ISSN 1669-9106

SUPPLEMENT

MEDICINA (Buenos Aires) 2023; Vol. 83 (Suppl. I): 36-41

CARDIOVASCULAR DISEASE IN WOMEN

VIRGINIA SALAZAR MATOS, TATIANA ESPINOSA, JORGE GONZÁLEZ RUIZ DÍAZ, SANTIAGO CARRASCO, ADRIANA ROMANI, LOURDES ESCALERA, RODOLFO PALENCIA DÍAZ

Current state of knowledge

Cardiovascular diseases (CVD) are the leading causes of death globally for both men and women. Despite this stark reality, the risk of CVD in women is often underestimated and undervalued, leading to a common misconception. Many women are unaware that ischemic heart disease is their primary health concern[1].

The endothelium plays a critical role in maintaining vascular tone and blood flow. When endothelial dysfunction occurs, it triggers an inflammatory cascade, leading to the production of prothrombotic factors and vasoconstriction, thereby increasing the risk of developing CVD[2]. The endothelium is responsive to the vasodilatory properties of estrogens. However, when estrogen levels decrease post-menopause, arterial stiffness and atherosclerotic disease gradually develop, escalating cardiovascular risk (CVR) in women[3,4]. Notably, endothelial function begins to decline during perimenopause, even before signs of subclinical atherosclerosis appear[5].

Atypical chest pain and dyspnea are the most common cardiac symptoms in women, often mistaken for menopausal symptoms. Women with atypical chest pain syndrome face a two-fold increased risk of experiencing an ischemic cardiac event within the next [5-7] years[6]. While the prevalence of CVD is lower in women than in men, women have a higher mortality rate due to cardiovascular issues across all age groups, and their prognosis is generally poorer[7].

Obstructive coronary artery disease manifests 7-10 years later in women than in men, with women presenting less focal coronary stenosis at any age[8]. Women have a lower plaque burden, fewer vascular calcifications, and a more diffuse pattern of atherosclerosis compared to men[9]. Coronary vasomotor disorders are the primary cause of ischemic disease in middle-aged women[10]. Women experience more angina but have less severe and extensive ischemic disease than men[11].

Hormonal changes in menopausal women are often linked to changes in body fat, which tends to increase predominantly in the central and visceral region, accompanied by a decrease in lean mass. Chronic inflammation and the ensuing oxidative stress heighten insulin resistance in these patients[12].

It is now recognized that there are distinct cardiovascular risk factors (CVRF) in men and women, both in terms of their prevalence and their impact and treatment. For instance, women with acute coronary syndrome are typically older than men, and more likely to be hypertensive, diabetic, have hypercholesterolemia, and have a history of angina, heart failure, and cerebrovascular disease[13].

Traditional CVRF are well established and common across the population; however, some pose a greater risk of CVD for women, such as diabetes and tobacco use. There are emerging or unconventional CVRF, some of which exhibit different behaviors in women, such as depression, stress, autoimmune diseases, and undergoing cancer treatment. Lastly, there are specific CVRF unique to women, which are detailed below[14].

- Age of menarche
- Premature ovarian insufficiency
- Hormonal contraceptives use.
- Polycystic ovarian syndrome
- Adverse pregnancy outcomes
  - Hypertensive disorders of pregnancy (HDP), childbirth preterm and low birth weight
  - Gestational diabetes
- Menopause

AGE AT MENARCHE

The onset of puberty, particularly early menarche occurring in children under 11 years of age, is gaining increasing recognition as a significant CVRF.

Risks

It has been shown that there is a significant increase in the risk of CVD such as ischemic heart disease, development of CVRF, and non-cardiac diseases in patients with early menarche. In these young women, there is a greater risk of obesity, high blood (BP) pressure and metabolic disorders such as glucose intolerance, increased abdominal adiposity and insulin resistance in adulthood[15,16].

