

Foundations of Cardiometabolic Health Certification Course

Certified
Cardiometabolic
Health Professional
(CCHP)



CVD Considerations in Women

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Disclosures

- Consultant to Sanofi, Novo-Nordisk, Novartis, Boehringer-Ingelheim, Bayer, Amarin Medtronic, Amgen, and Esperion
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 - Impact of time-restricted feeding (TRF) on glucose homeostasis and mitochondrial function in patients with metabolic syndrome The TIMET Study
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Talk Overview

- Overview of cardiometabolic disease across the lifespan of women
- Unique aspects of coronary artery disease and diabetes in women
- Pregnancy associated conditions (preeclampsia, gestational diabetes) and impact on CV outcomes
- Heart failure in women
- Menopause and CV risk
- Valvular heart disease in women with focus on aortic stenosis



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Overview of Cardiometabolic Disease Across the Lifespan of Women

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Infancy

If mother has gestational diabetes mellitus or preeclamsia during pregnancy
Risk of obesity and diabetes is increased in offspring.

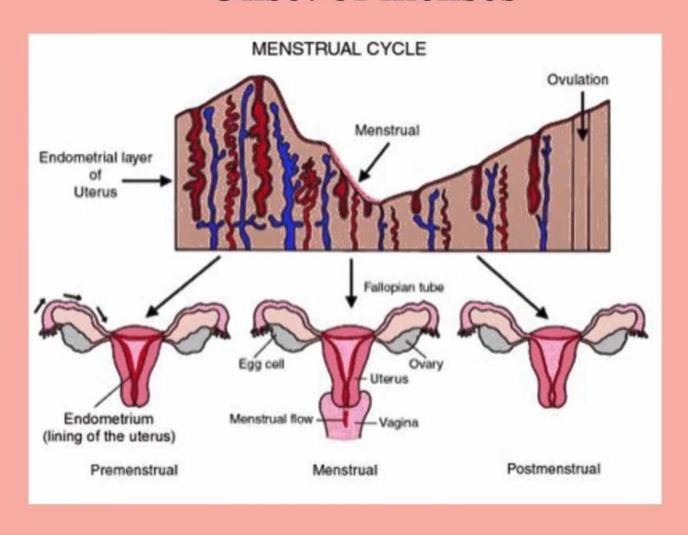




Adolescence



Onset of menses



Young Adulthood

Polycystic Ovary Syndrome





Contraception choice



Pregnancy

Gestational diabetes



Preeclampsia





Post-partum cardiomyopathy



Middle-Aged

Fertility issues



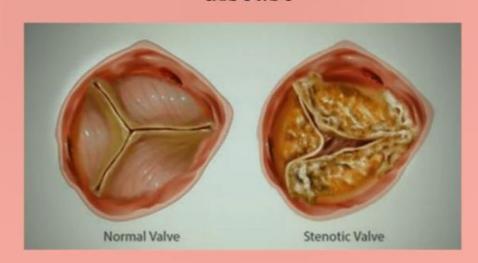


Cancers of Reproductive system



Postmenopause

Valvular Heart disease

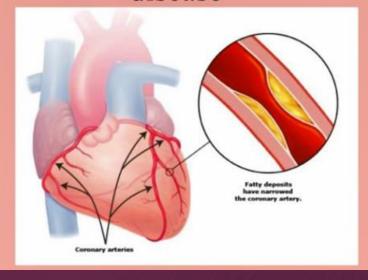




Cancers of Reproductive system



Coronary Heart disease



Cardiometabolic Health Challenges Across the Lifespan

- Infant: If mother had gestational diabetes mellitus or preeclampsia- at risk for obesity and/or diabetes
- Young adult: Polycystic ovary syndrome or contraception
- Middle-aged adult: Fertility issues and cancers of the reproductive system
- Menopause: Cancers of the reproductive system, osteoporosis, and menopausal symptoms in general
- Postmenopause: Cancers of the reproductive system, valvular heart disease, coronary heart disease

Overview of CVD in Women

- Cardiovascular disease (CVD) accounts for 35% of all deaths in women worldwide
- 8.9 women million died from CVD in 2019
- Women Have Worse Outcomes with acute myocardial infarction, yet women are less likely to receive guideline-indicated therapies
- Younger women at the greatest risk for poor outcomes after acute myocardial infarction
- Women are understudied, underdiagnosed, undertreated and under-represented in clinical trials



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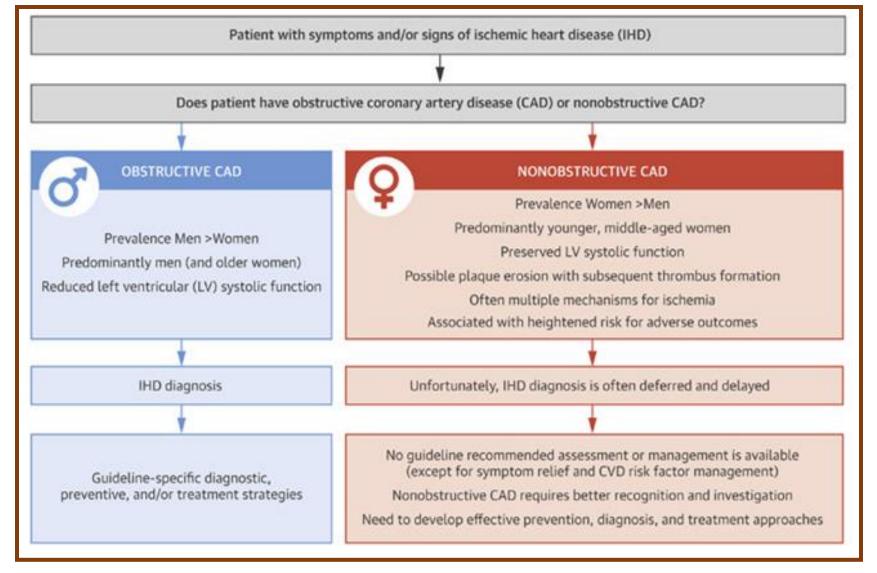


