Cardiovascular Disease in the Female Population

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Learning Objectives

1. Define risk factors for coronary artery disease in women in different stages of life
2. Describe pregnancy related cardiovascular risk factors and outcomes
3. List cardiovascular disease entities unique to the female population

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Introduction

- FACT: Cardiovascular Disease is the number one killer for BOTH Women and Men
- Before talking about the medicine, we must identify the disparities
  1. Coronary Heart Disease (CHD)
  2. Heart Failure
  3. Atrial Fibrillation
- Although now both male and female are getting same testing, there is still a significant lack in recognition of female pattern heart disease , this is true for CHD and HF
  - Women are more likely to have HFpEF and men HFrEF

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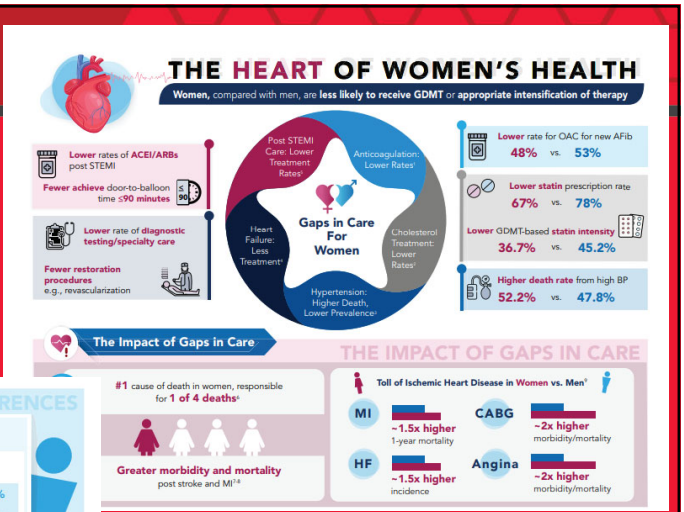
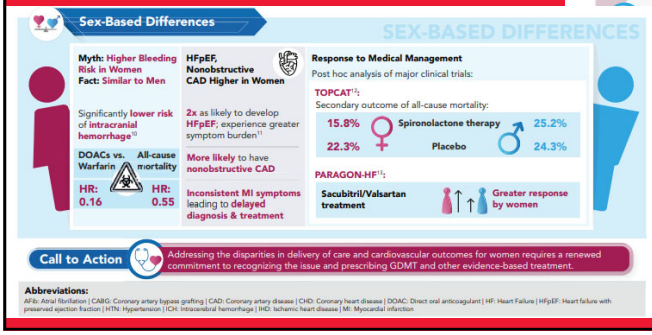
Where are the Disparities[1]

In 1997, only 30% of American women surveyed were aware that CVD was the leading cause of death in women; this increased to 54% in 2009 and has subsequently plateaued when last surveyed in 2012.





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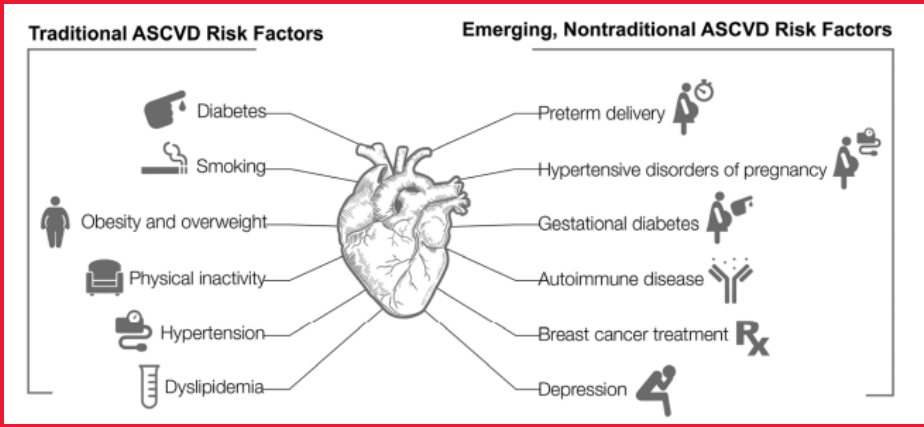
Risk Factors[7]



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Sex Based Differences in Traditional Risk Factors

