrogen and progestin preparations; progestin alone is the most used. According to the estrogen dose and the type of progestin, they are classified into four generations:

First generation: high-dose estrogen 150 µg and norethindrone, norethindrone acetate, or ethynediol diacetate.
Second generation: reduced the dose of estrogen to 50 µg and levonorgestrel (LNG).
Third generation: 20 to 35 µg estrogen doses and desogestrel or gestodene.
Fourth generation: maintains low doses of estrogen and drospirenone, a spironolactone analog, with anti-mineralocorticoid and antiandrogenic activity.[6]

POP contraceptives include injectable depot medroxyprogesterone acetate (DMPA), levonorgestrel-intrauterine device (LNG-IUD), and subdermal implant.[7]

CHARACTERISTICS OF THE WOMAN WITH SYSTEMIC ARTERIAL HYPERTENSION (SAH) WHO REQUIRE A CONTRACEPTIVE METHOD

Consulting for SAH in women is relatively common. In the USA, hypertension in women of reproductive age is increasing; it is reported that in approximately 1 of every four women. Less than half know their diagnosis, and only 10% receive treatment.[8] In Mexico, according to the 2021 National Health and Nutrition Survey (ENSANUT), the prevalence of SAH in women varies according to the age group: between 20-29 years, it is 5.2%; from 30-39 years, it is 9.8%, and in those between 40-49 years, it is up to 25.2%.[9] Choosing the correct contraceptive method for women with SAH is important because CHC increases BP, cerebrovascular event (STROKE) risk, and acute myocardial infarction (AMI). The American College of Gynecology and Obstetrics (ACOG) supports the USA Medical Eligibility Criteria for the Use of Contraceptives (USMEC)[10] and recommends considering four characteristics: a) age of the patient, with emphasis on women 35 years of age and older; b) risk factors for Cardiovascular Disease (CVD), it is necessary to investigate

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dyslipidemia, diabetes, overweight or obesity, smoking, physical activity and a family history of premature CVD; c) precise measurement of BP, to confirm the diagnosis of SAH and its classification; d) degree of hypertension.

Mortality in women between 35 and 44 who present a high rate of obesity, smoking, less physical activity, and increased CHC consumption is increasing.[11,12]

EFFECTS OF HORMONAL CONTRACEPTIVES ON HYPERTENSION

The effect of estrogens on BP is complex and can vary depending on the woman's age, health status, and hormonal balance. It is estimated that in women with SAH who use CHC, the relative risk of AMI is multiplied by 12 compared to those who do not use this method.[10] Women with established SAH who use CHC have a higher risk of stroke than normotensive non-users.[13] The use of POP contraceptives, as well as the copper IUD does not have a significant effect on BP or CVD risk.[10]

CHC act on BP through the renin-angiotensin-aldosterone system (RAAS), increasing hepatic production of angiotensinogen, and renal and adrenal production of renin and aldosterone, which causes an increase in sodium reabsorption and volume circulating with the subsequent elevation of BP *(Figure 1)*.[13,14]

On the other hand, possible pathways through which estrogens can induce BP elevation have been proposed, including activation of molecular signaling pathways such as endothelin-1 (ET-1) and accumulation of superoxide anions in the rostral ventrolateral medulla of the brain, as well as increased sensitivity and flow of calcium channels in smooth muscle cells mediated by the phosphorylation pathway of the myosin light chain (MLC) and the MLC kinase (CLMK) *(Figure 1)*.[14]

RECOMMENDATIONS FOR THE USE OF CONTRACEPTIVES IN WOMEN WITH SAH

The appropriate type of contraception for women with this comorbidity should consider the age and the severity of SAH. According to the USMEC guide, recommendations are classified into four categories *(Figure 2)*:

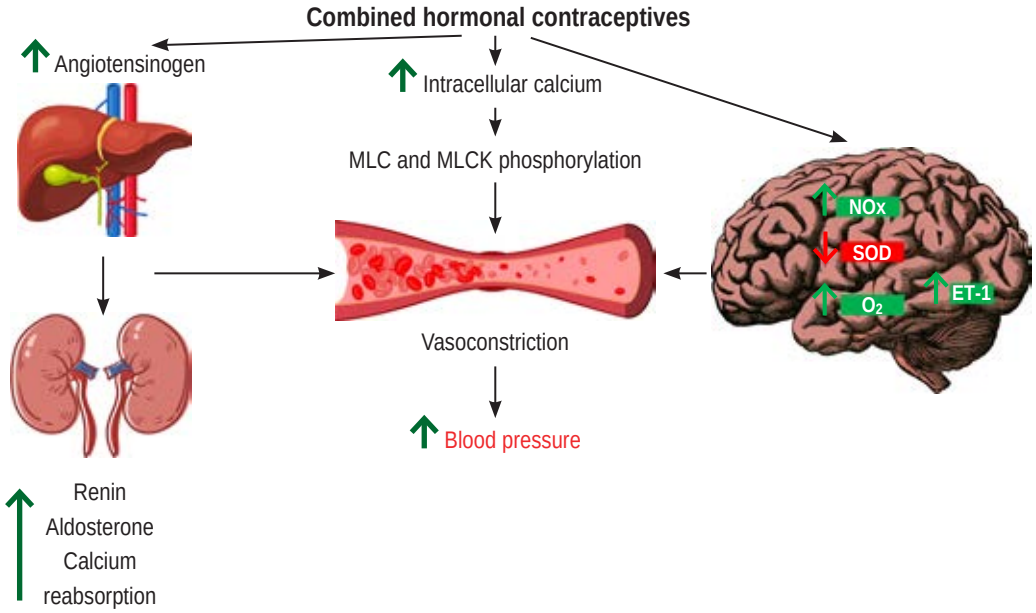

Figure 1: Effects of combined hormonal contraceptives on blood pressure. This scheme summarizes the mechanisms proposed at the systemic level generating vasoconstriction, causing elevation of blood pressure.
MLC = myosin light chain. MLCK = myosin light chain kinase. ET-1 = endothelin-1. NOx = oxides of nitrogen. SOD = superoxide dismutase.

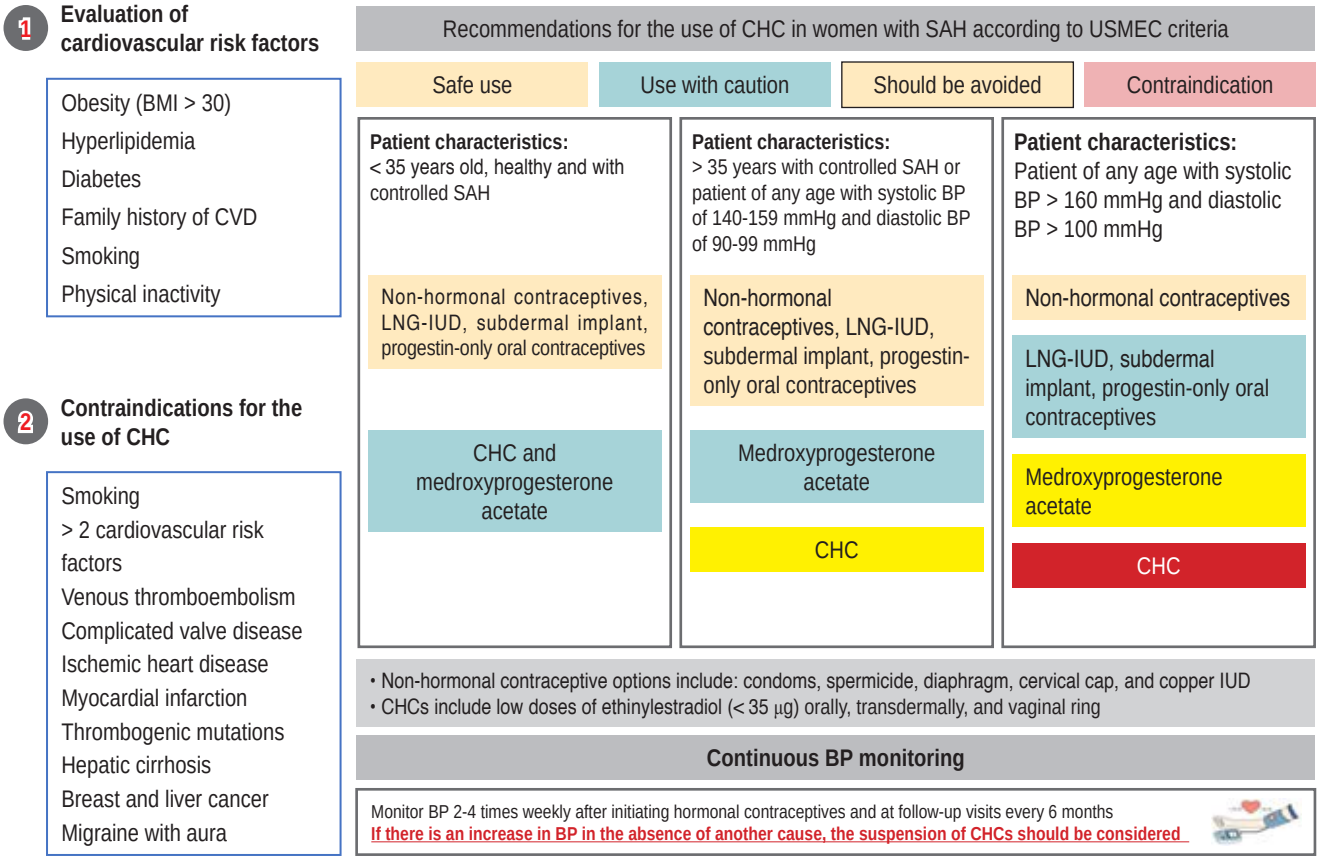

Figure 2: Recommendations for the use of CHC in women with SAH according to the USMEC criteria. Adapted from Shufelt C.[13]
CHC = combined hormonal contraceptives. CVD = cardiovascular disease. LNG-IUD = levonorgestrel intrauterine device. SAH = systemic arterial hypertension. BP = blood pressure. BMI = body mass index.