Unique Aspects of Coronary Artery Disease in Women

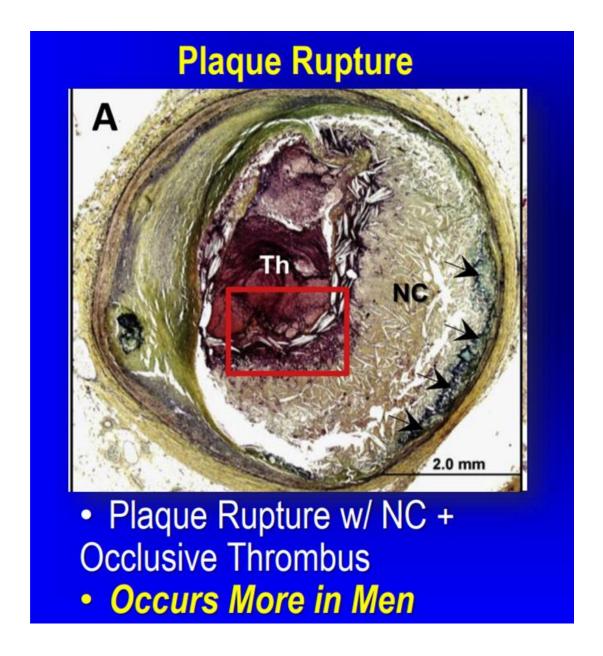
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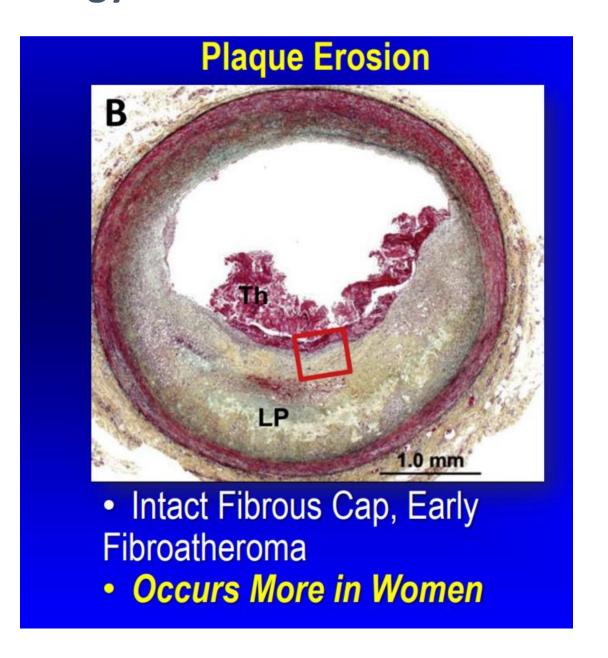


Sex Differences in CAD

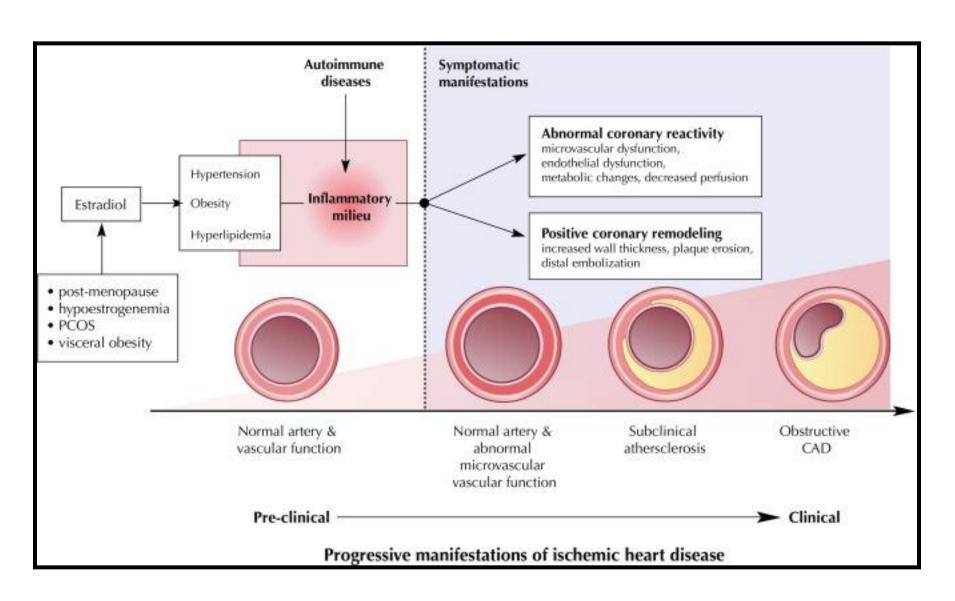


Sex Differences in Plaque Morphology in Sudden Cardiac Death

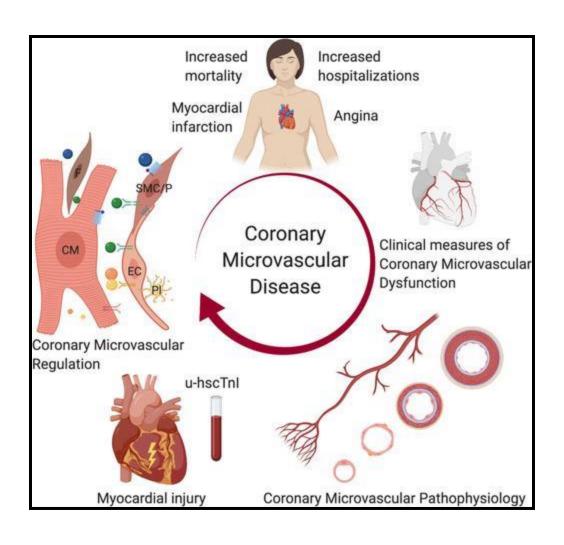




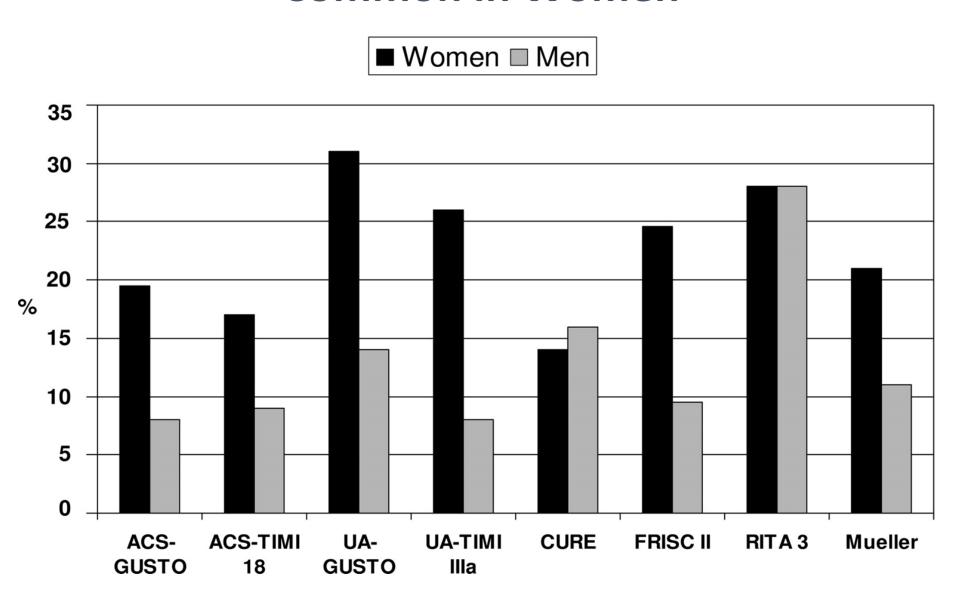
Impact of Factors Unique to Women on CAD Progression