Risk Factor	Sex-Based Differences	Recommendation
Diabetes mellitus	DM: women with DM have a 3-fold excess risk of fatal CAD compared with nondiabetic women.	Both women and men with DM should have aggressive management of their CVD risk factors. Observational studies suggest that women may require greater frequency/intensity of physical activity than men to reduce CVD events.
	MI: earlier occurrence and higher mortality in diabetic women compared with diabetic men. Lower revascularization rates in diabetic women compared with diabetic men.	
	HF: diabetic women have a higher risk of developing HF compared with diabetic men.	
	Stroke: DM is a stronger risk factor for stroke in women compared with men.	
	PAD: DM is a stronger risk factor for the development of claudication in women compared with men. Decreased long-term survival in women undergoing revascularization and increased postsurgical mortality are seen in diabetic women with PAD compared with diabetic men with PAD.	
Hypertension	Higher prevalence of HTN in women over age 60 than in men.	Encourage optimal BP through diet, exercise, and avoidance of excess alcohol and sodium.
	Less well controlled in women than men.	Pharmacotherapy is indicated when blood pressure is >140/90 mm Hg.
Dyslipidemia	Among women, dyslipidemia has the highest PAR at 47.1%, compared with all other known risk factors for CVD.	Statins are equally effective for secondary CVD prevention in both men and women; however, statins may contribute to a greater likelihood of developing DM and myalgias in women. Statins are recommended for primary prevention in women; however, randomized trial evidence in women is limited.
	Atheroma regression and LDL lowering may be even greater among women on statins than in men.	
Obesity	The impact of obesity on the development of CAD appears to be greater in women than in men. In the Framingham Heart Study, obesity increased the risk of CAD by 64% in women compared with 46% in men.	Women should maintain or lose weight through an appropriate balance of physical activity and diet. Women who need to lose weight should be advised to accumulate a minimum of 60 to 90 min of at least moderate-intensity physical activity preferably all days of the week.

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Physical inactivity 	The prevalence of inactivity and sedentary behaviors is higher among women than men.	Overwhelming evidence indicates that regular physical activity is one of the most powerful health-promoting practices that clinicians can recommend for patients.
		Women should be advised to accumulate at least 150 min/wk of moderate exercise, 75 min/wk of vigorous exercise, or an equivalent combination.
Smoking 	In a recent meta-analysis by Huxley et al, it was reported that in all age groups with the exception of the youngest (30–44 y), women had a significant 25% increased risk for CAD conferred by cigarette smoking compared with men	Smoking is associated with a decade of lost life, and cessation reduces that loss by about 90%.
		Women should be advised not to smoke and to avoid environmental tobacco smoke. Provide counseling at each encounter, nicotine replacement, and other pharmacotherapy/behavioral therapy as indicated.

BP indicates blood pressure; CAD, coronary artery disease; CVD, cardiovascular disease; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; IHD, ischemic heart disease; LDL, low-density lipoprotein; MI, myocardial infarction; PAD, peripheral arterial disease; and PAR, population attributable risk.

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Non-Traditional Risk Factors

Pre Term Delivery

Delivery < 37 weeks. Kasous et al. concluded PTD is an independent risk factor for subsequent long-term cardiovascular morbidity and cardiovascular-related hospitalizations. The risk for ASCVD was further increased with a history of early PTD (< 34 weeks)

Hypertensive Pregnancy Disorders

- *Gestational Hypertension*: new onset hypertension (>140/90 mmHg) after 20 weeks' gestation in a woman who was originally normotensive
- *Chronic hypertension*: Women who develop hypertension before 20 weeks of gestation
- *Pre-eclampsia*: new onset hypertension (>140/90 mmHg) after 20 weeks' gestation and proteinuria (0.3 g/24 hours) and end-organ dysfunction
- In a meta-analysis with 198 252 preeclamptic women, it was concluded that in comparison to women with normotensive pregnancies, women with preeclampsia had a 3.7-fold (95% CI, 2.70–5.05) relative risk for developing hypertension 14 years after pregnancy, a 2.16-fold (95% CI, 1.86–2.52) relative risk for IHD after 12 years, a 1.81-fold (95% CI, 1.45–2.27) relative risk of stroke after 10 years, and a 1.79-fold (95% CI, 1.37–2.33) relative risk for venous thromboembolism after 5 years

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Non-Traditional Risk Factors