1. In healthy women under 35 years of age with controlled SAH, it is recommended to use non-hormonal contraceptives (condoms, spermicides, diaphragm, copper IUD), POP, LNG-IUD, and subdermal implant (**category 1**: safe use). If the patient does not accept or tolerate POP, CHC or DMPA is allowed (**category 2**: use with caution).[13]
2. Non-hormonal contraceptives, POP, LNG-IUD, and subdermal implant (**category 1**) are recommended in women over 35 years of age with controlled SAH or patients of any age with systolic pressure of 140-159 mmHg and diastolic pressure of 90-99 mmHg. CHC should be avoided (**category 3**).[10,15]
3. In patients of any age with systolic pressure ≥ 160 mmHg and diastolic pressure ≥ 100 mmHg, the recommendation is non-hormonal contraceptives (**category 1**), POP, LNG-IUD, and subdermal implant (**category 2**) may be recommended, DMPA should be avoided (**category 3**), CHC are contraindicated (**category 4**).[13,15]

Although few women develop SAH after starting CHC use, blood pressure at follow-up visits should be measured, and discontinuation of the hormonal method should be considered if blood pressure increases significantly without other apparent causes.[10]

CONCLUSIONS

SAH is common in women older than 35. In this group of patients, it is common to observe overweight, obesity, smoking, decreased physical activity, and other factors that increase

the risk of CVD. Even though the absolute risk is low, CHCs increase the risk of stroke and AMI in women with SAH, so choosing the appropriate contraceptive method is relevant. In women with SAH, the US medical eligibility criteria (USMEC) recommend using non-hormonal contraceptives, POP oral contraceptives, LNG-IUD, and subdermal implants. Further studies are required to understand the safety profiles of non-oral hormonal preparations and ultra-low dose in women with SAH.

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Chapter 8

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Hypertensive disorders of pregnancy as a risk factor for cardiovascular disease

Trastornos hipertensivos del embarazo como factor de riesgo para enfermedad cardiovascular

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Keywords:
arterial hypertension, pregnancy, cardiovascular risk.

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INTRODUCTION

It is estimated that 10% of pregnant women have hypertensive disorders of pregnancy (HDP), and the increased risk of maternal complications depends on the disorder's severity and other comorbidities. Women with a history of HDP have a higher risk of developing hypertension, diabetes, dyslipidemia, and cardiovascular disease.[1] International guidelines on cardiovascular prevention indicate close follow-up in the postpartum period and recognize preeclampsia as a risk factor specific to gender.[2]

HYPERTENSIVE DISORDERS OF PREGNANCY: DEFINITION AND EPIDEMIOLOGY

HDPs comprise different types of systemic arterial hypertension (SAH) that occur with pregnancy, manifesting for the first time during pregnancy or overlapping with a previous hypertensive condition *(Figure 1)*. Within the spectrum of HDP, preeclampsia is recognized as a condition associated with increased gestational mortality and long-term adverse maternal outcomes.

Cardiovascular disease and preeclampsia share similar risk factors, such as diabetes and obesity. An increase in the prevalence of HDP has been observed recently, conditioned by a more significant number of comorbidities in pregnant women and gestation at advanced age.[1]

PATHOPHYSIOLOGY

During pregnancy, hemodynamic changes characterized by increased intravascular volume and cardiac output occur, requiring cardiovascular adaptations. Preeclampsia may be a maladaptive process to these changes.[3] In preeclampsia, abnormal trophoblast implantation and a failed remodeling process of the myometrium spiral arteries occur, causing decreased blood supply to the placenta, which translates into placental ischemia, increased circulating angiogenic markers, endothelial dysfunction, vasoconstriction, oxidative stress, and micro embolism phenomena in the maternal vascular tree. The release of proinflammatory cytokines has also been proposed resulting from mechanisms mediated by «helper T» cells.[4]

Placental abnormalities in early pregnancy are associated with local ischemia and uteroplacental insufficiency; the release of these pro-inflammatory substances into the maternal circulation clinically translates into the early onset of hypertension and preeclampsia. Chronic oxidative stress due to pre-existing metabolic abnormalities such as diabetes or obesity increases the risk of late-onset preeclampsia.[5]

Given that HDPs such as gestational hypertension and preeclampsia have a two-fold increased risk of developing cardiovascular disease, it is important to follow up with medical care since this CV risk is favored by

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underlying risk factors and factors typical of HDPs. According to the guidelines of the American Heart Association (AHA) and the National Institute for Health and Care Excellence, women should be given medical follow-up through an assessment six to eight weeks after delivery, considering; the measurement of blood pressure (BP), weight, and promoting changes towards healthy habits and monitoring serum glucose, lipids, and BP every year until the woman reaches 50 years of age is also advised.[1]

In women with a history of preeclampsia, chronic SAH, and later dyslipidemia develop earlier than those with a normotensive pregnancy.[1] The AHA and American College of Cardiology support the fact that preeclampsia is a factor that increases the risk of hypercholesterolemia.[6]