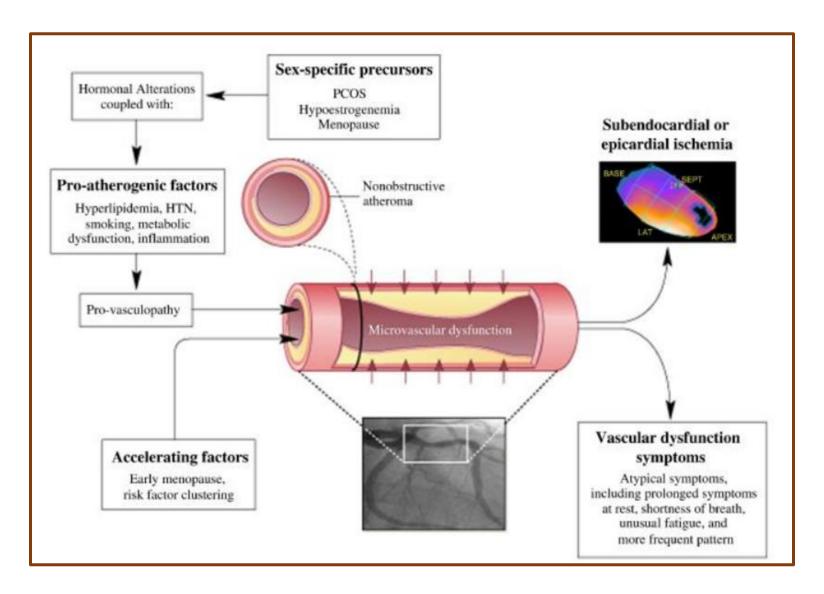
Coronary Microvascular Dysfunction (CMD) is More Common in Women



Prevalence of Normal or Non-obstructive Coronary Arteries: Common in Women



Factors Contributing to Microvascular Disease in Women



Women and Ischemic Heart Disease: Ischemia and No Obstructive CAD (INOCA):

Coronary Microvascular Dysfunction (CMD)

- CMD is prevalent in INOCA patients
- The majority of patients have coronary atherosclerosis
 - Treatment: low dose aspirin and a statin for prevention
- Persistent angina with evidence of ischemia
 - RX anti-ischemic/anginal therapies
- ESC guidelines endorse treatment consistent with stable angina (SIHD) guidelines¹
- Large outcome trials are needed

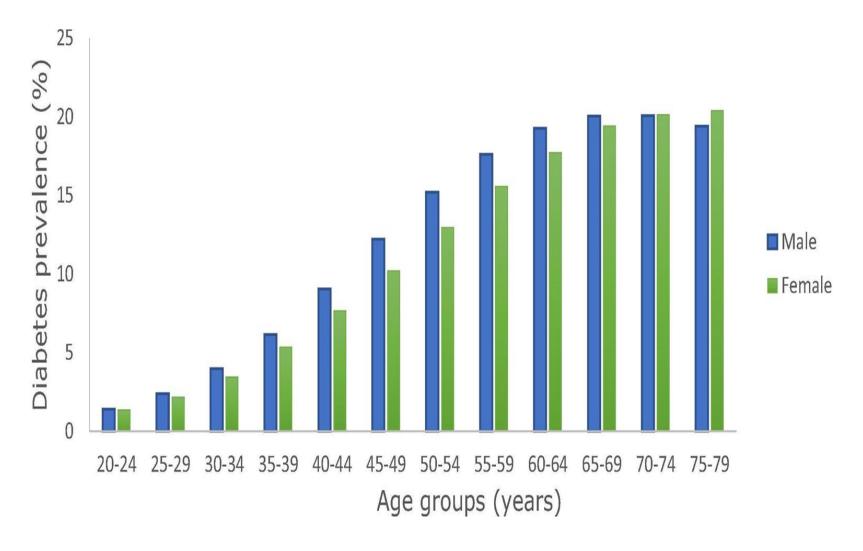


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Prevalence of Diabetes in Women

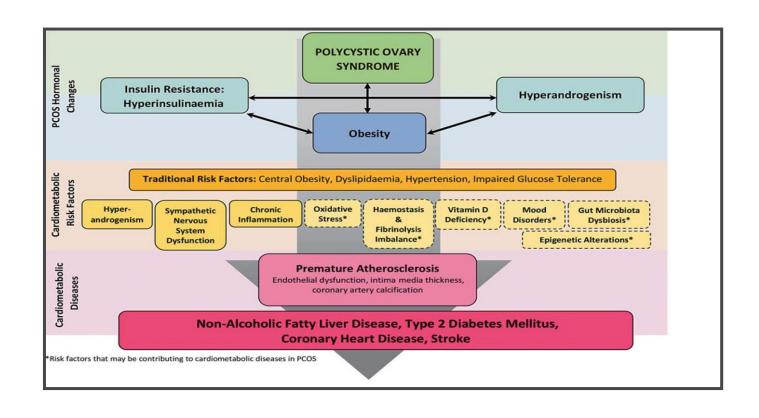


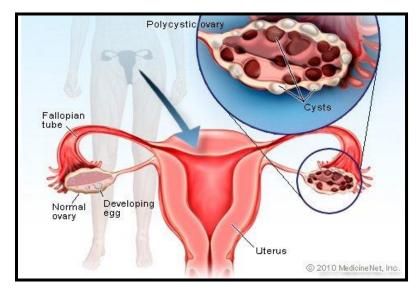
- Over 199 million women have diabetes, and this is projected to increase to 313 million by 2040.
- Diabetes is the ninth leading direct cause of death in women globally, causing 2.1 million deaths each year.
- Women with T2DM are ten times more likely to have CAD than women without T2DM.

Diabetes Impacts Women More Severely

- Elderly women with T2DM and end-stage renal disease have a significantly higher risk of death than men.
- Women with diabetes are four times more likely to suffer a stroke than women without diabetes
- Cyclical hormonal changes make diabetes control more difficult in pre-menopausal women, and the risk of diabetic ketoacidosis is higher amongst women than men.
- Across all countries, women tend to receive less intensive care and treatment for diabetes compared to men.

Long Term Risk of Diabetes Increases with Polycystic Ovarian Syndrome (PCOS)





PCOS increases risk of gestational diabetes and T2DM



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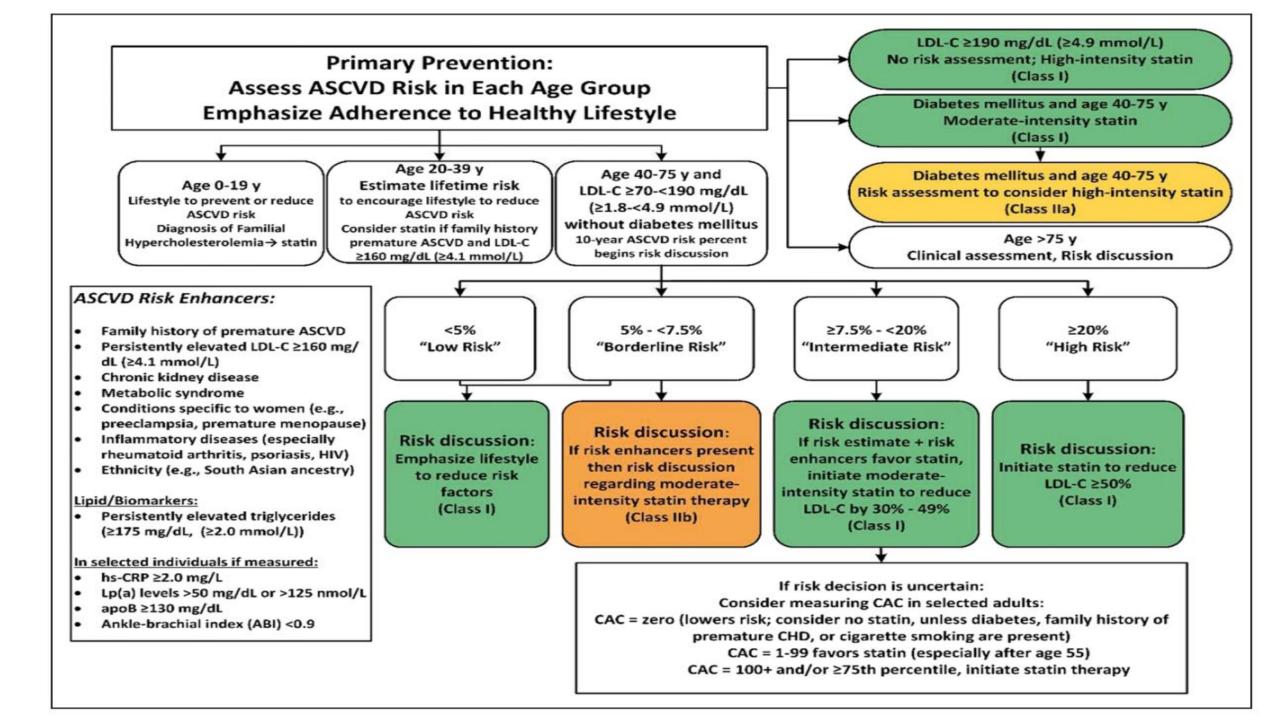
Pregnancy-associated Conditions and Impact on CV Outcomes