Additionally, there is an increase in the risk of osteoporosis, fractures in lumbar spine and hip, as well as anxiety and depression disorders in adolescents[17].

Recommendations

The recommendation is to investigate the medical history, specifically the age of onset of menarche, with the aim of recognizing and intervening early on associated CVRF[1].

Encourage these young individuals to adopt a healthy lifestyle, including a diet rich in fruits, vegetables, cereals, and fish, while limiting the consumption of alcohol. Additionally, they should engage in physical activity for 150-300 minutes per week at moderate intensity, incorporating muscle strengthening activities twice a week, and avoiding tobacco consumption. All these measures contribute to cardiovascular primary prevention[1].

PREMATURE OVARIAN INSUFFICIENCY (POI)

This condition is characterized by the loss of ovarian function before the age of 40, leading to amenorrhea, hypoestrogenism, and elevated levels of follicle-stimulating hormone (FSH). It affects 1 in 100 women. It can be genetic, infectious, or linked to environmental factors, or induced by radiotherapy, chemotherapy, or surgical procedures.

Risks

Patients with untreated POI have a higher risk of osteoporosis, autoimmune disorders, infertility, psychological disorders, CVD, and all-cause mortality, reducing quality and life expectancy[18].

Patients with POI and early menopause have a 50% higher CVR[19,20]. POI is an independent CVRF, since there is a greater risk of endothelial dysfunction, cardiac autonomic dysfunction, and metabolic alterations as insulin resistance and dyslipidemia. These patients have a higher body mass index (BMI) and altered lipid profile compared to women of the same age[21].

Recommendations

The identification of patients with POI offers an opportunity for the prevention and detection of CVD. For this reason, advice should be offered on CVRF, the need to maintain a healthy diet, engage in regular physical activity, maintain adequate body weight, and avoid tobacco use.

The CVRF must be evaluated annually in the women with POI and early menopause.

Hormone replacement therapy (HRT) is recommended for the alleviation of symptoms associated with hypoestrogenism. Initiating HRT early has demonstrated effectiveness in the primary prevention of CVD, osteoporosis, and cognitive decline. It is advisable to continue this therapy until reaching the typical age of menopause[22].

The beneficial impacts of HRT on CVRF hinge on factors such as dosage, timing of administration, and whether it is administered as monotherapy or in combination with progestogens. In patients undergoing HRT, particular attention should be given to promoting smoking cessation due to the elevated risks of heart attack and thrombosis[1].

The decision to employ HRT should be personalized, considering the patient's preferences, and carefully weighing the cardiovascular benefits against the potential risks of thrombotic events or breast cancer[22].

USE OF HORMONAL CONTRACEPTIVES

The estrogen plus progestin therapy (ethinylestradiol plus progestin) is an effective and globally accepted contraceptive method. Since its inception in 1960, its association with a heightened risk of cardiovascular events (ECV) has been recognized, attributed to its procoagulant effect, activation of the renin-angiotensin system (RAS), endothelial dysfunction, and oxidative stress. Combined formulations with low doses of ethinylestradiol have mitigated the risk of cardiovascular events. A Danish study demonstrated that the use of combined oral contraceptives (OC) containing 20 µg of ethinyl estradiol increases the relative risk by 1.60 (95% CI 1.37-1.86) for thrombotic ECV and by 1.40 (95% CI 1.07-1.81) for myocardial infarction (MI) compared to non-users of OC[23].

Risks

The use of the combined contraceptive pill may increase the risk of venous thrombosis, acute myocardial infarction, and CVD in users, especially those who are smokers[24].

Likewise, OC consumption is associated with elevated BP due to an increased production of angiotensinogen/angiotensin II; increased glycemia and alteration in lipids (increase in LDL and triglycerides, decrease in HDL)[25]. On the contrary, contraceptives that only contain progestin are not associated with increased vascular or venous risk; therefore, in women with high CVR, they can be prescribed orally, subcutaneously or intrauterine[26].