CVD risk increases if associated factors, including diabetes mellitus, obesity, and advanced maternal age, are present. A complicated pregnancy is considered to «mask» the woman with pre-existing CV risk factors. Various meta-analyses have shown that 32% of women with HDP develop chronic SAH in the first ten years after pregnancy, compared to 11% of women with normotensive pregnancies. The risk of chronic SAH is related to the number of pregnancies with HDP effects.[7]

Regarding women who present HDP at the age of 35, the Number Needed for Detection (NNT) for a diagnosis of a woman with chronic SAH is 9; at 39 years, the NNT for a diagnosis of dyslipidemia is 18, and between 50-55 years, the NNT for diagnosis of diabetes is 22.[1]

It is recommended that all women with HDP undergo evaluation of risk factors (RF); the period between pregnancy and the appearance of RF should be considered an opportunity to make changes towards a healthy lifestyle and reduce the appearance of cardiovascular disease.

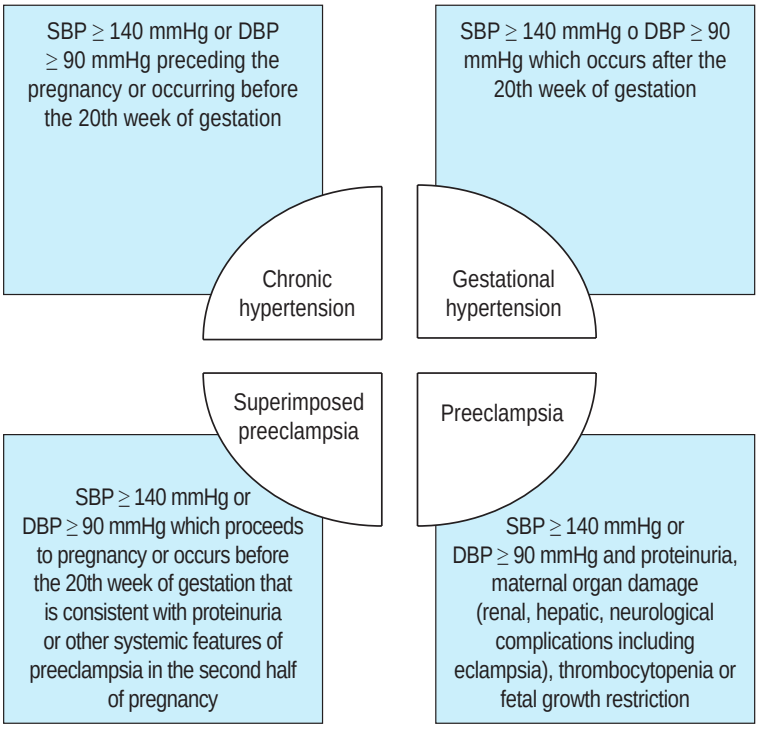

Figure 1: Hypertensive disorders in pregnancy.
SBP = systolic blood pressure. DBP = diastolic blood pressure.

CONCLUSIONS

HDPs are a relatively common complication during pregnancy; they are associated with early and late complications that increase the risk of cardiovascular disease, mainly chronic arterial hypertension. It is necessary to carry out a long-term monitoring of BP and metabolic evaluation after delivery for its detection and timely treatment, as well as to implement strategies with changes in lifestyle and weight control.

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Chapter 9

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INOCA and microvascular angina in hypertensive women

INOCA y angina microvascular en la mujer hipertensa

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Keywords:
INOCA in women, arterial hypertension, microvascular dysfunction, invasive studies, non-invasive studies.

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INTRODUCTION

Ischemic heart disease remains women's most common cardiovascular disease, accounting for one-third of all deaths. Myocardial ischemia can be caused by obstructive or non-obstructive atherosclerotic coronary disease, the latter known by its acronym INOCA (Ischemia with Non-Obstructive Coronary Artery disease), which includes non-significant epicardial coronary disease (< 50% stenosis), macro or microvascular coronary dysfunction (CMD), coronary artery spasm (CAS) and spontaneous coronary dissection.[1] Until now, it has been underdiagnosed due to the underutilization of functional studies evaluating microcirculatory or vasomotor disorders. It is estimated that 70% of patients with angina undergoing coronary angiography have INOCA. In the United States, they are around 3 to 4 million persons with this condition, and more than 60% correspond to women.[1,2] Women with INOCA are about four times more likely than men to have readmissions and cardiovascular mortality up to 32%.[3,4]