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Impact of Pregnancy Complications on Long Term CV Risk

- Pregnancy-specific complications such as gestational diabetes and preeclampsia continue to impact maternal health long after the pregnancy.
- Women with a history of adverse CV pregnancy outcomes are at increased risk of cardiovascular and metabolic diseases later in life.
- Pregnancy related complications should be incorporated into CV risk factor stratification.



Risk-enhancing Factors for Clinician-Patient Risk Discussion

- Family history of premature ASCVD; (males <55 years; females <65 years)
- Primary hypercholesterolemia (LDL-C 160-189 mg/dL (4.1- 4.8 mmol/L); non-HDL-C 190-219 mg/dL (4.9-5.6 mmol/L).
- Metabolic syndrome (Increased waist circumference, elevated TG (>150 mg/dL, elevated BP, elevated glucose, low HDL-C (<40 mg/dL in men, <50 mg/dL in women) are factors; tally of 3 makes the diagnosis)
- Chronic kidney disease (eGFR 15- 59 ml/mln per 1.73 m² with or without albuminum; not treated with dialysis
 or kidney transplantation)
- Chronic inflammatory conditions such as psoriasis, rheumatoid arthritis (RA) or human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS)
- History of premature menopause (before age 40) and history of pregnancy-associated conditions that increase later ASCVD risk such as pre-eclampsia
- High-risk ethnicities (e.g. South Asian ancestry)
- Lipid/Biomarkers: Associated with Increased ASCVD risk
 - -Persistently* elevated, primary hypertriglyceridemia (≥175 mg/dl);
 - -If measured:
 - High-sensitivity C-reactive protein (≥2.0 mg/L)
 - Elevated lipoprotein (a) A relative indication for its measurement is family history of premature ASCVD.
 An Lp(a) ≥ 50 mg/dL or ≥125 nmol/L constitutes a risk enhancing factor especially at higher levels of Lp(a).
 - Elevated apo B ≥130 mg/dL A relative indication for its measurement would be triglyceride ≥ 200 mg/dL.
 A level ≥ 130 mg/dL corresponds to an LDL-C ≥160 mg/dL and constitutes a risk enhancing factor.
 - ABI < 0.9

AIDS indicates acquired immunodeficiency syndrome; ABI, ankle-brachial index; apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); and RA, rheumatoid arthritis.

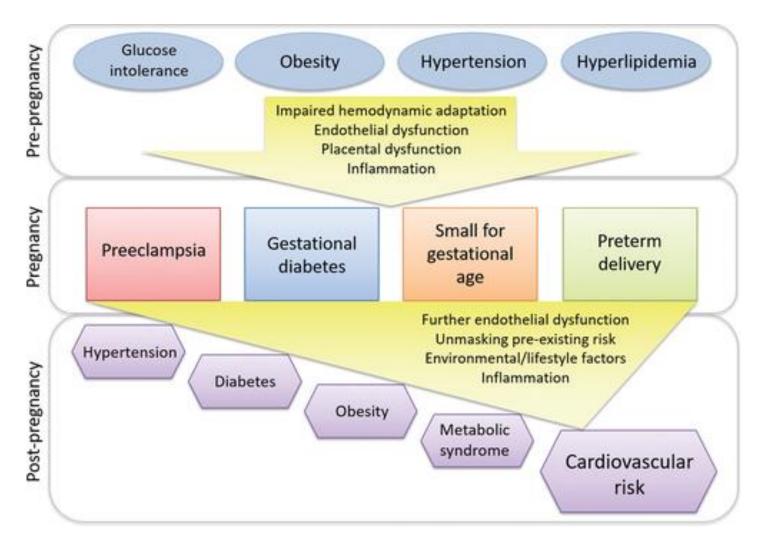


Optimally, 3 determinations

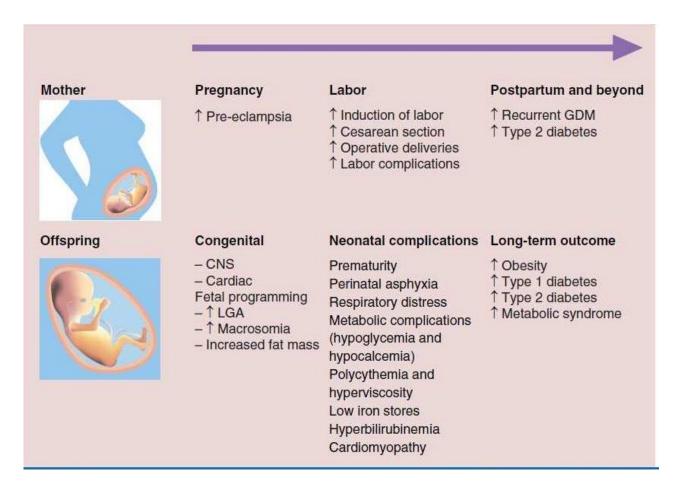
Adverse Pregnancy Outcomes

	Rates	Future Risk of Hypertension	Future Risk of Diabetes	Future Risk of ASCVD
Gestational HTN/Preeclampsia	3-14% of pregnancies			
	Preeclampsia: 25% of preterm births, and 2-5% of all births			
Gestational DM	5% of all pregnancies			
Preterm Delivery	6-12% of all births			
Fetal Growth Restriction	8% of all births			

Associations Between Pre-pregnancy Risk Factors, Adverse Pregnancy Outcomes, and Post-pregnancy Cardiometabolic Risk Factors and Outcomes



Complications of Gestational Diabetes (GDM)



- 1 in 7 births is affected by GDM
- 50% of women with GDM develop diabetes in 5-10 years after delivery
- 20.9 million women (16.2% of all births) had some form of hyperglycemia in pregnancy

Preeclampsia

 Preeclampsia is multisystem progressive disorder characterized by the new onset of hypertension with proteinuria in the second half of pregnancy.

 Occurs in 2% to 8% of pregnancies and is associated with endothelial dysfunction, systemic inflammation generalized vascular endothelial activation and vasospasm resulting in hypertension and multi-organ hypo-perfusion.