Recommendations

It is recommended that OC containing ethinyl estradiol should be avoided in women with a history of venous thromboembolism, CVD, or any other peripheral arterial disease. Furthermore, there are also contraindicated in those over 35 years of age, smokers and with severe dyslipidemia or obesity[27].

Women under 35 years of age with controlled pre-existing arterial hypertension can use OC, and regular BP control is advisable[28]. Progestin-only contraceptives may be recommended in women at high CV risk[29].

POLYCYSTIC OVARY SYNDROME (PCOS)

It is a common endocrinological alteration in women of reproductive age that is characterized by irregular or anovulatory menstrual cycles (ovarian dysfunction), polycystic ovaries and hyperandrogenism[30].

Risks

Women with PCOS have a higher risk of glucose intolerance (OR:2.48; 1.63-3.77), type 2 diabetes (OR:4.43;4.06-4.82) and metabolic syndrome (OR:2.88; 2.40-3.45), with double risk of ischemic heart disease and CVD when compared to patients without PCOS[31,32]. The prevalence of obesity is 30-60%[33]. The risk of endometrial cancer and complications during pregnancy such as preeclampsia, gestational diabetes and preterm birth have been described.

Recommendations

Given the heightened risk of overweight/obesity and type 2 diabetes mellitus (DM), it is advisable to embrace healthy lifestyles, regularly monitor body weight, and undergo periodic assessments, including a glucose tolerance test (GTT) every 3-5 years, to screen for prediabetes or type 2 DM[32].

In cases where lifestyle modifications fail to achieve weight loss in patients with PCOS, pharmacological therapy should be considered to address obesity, insulin resistance, and glucose intolerance[33].

It is recommended that all women of reproductive age who are overweight/obese should undergo studies to rule out PCOS[34].

Preconception consultation is essential to control BP, blood glucose and body weight and achieve optimal conditions for the start of pregnancy.

ADVERSE PREGNANCY OUTCOMES

a. **Hypertensive disorders of pregnancy (HDPs),** preterm birth and low birth weight: HDPs continue to be the largest cause of maternal and fetal morbidity and mortality related to pregnancy in the world. Its prevalence ranges between 10-15%[35]. The HDPs includes several disorders that cause high BP (HBP) in pregnant women (BP >140/90 mmHg) such as gestational hypertension, preeclampsia (PE)/eclampsia, chronic hypertension and chronic hypertension with superimposed PE.

There is a significant increase in the risk of future CVD in women with a history of HDPs (PE and gestational hypertension), regardless of having traditional CVRF[36]. Likewise, the severity of HDP and its recurrence increases the possibility of subsequent CV events at an earlier stage[37].

Risks

Women with a previous history of PE have a 2-3 times greater risk of chronic hypertension and heart failure and a 2-fold greater risk of ischemic heart disease, heart failure, arrhythmias, cerebrovascular disease, and CV death[38]. Furthermore, they have a higher risk of developing type 2 DM, end-stage renal disease, vascular dementia, dyslipidemia, and venous thromboembolism at a younger age compared to those who do not develop PE[36].

It has been observed that 30% of women with a history of HDPs have signs of calcium in the coronary arteries around 50 years of age, compared to 18% of the group without a history of HD[39]. They also show premature markers of atherosclerosis such as arterial stiffness and increased thickness of the carotid intima media[40].

Conversely, the risk of maternal death from CVD after presenting PE is twofold compared to patients without PE. Specifically, there is a 2.3 times greater risk of dying from ischemic disease and heart failure and 2 to 3 times greater of dying from cerebrovascular disease[41]. Women with a history of PE and preterm delivery (< 37 weeks of gestation) are 7 times more likely to develop ischemic heart disease compared to normotensive women who delivered at term (RR: 7.7; 95% CI: 4.4-13.52). Furthermore, maternal cerebrovascular mortality is 5 times higher if the birth was before 37 weeks of gestation (RR: 5.08; 95% CI: 2.09-12.35) vs. after 37 weeks of gestation (RR: 0.98; 95% CI: 0.5-1.92)[41].