PATHOPHYSIOLOGY

The pathophysiology of INOCA is multifactorial, not yet fully clarified, and shares the same traditional risk factors associated with coronary atherosclerosis. Systemic arterial hypertension (SAH) is the most prevalent factor in 45 to 59% of cases.[4,5] The development of secondary left ventricular hypertrophy (LVH) is associated with symptomatic myocardial ischemia even without coronary lesions.[6] Bairey Merz et al[3] reported that SAH can also influence myocardial perfusion through vasomotor alterations, endothelial dysfunction (ED), atherosclerosis, and poor vascular autoregulation capacity due to remodeling or hardening of the coronary microvasculature, which together with the deregulation of the aortic-ventricular coupling and subendocardial hypoperfusion contribute to CMD.[6] Different studies have shown that ED includes attenuation of endothelium-dependent vasodilation due to reduced bioavailability of nitric oxide (NO) and increased vasoconstrictor response of endothelin-1 (ET-1), prostaglandin H2 and thromboxane A2, in porcine models.[7] Additionally, the increase in aortic stiffness is associated with an increase in systolic blood pressure (SBP) and a decrease in diastolic blood pressure (DBP), which leads to an increase in left ventricular afterload and oxygen demand, with subsequent derived ischemia of the reduction of the diastolic perfusion pressure of the myocardium.[8]

CLINICAL PICTURE

The most frequent symptom is angina, which unlike the typical presentation in obstructive coronary disease, in INOCA, is less intense and with different patterns and location variations. It is more frequently associated with dyspnea, nausea, weakness, fatigue, jaw pain, and intense tiredness, sometimes disabling. Angina can occur during stressful situations or at rest.

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The aggregation of several comorbidities is less frequent.[9] Uncontrolled BP accelerates structural and functional changes in blood vessels, which can potentially trigger myocardial ischemia events.

DIAGNOSIS

It is necessary to assess coronary vascular function to define pathophysiology with invasive or non-invasive diagnostic tests *(Table 1)*, according to the clinical context, risk factors, availability of resources, operator experience, and with the following criteria *(Figure 1)*:[1,10]

1. Clinical picture and objective evidence of ischemia.
2. Coronaries without significant obstructive lesions and fractional flow reserve (FFR) > 0.80.
3. Coronary flow changes: coronary flow reserve (CFR) < 2.0 in response to a vasodilator (adenosine), evidence of coronary spasm with acetylcholine (ACh) or

Table 1: Diagnostic methods in INOCA according to the pathophysiological mechanisms.

Pathophysiological mechanism	Diagnostic method
Atherosclerotic lesions and their characteristics • Plaque erosion (acute thrombosis in the presence of an intact fibrous cap) • Plaque ulceration (atherosclerotic plaque ulceration with superimposed thrombus) • TIMI frame count	AngioCT, OCT, IVUS
Coronary microvascular dysfunction • FFR > 0.8 • CFR < 2.0 • IMR ≥ 25	Functional tests with adenosine: FFR, CFR, IMR, angiography + diagnostic guide, PET, AngioTC, RMC in stress TTE dipyridamole stress Doppler
Epicardial coronary spasm • Luminal diameter reduction ≥ 90% • Angina • ECG changes suggestive of ischemia	Coronary angiography, ACh test, resolution with IC-NTG
Coronary embolism/thrombosis • Presentation as ACS • Filling defects with partial or total occlusion of the vessel lumen • Floating filling defect in the lumen with the passage of contrast medium on both sides of the defect	Coronary angiography, IVUS, OCT, search for hypercoagulable states, Holter (AF)
Spontaneous coronary dissection • Presentation as ACS or shock, in a young woman • Multiple radiolucent lumens and extraluminal contrast staining • Obstruction of the coronary artery by IMH • Intima disruption	Coronary angiography, OCT, IVUS
Contribution/demand mismatch • Angina or equivalent • ECG changes suggestive of ischemia • Evaluation of the mass index (LVH)	Identifying triggering factors: stress, pregnancy, anemia, thyrotoxicosis, inflammatory or connective tissue diseases, and others TTE and stress test

Data can be found in the diagnostic methods according to each pathophysiological mechanism.
OCT = optical coherence tomography. IVUS = intravascular ultrasound. AngioCT = coronary angiotomography. PET = positron emission tomography. ACh = acetylcholine. IC-NTG = intracoronary nitroglycerin. FFR = fractional flow reserve. CFR = coronary flow reserve. IMR = index of microcirculatory resistance. TTE = transthoracic echocardiogram. ECG = electrocardiogram. IMH = intramural hematoma. ACS = acute coronary syndrome. AF = atrial fibrillation. LVH = left ventricular hypertrophy.