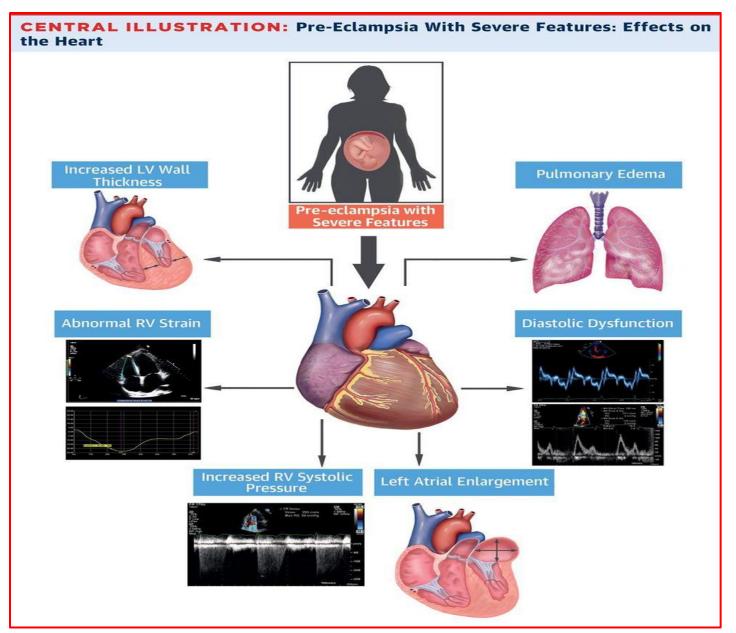
 Women with preeclampsia at increased risk for future cardiovascular disease (even after adjustment for albuminuria).

Long-term Impact of Preeclampsia on CV Risk

Increased relative risks for development of:

- Chronic hypertension (RR 2.2 to 2.8),
- Type 2 diabetes (RR 1.7 to 1.8),
- Hypercholesterolemia (RR 1.3 to 1.4),
- Heart failure (RR 4.19, 95% CI 2.09-8.38),
- Coronary heart disease (RR 2.50, 95% CI 1.43-4.37),
- Death from cardiovascular disease (RR 2.21, 95% CI, 1.83-2.66),
- Stroke (RR 1.81, 95% CI 1.29-2.55)
- The prevelance of preeclampsia is also higher in women with peripartum cardiomyopathy.

Pre-Eclampsia the HFPEF of Pregnancy?



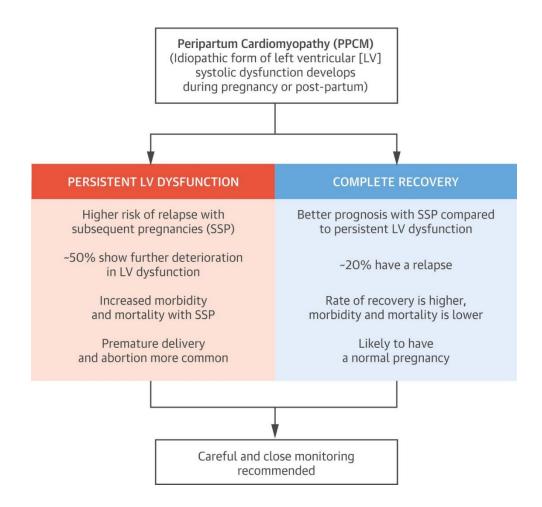
Women with Early-onset/severe Preeclampsia With Preterm Delivery Are at the Highest Risk of Cardiovascular Disease

Deaths from cardiovascular causes

Population	Relative hazard rate (95% CI)	
No preeclampsia, term delivery	1	
No preeclampsia, preterm delivery	2.95 (2.12-4.11)	
preeclampsia, term delivery	1.65 (1.01-2.70)	
preeclampsia, preterm delivery	8.12 (4.31-15.33)	

Peripartum Cardiomyopathy

- Prevalence in the US ranges from ≈ 1 in 1000 to 4000 live births.
- Subsequent pregnancies are associated with significant morbidities.
 - 19% mortality in patients with persistent reduction in EF.
 - 10% mortality even in patients with recovered EF.



Spontaneous Coronary Artery Dissection (SCAD)

CENTRAL ILLUSTRATION: Features of Pregnancy-Associated Spontaneous **Coronary Artery Dissection**

Spontaneous Coronary Artery Dissection (SCAD)



Pregnancy-associated SCAD (P-SCAD)

Recommended areas of P-SCAD research:

- A coronary artery hematoma ± tear limits coronary blood flow to the myocardium

Hematoma

- Frequently occurs in first month postpartum (majority of these within first week after delivery)
- P-SCAD presentation often severe:
- ST-segment elevation myocardial infarction
- Reduced left ventricular function
- Left main and/or multivessel SCAD
- Compared to non-pregnancy-associated SCAD:
- P-SCAD has a higher risk presentation
- P-SCAD patients are older at time of first childbirth and more frequently have history of multiple pregnancies
- P-SCAD patients have fewer extracoronary vascular abnormalities

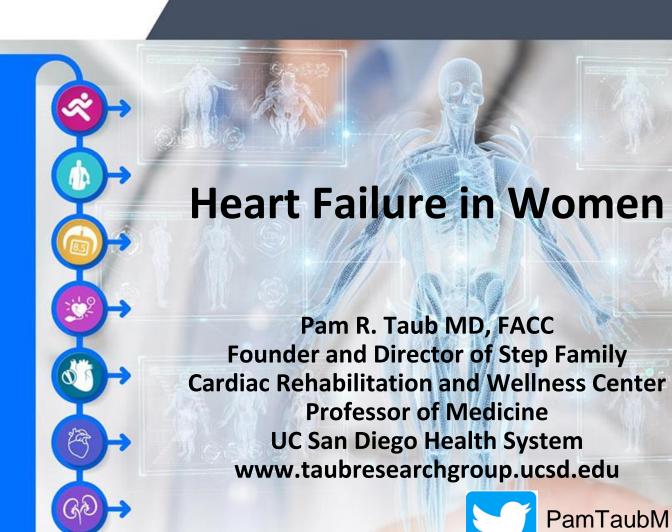
- Hemodynamic stressors
- A Hormonal fluctuations
- Oxytocin release in breastfeeding mothers
- Q Older, multiparous mothers
- Relationship to:
 - Eclampsia/ pre-eclampsia
 - Peripartum cardiomyopathy
 - Fibromuscular dysplasia and other extracoronary vascular abnormalities