Gestational Diabetes Mellitus

Gestational DM is defined as newly diagnosed DM **beyond the first** trimester of pregnancy. Gestational DM increases the risk of developing T2DM by 7-fold, which is a major risk factor for subsequent ASCVD, but also raises CVD risk (2- fold for stroke and 4-fold for MI) **independently** of the overt development of T2DM

Persistence of Weight Gain after Pregnancy

- Weight at 1 year postpartum is a stronger predictor of the likelihood of being overweight 15 years later than the weight gained during the pregnancy itself
- A recent study observed that weight trend in the first year postpartum reported that an adverse cardiometabolic profile emerges as early as 1 year postpartum in women who do not lose weight between 3 and 12 months after delivery

Autoimmune disease

- The microvasculature in women may play an important role in the predisposition of women with autoimmune diseases to develop accelerated CVD.
- The female to male ratio for rheumatoid arthritis is 2.5:1 and for SLE is 9:1.
- Patients with rheumatoid arthritis have a 2- to 3-fold higher risk of MI and a 50% higher risk of stroke
- SLE Pts recent case–control series has indicated that the risk of MI is increased between 9- and 50-fold over that in the general population

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Non-Traditional Risk Factors

Treatment for Breast cancer

- Radiotherapy for breast cancer often involves incidental exposure of the heart to ionizing radiation, increasing the subsequent rate of IHD
- beginning within a few years after exposure, and continuing for at least 20 years
- In a recent population-based case–control study, women irradiated for cancer of the left breast had higher rates of CAD events than women receiving radiation to the right breast. Moreover, the rate of CAD events increased by 7.4% per gray of the mean radiation dose delivered [8]
- can also manifest as valvular and cardiomyopathic processes

Depression

- Limited evidence suggests that depression and other psychosocial risk factors might be more powerful risk factors in younger individuals, and especially in young women. Although few women develop CVD at a young age the lifetime risk in women at age 50 years is ≈40%, and therefore, identification of risk factors in young populations may provide long-term benefit by facilitating early prevention.
- Furthermore, young women have been underrepresented in studies of CVD, have higher rates of depression, and have higher mortality rates after acute MI compared with men

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Ischemic Heart Disease

IHD in women includes not only atherosclerotic obstructive CAD, but also an expanded spectrum of coronary disease, including coronary microvascular dysfunction (CMD), endothelial dysfunction, vasomotor abnormalities, spontaneous coronary artery dissection (SCAD) and stress induced cardiomyopathy

The most important characteristics of IHD in women are that they have

(1) a higher prevalence of angina

(2) a lower burden of obstructive CAD on angiography,

(3) a poorer prognosis in comparison to men.

current risk scores, based on ACS thresholds determined in predominantly male-based populations, do not accurately predict risk in women, showing the need for sex-specific biomarker ranges and risk stratification tools to improve the diagnosis, treatment, and follow-up in female populations

Although it has been recognized that a wide range of atypical symptoms occur more frequently in women, including weakness, fatigue, nausea, dyspnea, as well as unconventional descriptors, triggers, and locations of chest-related symptoms, such as in the neck, jaw, and back, the most common presenting symptom of ACS is chest pain in both men and women

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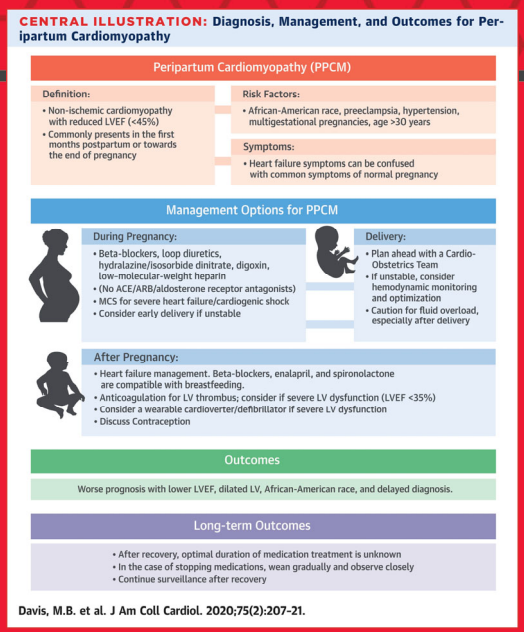
Peripartum Cardiomyopathy[2]