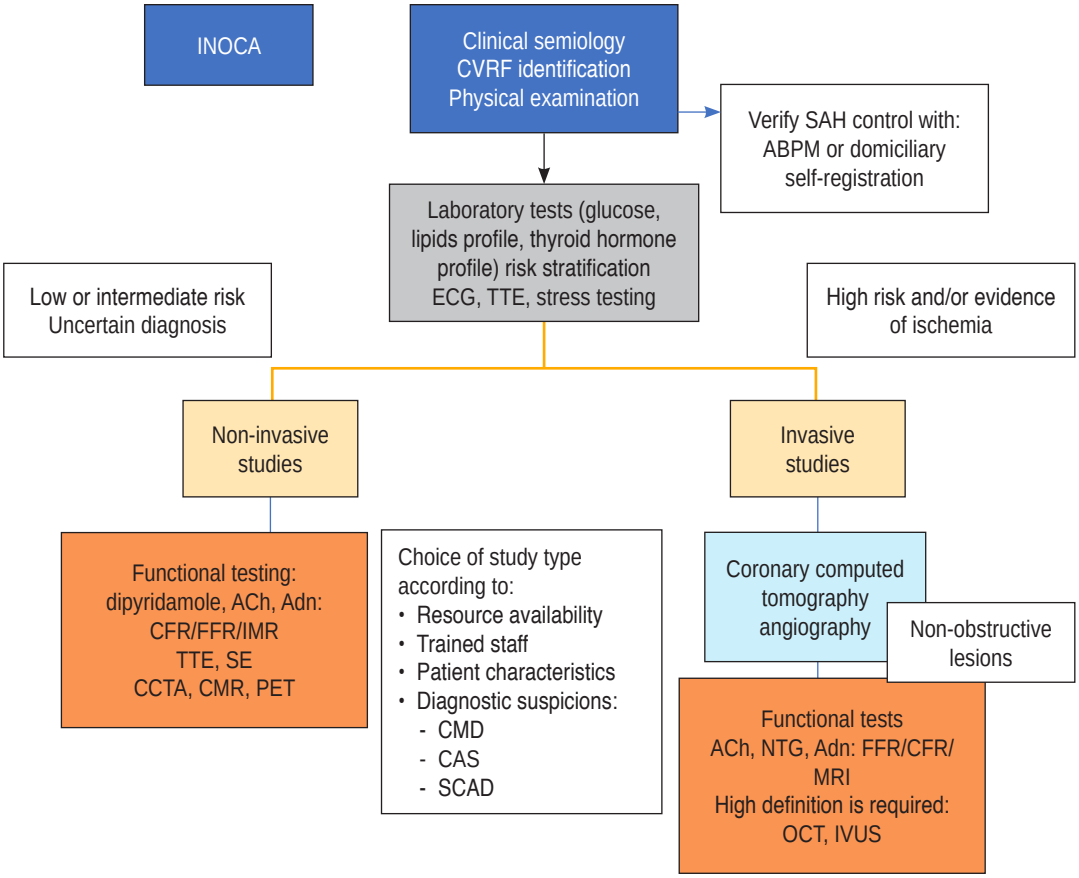

Figure 1: Flowchart for the evaluation of hypertensive patients with INOCA. Diagnostic evaluation of patients with a suspected diagnosis of INOCA.

CVRF = cardiovascular risk factors. SAH = systemic arterial hypertension. ABPM = ambulatory blood pressure monitoring. ECG = electrocardiogram. TTE = transthoracic echocardiogram. CMR = cardiac magnetic resonance. PET = positron emission tomography. CTA = coronary angiotomography. ACh = acetylcholine. Adn = adenosine. NTG = nitroglycerin. FFR = fractional flow reserve. CFR = coronary flow reserve. MRI = microcirculatory resistance index. OCT = optical coherence tomography. IVUS = intravascular ultrasound. CMD = coronary microvascular dysfunction. CAS = coronary artery spasm. SCAD = spontaneous coronary artery dissection. SE = stress echocardiography.

TIMI (thrombolysis in myocardial infarction) flow change frame count (> 3 beats for vessel filling at rest).

NON-INVASIVE METHODS

The transthoracic echocardiogram (TTE) evaluates the degree of LVH. The velocity of the coronary flow can also be measured through pulsed wave Doppler in the coronary artery at rest and after the administration of dipyridamole. Using this method, the iPOWER study demonstrated that 26% of women with INOCA had changes in FRC velocity < 2.0.[11] Functional studies with coronary tomography angiography (CT angiography) and cardiac magnetic resonance imaging (CMR) of stress with dobutamine or adenosine allow detection of alterations in subendocardial perfusion in patients with INOCA, calculating the myocardial perfusion reserve index and the index of microcirculatory resistance (IRM) (≥ 25 U is indicative of CMD).[1,10] Positron emission tomography (PET) helps evaluate CFR, calculating the ratio of coronary myocardial flow during adenosine induction of maximal hyperemia and at rest.

INVASIVE METHODS

Angiography is the gold standard. If significant coronary lesions are not observed, it is indicated to assess coronary flow and the arteries' diameter with endothelium-dependent tests such as acetylcholine (Ach) and with endothelium-independent tests such as adenosine and nitroglycerin, the CFR, the IMR, and the FFR.

Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) allow the evaluation of vascular remodeling and morphology with functional studies. OCT has been shown to have prognostic value when linked to the assessment of adventitial vasa vasorum and intraplaque neo-vessels to indices of microvascular spasm, epicardial spasm, and IMR in patients with INOCA.[12]

TREATMENT

Maintaining strict BP control, secondary prevention with lifestyle modifications, cardiac rehabilitation, and drug treatment is essential. However, most of the pharmacological recommendations are based on observational studies with inconsistent results, and to date, the underuse of drugs in adherence to the guidelines has been observed. Pauly et al. reported that administering quinapril compared with a placebo for 16 weeks improved CFR and symptoms.[13] In another study in patients with SAH, administration of perindopril for one year produced regression of periarteriolar fibrosis and increased CFR.[14] In patients with abnormal vasodilator reserve or CD, calcium antagonists improve exercise tolerance and symptoms. An observational analysis showed that statins, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and beta-blockers significantly reduced major cardiovascular events and heart failure.[15] Dual antiplatelet therapy without thrombi, coronary embolism, and ulcerated or eroded plaques is controversial and has not shown risk reduction.[10]

CONCLUSIONS

SAH is a highly prevalent CVRF in patients with INOCA and contributes to CMD, so its control is essential to reduce ischemia events. Diagnosis should include vascular function tests, and specific treatment should be established based on the phenotyping of the patient with INOCA.

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Chapter 10

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Chronic kidney disease in women with a history of hypertensive disorders of pregnancy

Enfermedad renal crónica en la mujer con antecedente de enfermedad hipertensiva del embarazo

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Keywords:
hypertensive disorders, pregnancy, chronic kidney disease, arterial hypertension, preeclampsia.

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INTRODUCTION

Chronic kidney disease (CKD) is a significant health problem, increasing exponentially in Mexico and Latin America (LATAM). The biological characteristics that regulate the life cycle of women are characterized by the interrelationship of various traditional and sex-specific cardiovascular (CV) risk factors, which combine to favor hypertensive disorders of pregnancy (HDP), where the transient and long-term kidney disease, complicate the CV health of women in later years. A history of HDP increases the risk of CKD, especially in women with comorbidities such as diabetes and high blood pressure (HBP), recognized as the main causes of chronic renal failure (CKD) worldwide.

EPIDEMIOLOGICAL ASPECTS OF CKD AND HDP IN MEXICO AND LATAM

In Mexico, it is estimated that approximately 11% of the population has CKD, equivalent to 13 million people, while in South America, the prevalence is between 7-13%. The incidence is approximately 1,142 cases/million inhabitants, and CKD mortality is about 9.14% and ranks 6th among the causes of death in Latin America.[1] In Mexico, the *Instituto Mexicano del Seguro Social* is the public institution that cares for most kidney patients. Caring for patients in substitution therapy costs approximately 25,700 million pesos (1,427.77 million USD) annually.[2]

HDP is the general term to describe various diseases characterized by hypertension and kidney damage. Includes preeclampsia, gestational hypertension, superimposed preeclampsia, and chronic HBP.[3] The clinical definition is summarized in *Table 1*. HDP continues to cause maternal and fetal mortality in low-income countries and the first world. They generate approximately 50,000 maternal deaths and 900,000 perinatal deaths and represent a predisposition for the development of CV complications in the future.[4] Worldwide, its incidence is 5-10%, the most prevalent being gestational hypertension and preeclampsia. This incidence depends on whether the event is analyzed by pregnancy or by the affected woman. In the first case, the incidence is around 7.3%; in the second, it rises to 15.3%.[5] The sub-analysis of the may measurement month (MMM) 2019 campaign in the States of Mexico and Michoacán, included 5,901 adults, of whom 77.5% were women. 14.5% of the women reported having had HDP, 16.4% continued to be hypertensive with antihypertensive treatment, and 8.3% were unaware that they were hypertensive and were detected in the campaign.[6]

LONG-TERM CARDIOVASCULAR INVOLVEMENT ASSOCIATED WITH HDP

HDP is considered a CV risk factor for the development of stroke and CV disease, particularly gestational hypertension, and preeclampsia, since they double the risk

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of developing cardiovascular disease in a woman, especially in those who achieve pregnancy despite living with hypertension, CKD, dyslipidemia, diabetes, and subclinical atherosclerosis. Recent studies have reported that coronary heart disease risk ratio (HR) is 1.89 (95% CI, 1.26-2.82), for stroke 2.27 (95% CI, 1.37-3.76), arrhythmias 1.62 (95% CI, 1.28-2.05), CKD 2.41(95% CI, 1.54-3.78) and for combined morbidities of 1.25 (95% CI, 1.15-1.35. The Relative Risk (RR) for a peripheral arterial disease is 1.87, and it increases considerably the more early the HDP is presented.[5] The most relevant mechanisms involved are: 1) pregnancy induces CV risk; 2) genetic predisposition before pregnancy; 3) combination of both factors. The delay in the first pregnancy is the common denominator, especially in developed countries. Maternal comorbidities such as obesity, a family history of hypertension, gestational diabetes, multiple pregnancies, and rheumatic, autoimmune, renal, or hematological diseases are other associated factors. Likewise, it has been described that African-American women with a previous history of preeclampsia or hydatidiform mole and a low socioeconomic level are particularly susceptible to presenting preeclampsia.[7,8]

The problem is of such magnitude that recently, International Societies included HDP as part of the CV risk factors for women, encouraging physicians to stratify CV risk in the immediate postpartum period and to implement the best strategy to care for the CV health of women with a history of HDP. At least during the first five years of BP, lipids, and glucose, annual monitoring is part of primary care.