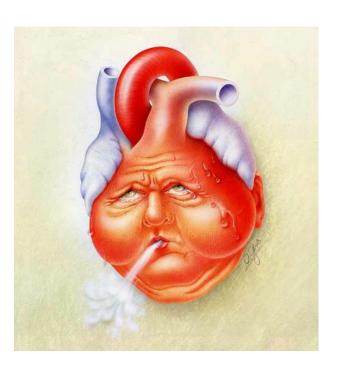




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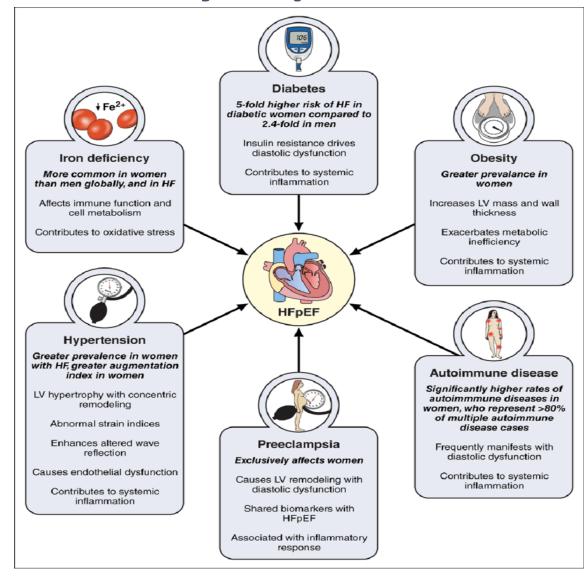
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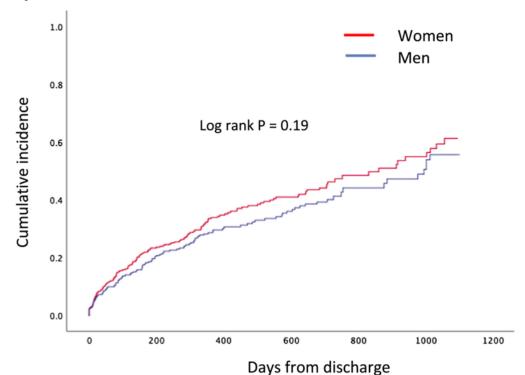
HFPEF Disproportionally Impacts Women

- HFPEF is intricately linked to T2DM and risk factors for T2DM
- Female sex was independently associated with the presence of diastolic dysfunction and worse clinical outcomes in a cohort of elderly patients with HFpEF.



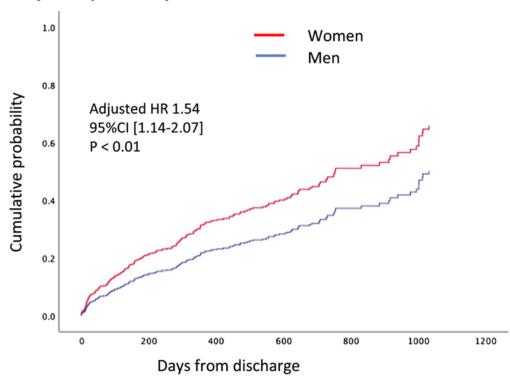
Women with HFPEF Have Worse Outcomes

A Clinical endpoint (all-cause death and HF readmission) Kaplan Meier curves



Number at risk Women 481 261 149 118 43 32 Men 389 220 131 103 37 29

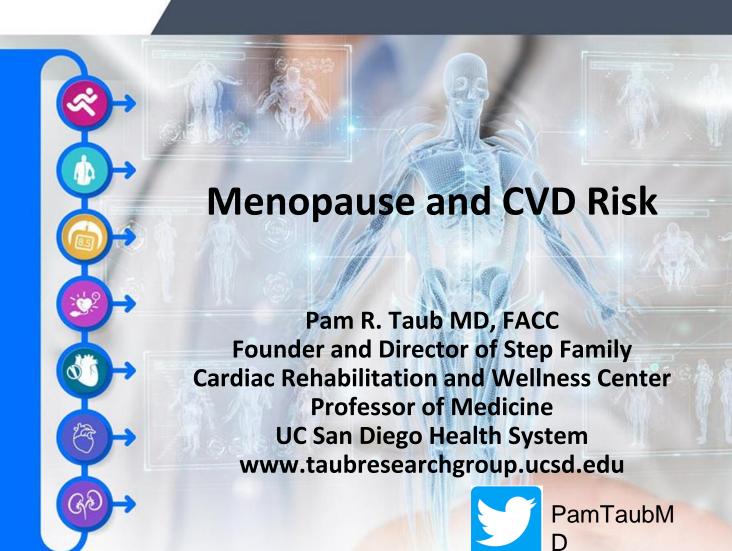
B Clinical endpoint (all-cause death and HF readmission) Adjusted probablity curves

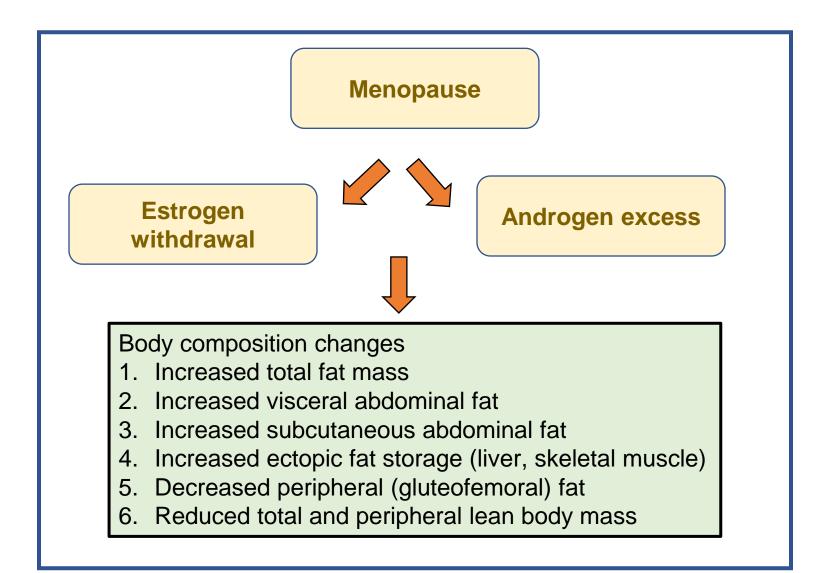




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Stefanska et al. Advances in clinical chemistry 72 (2015): 1-75.



Health Effects of Menopause

Vasomotor symptoms (VMS)

Weight gain and/or shift in adiposity to the visceral sites

Evolution of metabolic syndrome (MetS)

Multidecade, progressive insulin resistance leading to type 2 diabetes mellitus

- Impaired glucose tolerance
- Diminished beta cell function, reserve
- Precedes eventual micro- and macrovascular changes

Progression of atherosclerosis leading to CHD, stroke

Silent breast DCIS, becoming mammographically evident over decades with sharp increase in ER⁺ PR⁺ cancer from fifth decade

Sarcopenia

Acute and progressive trabecular and cortical bone loss, vulnerable to adequacy of bone deposition in adolescence and early adulthood, correlated with estrogen loss, silently progresses to fracture, pain disability

Appearance of progressive osteoarthritis

Appearance of first episodes and/or recurrence of depression

Vasomotor Symptoms

- Hot flashes are associated with higher carotid intima-media thickness and lower BMD.
- Hot flashes are associated with lower HDL and ApoA1 and higher ICAM-1 (intracellular adhesion molecule-1) suggesting higher vascular risks.
- Hot flashes are associated with a higher risk of depression.