Recommendations

Previous history of HDP, preterm birth and low birth weight children are major CVRF. These mothers require postnatal evaluation at 6-8 weeks to inform them about the implications for future pregnancies and long-term CVR, as well as to educate them about primary prevention of future CV events. It is recommended in patients with a history of HDP/PE to perform periodic evaluations for hypertension and DM[42-44,45].

b. **Gestational diabetes (GD):** The prevalence is 16.7% worldwide according to the International Diabetes Federation (IDF) for the year 2021. Hyperglycemia in pregnancy is associated with an increased risk of adverse events for both the mother and the baby[46].

These children have a higher risk of obesity, insulin resistance and type 2 DM throughout their lifetimes[47].

Risks

GD is a strong predictor of maternal risk of type 2 DM later in life. 40-60% of patients with GD will be diabetic in 5-10 years[3].

Moreover, women with GD have a twofold increased risk of major cardiovascular events 10 years after childbirth, as compared to women without GD. Notably, this risk is independent of the subsequent development of type 2 DM[3].

A recent meta-analysis showed that those with a history of GD have a higher risk of presenting CVRF such as chronic hypertension, dyslipidemia, obesity, and type 2 DM within a period of 10 years, but their presence can be as early as one-year postpartum[48].

Recommendations

GD screening should be performed on ALL pregnant women, even without RF, between 24-28 weeks of gestation with 100g of oral glucose by glucose tolerance test (OGTT)[49].

Patients diagnosed with GD should be provided with education regarding the heightened future risks of developing type 2 DM, obesity, metabolic syndrome, and CVD, encouraging them to acquire healthy lifestyles, control body weight, engage in regular physical activity and strictly control pre-existing CVRFs[7].

All women with GD should be screened for DM at 8-12 weeks postpartum, through the OGTT with 75 g of glucose, to evaluate the maternal metabolic status. If it is normal, it should be repeated every 1-3 years[49].

It is indisputable that making the diagnosis of GD or HDP gives us a unique opportunity to identify the future risk of CVD in young women at a very early time in the natural history of the disease, when modifiable RF and primary prevention are still potentially effective[1].

MENOPAUSE

Menopause is an important stage in a woman's life, with an average onset of 51 years (40-60 years).

Risks

Perimenopause and postmenopause lead to states of hypoestrogenemia, which result in an increased risk of CVD and death from this cause. Traditionally, men exhibit a higher cardiovascular risk at an early age than women, but after menopause this risk equals[50]. The changes in estrogen levels following menopause contribute to heightened inflammation, activity of the renin-angiotensin-aldosterone axis, sympathetic response and decreased nitric oxide[51]. Elevated central and visceral adiposity, atherogenic dyslipidemia, increased BP lood pressure, and non-traditional factors such as autoimmune and pregnancy-related diseases have an impact on CVD[4].

Recommendations

A helpful tool for assessing coronary heart disease in middle-aged women is the calcium score, which exhibits a higher predictive value than in men[52]. Women with severe menopausal symptoms and sympathetic hyperactivity have increased heart rate variability, with a predisposition to endothelial damage and the development of subclinical atherosclerosis, which increases CVR. Promoting healthy lifestyle habits and the use of HRT can impact the health of postmenopausal women[53].

Systemic and topical HRT is effective for genitourinary syndrome and prevents bone loss[54].

HRT can help improve symptoms onset and reduce CVD in women < 60 years of age and within 10 years of menopause, with early initiation representing better benefits[55].

However, HRT in individuals over 65 years old may lead to cognitive function deterioration[56].

HRT is not recommended for women with a high risk of cardiovascular disease or those with a previous cardiovascular event[56].