LONG-TERM RENAL INVOLVEMENT IN WOMEN WITH A HISTORY OF HDP

Several studies have established that HDP impacts long-term renal function, regardless of whether the woman was already living with chronic SAH. Malek et al., in the United States of America,[9] evaluated the incidence of CKD in 391,838 women 14 years postpartum. 0.4% lived with chronic SAH, 16.3% had HDP, and 2.5% had chronic SAH and superimposed HDP, particularly preeclampsia. Fourteen years after delivery, both non-Hispanic black and white women with chronic SAH or HDP during pregnancy had a higher incidence of CKD five years after delivery (black HR 2.30 (95% CI, 1.94-2.73); whites HR 1.97 (95% CI, 1.64-2.37).

Table 1: Clinical definition of hypertensive disease of pregnancy (HDP).

	Definition
Preeclampsia (1)/ eclampsia (2)	1. SBP elevation ≥ 140 mmHg or DBP ≥ 90 mmHg after 20 weeks of gestation, accompanied by any of the following clinical data: a) proteinuria ≥ 300 mg/day or ≥ 1 g/L per test strip; b) organic dysfunction of any of the maternal organs: kidney, liver, brain and hematological system; c) fetal growth restriction 2. Presence of unexplained generalized seizures in patients with preeclampsia
Gestational hypertension	Elevated SBP ≥ 140 mmHg or DBP ≥ 90 mmHg after 20 weeks of gestation without any systemic complications
Chronic hypertension added to preeclampsia	It is the development of preeclampsia or eclampsia in a woman with pre-existing chronic SAH
Chronic hypertension	SBP ≥ 140 mmHg or DBP ≥ 90 mmHg before pregnancy or before the 20th week of pregnancy, or when blood pressure does not return to normal within 12 weeks postpartum, associated or not with proteinuria

SAH = systemic arterial hypertension. SBP = systolic blood pressure. DBP = diastolic blood pressure. mmHg = millimeters of mercury.
Adapted from Brown MA et al.[3]

In hypertensives with superimposed HDP, black women had the highest risk: HR 3.88 (95% CI, 3.05-4.93) vs. white women HR 1.86 (95% CI, 1.20-2.87, $p < 0.003$). Clinical criteria for CKD diagnosis in these studies could be met five years after delivery.[10,11] Ishaku et al.[12] prospectively measured changes in estimated glomerular filtration rate (eGFR) at nine weeks, six months, and one year after delivery in 488 women in Nigeria, of whom 418 developed HDP. Considering an eGFR < 60 mL/min/1.73 m^2, women with HDP had a CKD prevalence of 7.6%. The older age of the woman was a statistically significant factor for the deterioration of the eGFR. Sandvik et al.'s meta-analysis of Norwegian[13] women with preeclampsia did not show any 10-year markers of renal damage (albuminuria and changes in eGFR). The eGFR remained within ranges considered normal according to the definitions of the time (average of 107 mL/min/1.73 m^2). The authors consider that the surprise of these results is due to the characteristics of the sample studied, which are unique in that region of the world.

In Mexico, the risk factors for CKD in women with a history of HDP are highly prevalent: pregnancy at extreme ages, poverty that hinders access to medical services, traditional CV risk factors that are increasing, and the non-modifiable influence of genetic factors are a call to attention.

CONCLUSIONS

HDP increases cardiovascular risk and the risk of presenting CKD in the future, particularly in women with comorbidities such as chronic hypertension. The other traditional CV risk factors, such as overweight, obesity, and diabetes, increase the probability of presenting HDP and future CV complications and CKD. This vicious circle requires specific actions ranging from identifying and monitoring renal function and metabolic profile at least during the first five years after delivery and raising awareness of the importance of modifying traditional CV risk factors throughout life.

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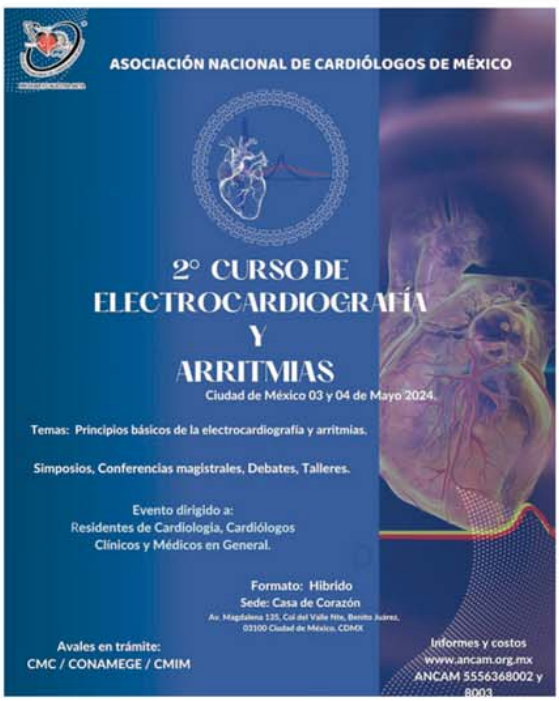

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