1. PPCM is an idiopathic condition with left ventricular (LV) systolic dysfunction (ejection fraction [EF] <45%) towards the end of pregnancy or following delivery, when no other cause of heart failure (HF) is found.
2. In the United States, incidence varies from 1 in 1,000 to 1 in 4,000. Risk factors for PPCM include African ancestry, pre-eclampsia and hypertension, multifetal pregnancies, and older maternal age.
3. Etiology of PPCM is poorly understood. Existing studies suggest that PPCM is a vascular disease, triggered by peripartum hormonal changes with prolactin breakdown products having vasculotoxic effects. Genetic studies have identified pathogenic variants in the titin gene in afflicted patients supporting a two hit hypothesis.
4. Diagnosis is often delayed, as symptoms overlap those of normal pregnancy. Echocardiography is needed for diagnosis, and intracardiac thrombi should be ruled out when EF is severely reduced due to high risk for thromboembolism.
5. Predictors of adverse outcomes include EF at the time of diagnosis (EF <30% is associated with worse outcomes), African ancestry, obesity, pre-eclampsia, LV dilatation, right ventricular systolic dysfunction, and LV thrombus. PPCM is associated with higher recovery rates compared to other forms of HF, occurring as late as 2 years.



Peripartum Cardiomyopathy[2]

1. Management has to ensure fetal safety. During pregnancy and lactation, loop diuretics, beta-blockers, digoxin, and hydralazine/nitrates can be used. Renin-angiotensin-aldosterone inhibitors are contraindicated during pregnancy, but during lactation, enalapril, captopril, and spironolactone can be used.
2. Anticoagulation for LV thrombus is endorsed by the American Heart Association if EF is <30% during late pregnancy and up to 8 weeks postpartum. Warfarin is contraindicated during pregnancy, but low molecular weight heparin can be used. Both of these agents are safe during lactation. Novel oral anticoagulants have not been studied during pregnancy and are best avoided.
3. The role of bromocriptine as a therapeutic agent is currently experimental. If used, therapeutic anticoagulation is recommended, as it is prothrombotic and it suppresses lactation.
4. PPCM is the most common cause of cardiogenic shock during or shortly after pregnancy. Nitroprusside should be avoided due to possible cyanide toxicity, and outcomes may be worse with dobutamine. Temporary mechanical support has been used successfully and should be considered early. Cardiac transplant in this population has been associated with higher rejection rates and lower survival.

MEDICATION	DURING PREGNANCY	POTENTIAL ADVERSE EFFECTS	INDICATIONS	DURING LACTATION
HEART FAILURE MEDICATIONS				
Loop diuretics	Yes	Caution for hypovolemia or hypotension that may lead to decreased placental perfusion	For signs and symptoms of congestion and fluid overload.	Yes, but over-diuresis can lead to decreased milk production.
Beta blockers (metoprolol tartrate used most commonly)	Yes	IUGR; fetal bradycardia and hypoglycemia	For standard treatment of HF; consider treatment of women with subsequent pregnancy.	Yes
Hydralazine/nitrates	Yes	Caution with hypotension	Use for afterload reduction during pregnancy (instead of ACE I/ARB) when needed.	Yes, but ACE-I/ARB typically chosen post partum
Digoxin	Yes	No associated congenital defects	Can be used with symptomatic heart failure and/or systolic dysfunction during pregnancy, or afterwards per guidelines.	Yes
ACE-I/ARB	No	Anuria, oligohydramnios, fetal limb contractures, craniofacial deformation, pulmonary atresia, fetal hypocalvaria, intra uterine growth restriction, prematurity, patent ductus arteriosus, stillbirth, neonatal hypotension and death	Cannot use during pregnancy. After delivery, should be used as part of guideline-directed medical therapy for afterload reduction and LV remodeling.	Enalapril and captopril can be used
Aldosterone receptor antagonists	No	Spironolactone has been associated with antiadrenergic activity, feminization of male rat fetuses and permanent changes in reproductive tract in both sexes	As per guideline-directed medical therapy for heart failure.	Spironolactone can be used
Sacubitril-valsartan	No	Same as ACE-I/ARB	As per guideline-directed medical therapy for heart failure.	No information in human, present in rat milk
Ivabradine	Scant data in humans; would avoid due to concerns in animal studies	Scant data in humans, animal data suggest risk	As per guideline-directed medical therapy for heart failure.	No information in human, present in rat milk
ANTICOAGULANTS				
Low molecular weight heparin	Yes	Caution at time of delivery and with neuraxial anesthesia; does not cross placenta; consider the need for monitoring anti-Xa levels	For prevention and treatment of thromboembolic complications during pregnancy and as bridge to warfarin postpartum.	Yes
Warfarin	Avoid	Warfarin embryopathy and fetopathy	For prevention and treatment of thromboembolic complications postpartum.	Yes