VMS and Endothelial Dysfunction

- Flow-mediated dilation was lower in early menopause compared to age matched non-menopausal women
- Intima-media thickness was not different
- Severity of hot flashes correlated with endothelial dysfunction
- Suggesting that endothelial dysfunction, not atherosclerosis occurs early in the menopausal transition

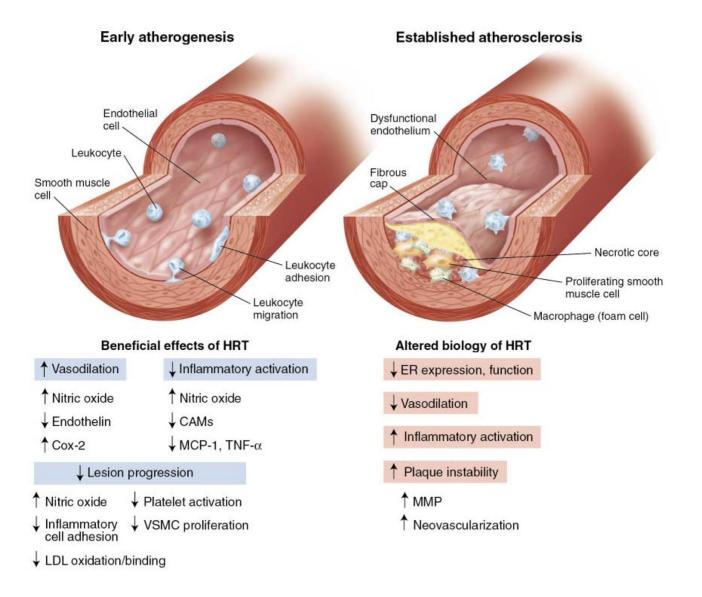
Increasing Visceral Adiposity

	Premenopausal n = 405	Postmenopausal n = 405	р
Age	33.28 <u>+</u> 7.62	52.36 <u>+</u> 7.50	< 0.001
Weight (kg)	92.0 <u>+</u> 17.5	91.2 <u>+</u> 16.0	NS
Height (cm)	155.9 <u>+</u> 5.3	155.6 <u>+</u> 5.8	NS
BMI (kg/m ²)	37.83 <u>+</u> 6.91	37.77 <u>+</u> 6.84	NS
Waist circ (cm)	99.19 <u>+</u> 13.45	103.34 <u>+</u> 13.20	<0.001
Hip circ (cm)	123.10 <u>+</u> 13.10	123.83 <u>+</u> 13.09	NS
WHR	0.80 <u>+</u> 0.07	0.84 ± 0.08	<0.001
IAF (L)	3.19 <u>+</u> 1.42	3.97 <u>+</u> 2.17	<0.001

Timing of HT Initiation

Timing hypothesis

- There may be less risk associated with HT use and potential coronary heart disease (CHD) benefit if initiated closer to the time of menopause
- In contrast, HT use initiated further from menopause may be harmful
- Evidence from the WHI
 - Absolute risk of CHD was lower in younger, recently postmenopausal women
 - Heart attack risk increased during the first year of EPT in older women
 - Use of HT within 10 y of the onset of menopause was associated with a lower CHD risk than if it was started ≥20 y from LMP
 - Women aged 50-59 y in the ET arm had a more favorable all-cause mortality and fewer MIs
- Early Estrogen Prevention Study and the Early Versus Late Intervention
 Trial With Estradiol also showed safety of HT use initiated early in
 menopause



HT Initiation Assessment

1) Vasomotor symptom assessment

Confirm that hot flashes and/or night sweats are adversely affecting sleep, daytime functioning, or quality of life.

(2) Risk factor assessment

Confirm that there are no absolute contraindications to menopausal hormone therapy:

- · Breast or endometrial cancer
- Cardiovascular disease (heart disease, stroke, transient ischemic attack)
- Active liver disease
- · Undiagnosed vaginal bleeding

3 Menopausal hormone therapy initiation			
Recommend	Consider with caution	Avoid	
Age <60 years and Menopause onset within 10 years and Low risk of breast cancer and cardiovascular disease	Age ≥60 years or Menopause onset >10 years prior or Moderate risk of breast cancer or cardiovascular disease	High risk of breast cancer or cardiovascular disease or Age ≥60 years or menopause onset >10 years prior and Moderate risk of breast cancer or cardiovascular disease	

Diabetes and Menopause

- During menopause estrogen and progesterone levels decrease and insulin resistance occurs.
- There maybe weight gain during menopause further exacerbating insulin resistance.
- This decrease in estrogen/progesterone and insulin resistance increase the risk of heart disease.



Considerations for Initiation of HRT

- Indicated for Women <60 or within 10 years after onset of menopause who have symptomatic hot flashes/night sweats
- Generally, not recommended for women >65 or >10 from menopause
- Oral estrogens should be avoided in women with history of CVD, VTE, hypertriglyceridemia, gallbladder disease, or hypercoaguable state
- Hormone therapy is not recommended for primary or secondary prevention of cardiovascular disease
- Not used for osteoporosis prevention Prevention: Calcium, vitamin D, weight bearing exercise, smoking cessation – Treatment: Raloxifene, Bisphosphonates
- Guiding principle for HRT Use Minimal Dose for Shortest Period of Time Required – Consider Non-Hormonal Alternative such as SSRIs and SNRI





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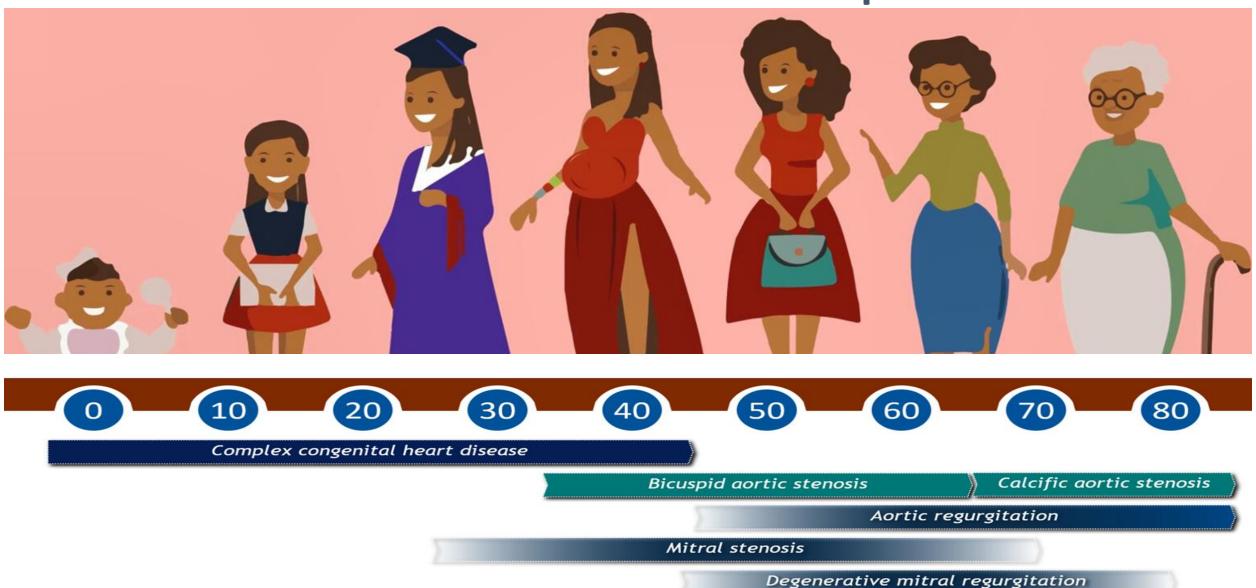


Valvular Heart Disease in Women

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Valvular Heart Disease Across the Lifespan of Women