In asymptomatic women, the use of HRT is not pertinent. Women with premature ovarian failure benefit from its use in terms of symptoms, CVD, risk of osteoporosis and cognitive impairment[57].

References

1. Del Sueldo MA, Mendonça-Rivera M, Sánchez-Zambrano M, et al. Clinical practice guideline of the Interamerican Society of Cardiology on primary prevention of cardiovascular disease in women. *Arch Cardiol Mex* 2022; 92 (Suppl): 1-72.
2. Khalil RA. Estrogen, vascular estrogen receptor and hormone therapy in postmenopausal vascular disease. *Biochem Pharmacol* 2013; 86: 1627-42.
3. Maas AH, Rosano G, Cifkova R, et al. Cardiovascular health after menopause transition, pregnancy disorders, and other gynaecologic conditions: a consensus document from European cardiologists, gynecologists, and endocrinologists. *Eur Heart J* 2021; 42: 967-84.
4. Collins P, Maas A, Prasad M, Schierbeck L, Lerman A. Endothelial vascular function as a surrogate of vascular risk and aging in women. *May Clin Proc* 2020; 95: 541-53.
5. Moreau KL, Hildreth KL, Meditz AL, Deane KD, Kohrt WM. Endothelial function is impaired across the stages of the menopause transition in healthy women. *J Clin Endocrinol Metab* 2012; 97: 4692-700.
6. Robinson JG, Wallace R, Limacher M, et al. Cardiovascular risk in women with nonspecific chest pain (from the Women's Health Initiative Hormone Trials). *Am J Cardiol* 2008; 102: 693-9.