Legend:
- Data or experience to support use
- Caution with using this medication
- Data is limited or inconclusive

Peripartum Cardiomyopathy

1. Early delivery or termination of pregnancy should be considered in case of hemodynamic instability. Stable patients are delivered vaginally unless there are obstetric reasons for a cesarean section. Postpartum risk of decompensation should be anticipated.
2. Since prolactin has been implicated in the pathogenesis of PPCM, 2010 European guidelines on PPCM advise against breastfeeding. However, a small study in United States and data from an observational registry suggest that breastfeeding is safe.
3. Data on risk for arrhythmias are conflicted. It is reasonable to consider wearable defibrillators for women with new-onset PPCM and severe LV dysfunction until recovery or until an implantable cardioverter-defibrillator is indicated.
4. Contraception should be discussed as soon as feasible. Progesterone-releasing subcutaneous implants or Mirena intrauterine devices are first-line choices and estrogen should be avoided.

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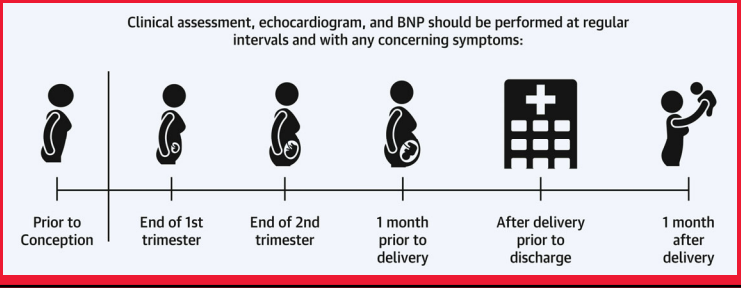
Peripartum Cardiomyopathy

1. If LV dysfunction persists, medications should be continued indefinitely. In those with LV recovery, available observational data support continued therapy indefinitely. If HF medications are stopped, they should be weaned in a stepwise manner with frequent clinical and echocardiographic assessments.
2. Appropriate counseling should be provided for patients considering additional pregnancies. If LV dysfunction persists, women must be counseled about worse maternal and fetal outcomes. Women who recover to EF >50% still have an increased risk for HF, which may persist after pregnancy.
3. During subsequent pregnancies, women with PPCM should be closely followed with serial clinical assessments, echocardiograms, and B-type natriuretic peptide levels from prior to conception until after delivery. Angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers and aldosterone antagonists should be discontinued prior to conception and restarted after delivery.



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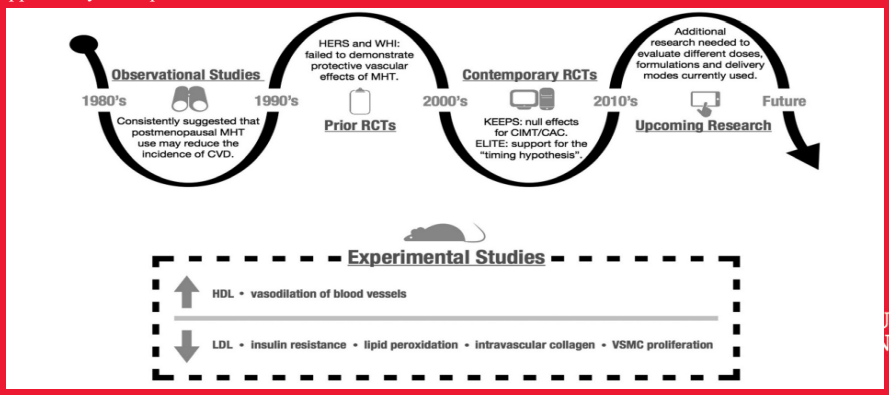
Menopause and CVD

- Premenopausal women are relatively protected against CVD, compared with age-matched men
- this sex gap narrows after menopause.
- This long-standing observation led to a hypothesis that ovarian steroid hormones and, in particular, estrogens, were cardioprotective, initially supported by retrospective observational studies.



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Thank you!