Functional mitral regurgitation

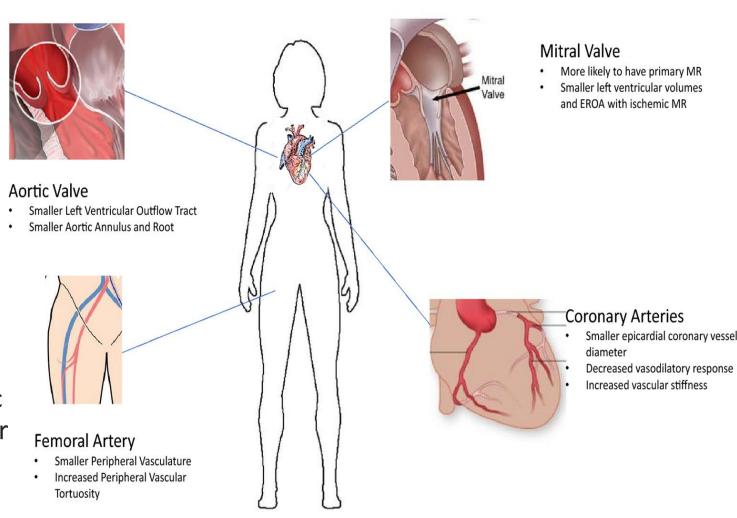
Functional tricuspid regurgitation

Unique Aspects of Aortic Stenosis in Women: Prognosis

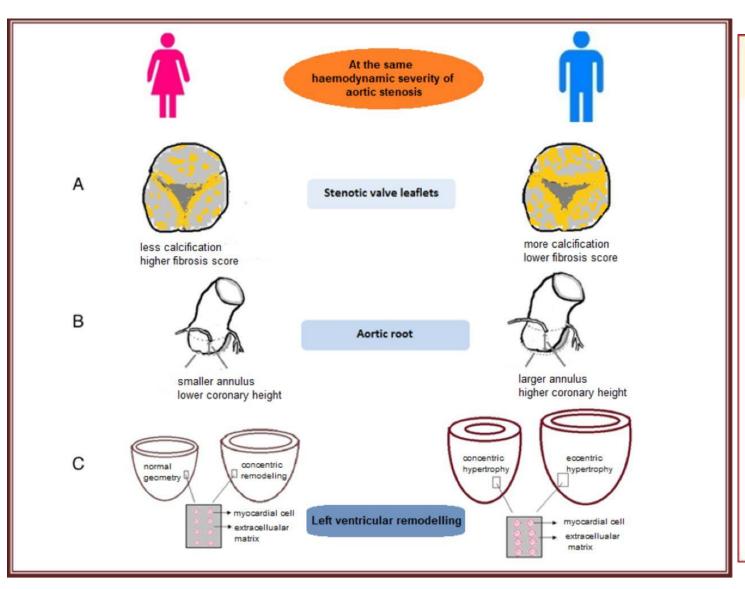
- Women with aortic stenosis are underdiagnosed and undertreated.
- At time of diagnosis women are older with higher prevalence of diastolic dysfunction and hypertension.
- Given the later stage of diagnosis they are more symptomatic with worse prognosis.
- Because they are referred later in the disease course, women have higher baseline operative risk and worse outcomes with surgical aortic replacement.

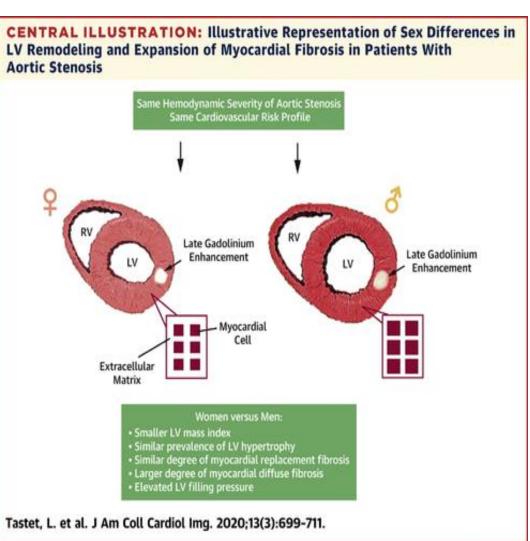
Unique Aspects of Aortic Stenosis in Women: Valve Specific Features

- Women can have the degree of hemodynamic stenosis as men with less calcification.
- The paradoxic low-flow, low-gradient aortic stenosis which can be hard to detect on physical exam is a more common presentation in women and has worse prognosis.
- Women have smaller body surface area and smaller annulus and interventions can be more technically difficult.
- Women often need smaller prosthetic valves and/or additional aortic annular enlargement.



Sex Differences in the Pathophysiology of Aortic Stenosis



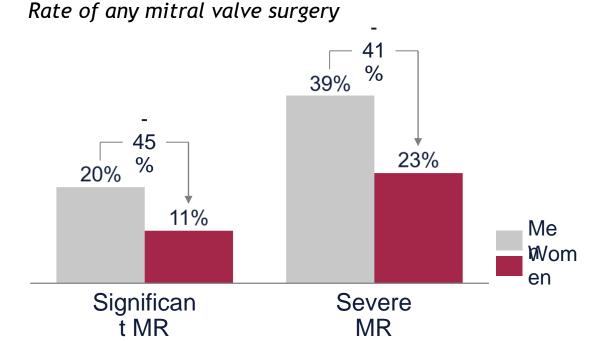


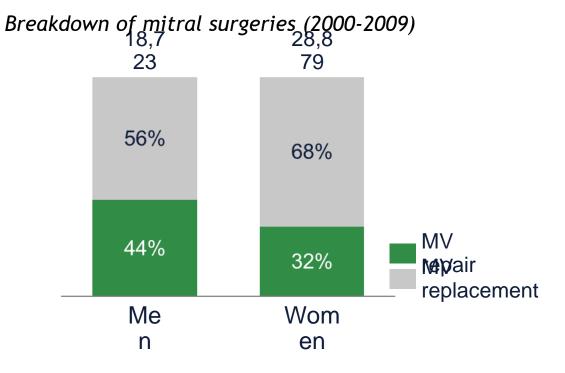


Mitral regurgitation | Women Less Likely to be Treated and to Receive Procedures Associated with Improved Outcomes

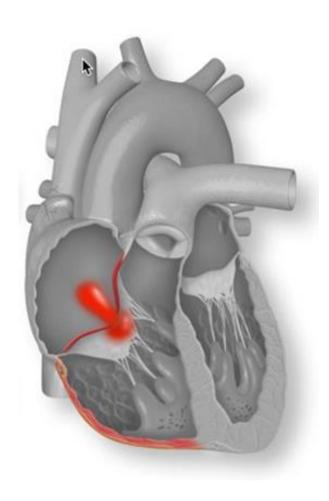
Mayo/Olmsted review showed that women had significantly lower mitral surgery rates than men¹

Medicare data also showed women less likely to receive repair which is associated with better outcomes²





No Longer Forgotten - Tricuspid Disease in Women



- Tricuspid regurgitation more common in women than men¹
 - Linked to heart failure with persevered ejection fraction which is more common in elderly women²
- Moderate and severe TR associated with increase in mortality risk³
- Early evidence that reducing tricuspid regurgitation via percutaneous procedures improves quality of life
 - Reducing TR was associated with significant clinical improvements in New York Heart Association (NYHA) functional class, 6-minute walk test, & Kansas City Cardiomyopathy Questionnaire (KCCQ) score