7. Parikh NI, Gonzalez JM, Anderson CAM, et al. Adverse pregnancy outcomes and cardiovascular disease risk: unique opportunities for cardiovascular disease prevention in women: A scientific statement from the American Heart Association. *Circulation* 2021; 143: e902-16.
8. EUGenMed Cardiovascular Clinical Study Group, Regitz-Zagrosek V, Oertelt-Prigione S, et al. Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes. *Eur Heart J* 2016; 37:24-34.
9. Qureshi W, Blaha MJ, Nasir K, Al-Mallah MH. Gender differences in coronary plaque composition and burden detected in symptomatic patients referred for coronary computed tomographic angiography. *Int J Cardiovasc Imaging* 2013; 29: 463-9.
10. Kunadian V, Chieffo A, Camici PG, et al. An EAPCI expert consensus document on ischaemia with non-obstructive coronary arteries in collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International *Study Group. Eur Heart J* 2020; 41:3504-20.
11. Reynolds HR, Shaw LJ, Min JK, et al. ISCHEMIA Research Group. Association of sex with severity of coronary artery disease, ischemia, and symptom burden in patients with moderate or severe ischemia: secondary analysis of the ISCHEMIA Randomized Clinical Trial. *JAMA Cardiol* 2020; 5: 773-86.
12. Leeners B, Geary N, Tobler PN, Asarian L. Ovarian hormones and obesity. *Hum Reprod Update* 2017; 23: 300-21.
13. Mosca L, Hammond G, Mochari-Greenberger H, Towfighi A, Albert MA, American Heart Association Cardiovascular Disease and Stroke in Women and Special Populations Committee of the Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on High Blood. Fifteen-year trends in awareness of heart disease in women: Results of a 2012 American Heart Association National Survey. *Circulation* 2013; 127: 1254-63.
14. Garcia M, Mulvagh SL, Merz CNB, Buring JE, Manson JE. Cardiovascular disease in women clinical perspectives. *Circ Res* 2016; 118: 1273-93.
15. Canoy D, Beral V, Balkwill A, et al. Age at menarche and risks of coronary heart and other vascular diseases in a large UK Cohort. *Circulation* 2015; 131: 237-44.
16. Bubach S, De Mola CL, Hardy R, Dreyfus J, Santos AC, Horta BL. Early menarche and blood pressure in adulthood: Systematic review and meta-analysis. *J Public Health* 2018; 40: 476-84.
17. Karapanou O, Papadimitriou A.Determinants of menarche. *Reprod Biol Endocrinol* 2010; 8:115.
18. Mondul AM, Rodriguez C, Jacobs EJ, Calle EE. Age at natural menopause and cause-specific mortality. *Am J Epidemiol* 2005; 162: 1089-97.
19. Honigberg MC, Zekavat SM, Aragam K, et al. Association of premature natural and surgical menopause with incident cardiovascular disease. *JAMA* 2019; 322: 2411-21.
20. Quinn MM, Cedars MI. Cardiovascular health and ovarian aging. *Fertil Steril* 2018; 110: 790-3.
21. Atsma F, Bartelink M-LEL, Grobbee DE, van der Schouw YT. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. *Menopause* 2006; 13: 265-79.
22. Hamoda H. The British Menopause Society and Women's Health Concern recommendations on the management of women with premature ovarian insufficiency. *Post Reprod Health* 2017; 23:22-35.
23. Lidegaard O, Lokkegaard E, Jensen A, Skovlund CW, Keiding N. Thrombotic stroke and myocardial infarction with hormonal contraception. *N Engl J Med* 2012; 366: 2257-66.
24. Plu-Bureau G, Maitrot-Mantelet L, Hugon-Rodin J, Canonico M. Hormonal contraceptives and venous thromboembolism: an epidemiological update. *Best Pract Res Clin Endocrinol Metab* 2013; 27:25-34.
25. Liu H, Yao J, Wang W, Zhang D. Association between duration of oral contraceptive use and risk of hypertension: A meta-analysis. *J Clin Hypertens* 2017; 19: 1032-41.
26. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins-Gynecology. ACOG Practice Bulletin N° 206: use of hormonal contraception in women with coexisting medical conditions. *Obstet Gynecol* 2019; 133: e128-e50.
27. Shufelt CL, Bairey Merz CN. Contraceptive hormone use and cardiovascular disease. *J Am Coll Cardiol* 2009; 53:221–31.
28. Shufelt C, LeVee A. Hormonal contraception in women with hypertension. *JAMA* 2020; 324:1451.
29. Plu-Bureau G, Sabbagh E, Hugon-Rodin J. Hormonal contraception and vascular risk: CNGOF Contraception Guidelines. *Gynecol Obstet Fertil Senol* 2018; 46: 823-33.
30. Kar S. Anthropometric, clinical, and metabolic comparisons of the four Rotterdam PCOS phenotypes: A prospective study of PCOS women. *J Hum Reprod Sci* 2013; 6: 194-200.
31. de Groot PCM, Dekkers OM, Romijn JA, Dieben SWM, Helmerhorst FM. PCOS, coronary heart disease, stroke and the influence of obesity: a systematic review and meta-analysis. *Hum Reprod Update* 2011; 17: 495-500.
32. Zhao L, Zhu Z, Lou H, et al. Polycystic ovary syndrome (PCOS) and the risk of coronary heart disease (CHD): a meta-analysis. *Oncotarget* 2016; 7:33715-21.
33. Cibula D, Cífková R, Fanta M, Poledne R, Zivny J, Skibová J. Increased risk of non-insulin dependent diabetes mellitus, arterial hypertension and coronary artery disease in perimenopausal women with a history of the polycystic ovary syndrome. *Hum Reprod* 2000; 15: 785-9.
34. Del Castillo Tirado FJ, Martínez Ortega AJ, del Castillo Tirado RA. Clinical practice guideline for polycystic ovary syndrome. *Archives of Medicine* 2014; 10:14.
35. Benschop L, Duvekot J, Roeters van Lennep J. Future risk of cardiovascular disease risk factors and events in women after a hypertensive disorder of pregnancy. *Heart* 2019; 105: 1273-8.
36. Garovic V, Dechend R, Easterling T, et al. Hypertension in pregnancy. A scientific statement from the American Heart Association. *Hypertension* 2022; 79: e21-e41.
37. Brouwers L, van der Meiden-van Roest AJ, Savelkoul C, et al. Recurrence of preeclampsia and the risk of future hypertension and cardiovascular disease: a systematic review and meta-analysis. *BJOG* 2018; 125: 1642–54.
38. Wu P, Haththotuwa R, Kwok CS, et al. Preeclampsia and future cardiovascular health: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 2017; 10: e003497.
39. Zoet GA, Benschop L, Boersma E, et al. Prevalence of subclinical coronary artery disease assessed by coronary computed tomography angiography in 45- to 55-year-old women with a history of preeclampsia. *Circulation* 2018; 137: 877-9.
40. Honigberg MC, Zekavat SM, Aragam K, et al. Long-term cardiovascular risk in women with hypertension during pregnancy. *J Am Coll Cardiol* 2019; 74: 2743-54.
41. Wu P, Gulati M, Kwok CS, et al. Preterm delivery and future risk of maternal cardiovascular disease: a systematic review and meta-analysis. *J Am Heart Assoc* 2018; 7: e007809.

42. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHAGuideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019; 140: e596-646
43. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/ AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019; 139: e1082-143.
44. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021; 42: 3227-337.
45. ACOG COMMITTEE OPINION 743. Low-dose aspirin use during pregnancy. *Obstet Gynecol* 2018; 132: e44-e52.
46. Salzberg S, Alvariñas J, López G, et al. Latin American Diabetes Association. Guidelines for diagnosis and treatment of gestational diabetes. *Rev ALAD* 2016; 6: 155-69.
47. Kramer CK, Campbell S, Retnakaran R. Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis. *Diabetologia* 2019; 62: 905-14.
48. Pathirana M, Lassi Z, Ali A, Arstall M, Roberts C, Andraweera P. Cardiovascular risk factors in women with previous gestational diabetes mellitus: A systematic review and meta-analysis. *Rev Endocr Metab Disord* 2020; 22: 729-61.
49. Zhang M, Zhou Y, Zhong J, Wang K, Ding Y, Li L. Current guidelines on the management of gestational diabetes mellitus: a content analysis and appraisal. *BMC Pregnancy Childbirth* 2019; 19:200.
50. Oliver-Williams C, Glisic M, Shahzad S, et al. The route of administration, timing, duration and dose of postmenopause hormone therapy and cardiovascular outcomes in women: a systematic review. *Hum Reprod Update* 2019; 25: 257-71.
51. Yanes LL, Romero DG, Iliescu R, Zhang H, Davis D, Reckelhoff JF. Postmenopausal hypertension: role of the renin-angiotensin system. *Hypertension* 2010; 56: 359-363.
52. Shaw LJ, Min JK, Nasir K, et al. Sex differences in calcified plaque and long-term cardiovascular mortality: observations from the CAC Consortium. *Eur Heart J* 2018; 39: 3727-35.
53. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J* 2016; 37: 15-2381.
54. Lumsden MA, Davies M, Sarri G. Diagnosis and Management of Menopause: The National Institute of Health and Care Excellence (NICE) Guideline. *JAMA Intern Med* 2016; 176: 1205-06.
55. Neves ECM, Birkhauser M, Samsioe G, et al. EMAS position statement: the ten point guide to the integral management of menopause health. *Maturitas* 2015; 81: 88-92.
56. Armeni E, Lambrinoudaki I, Ceausu I, et al. Maintaining post-productive health: a care pathway from the European Menopause and Andropause Society (EMAS). *Maturitas* 2016; 89: 63-72.
57. Rivera CM, Grossardt BR, Rhodes DJ, et al. Increased cardiovascular mortality after early bilateral oophorectomy. *Menopause* 2009; 16:15-23.