Reproductive Life Cycle and Cardiovascular Health

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OUTLINE

- **Reproductive years**
  - Menarche
  - Pregnancy counseling and contraception
  - Physiologic changes of pregnancy
  - Cardiac complications of pregnancy
  - Postpartum
- Menopause
  - Impact on cardiovascular risk
  - Hormonal therapy

CARDIOVASCULAR DISEASE IN WOMEN

- Heart disease is the leading cause of morbidity and mortality in women the US and worldwide (Benjamin et al, 2019)
- Approximately one third of women will die from heart attack or stroke (CDC, 2020)
- Women have unique risk factors for cardiovascular disease

THE REPRODUCTIVE STAGES

Stage	Menarche	Reproductive			Menopause/ Transition		Postmenopause	
Terminology		Early	Peak	Late	Early	Late	Early	Late
Menstrual Cycles	Irregular	Variable to regular	Regular	Regular	Variable (>7 days different from normal)	>2 skipped cycles and an interval of amenorrhea (>60 day)	Amenorrhea~12 months	None	None
Age	9-13	14-16	17-30	31-early 40s	Mid 40s	Late 40s-early 50s		Late 50s and beyond	

Harlow et al., 2012.

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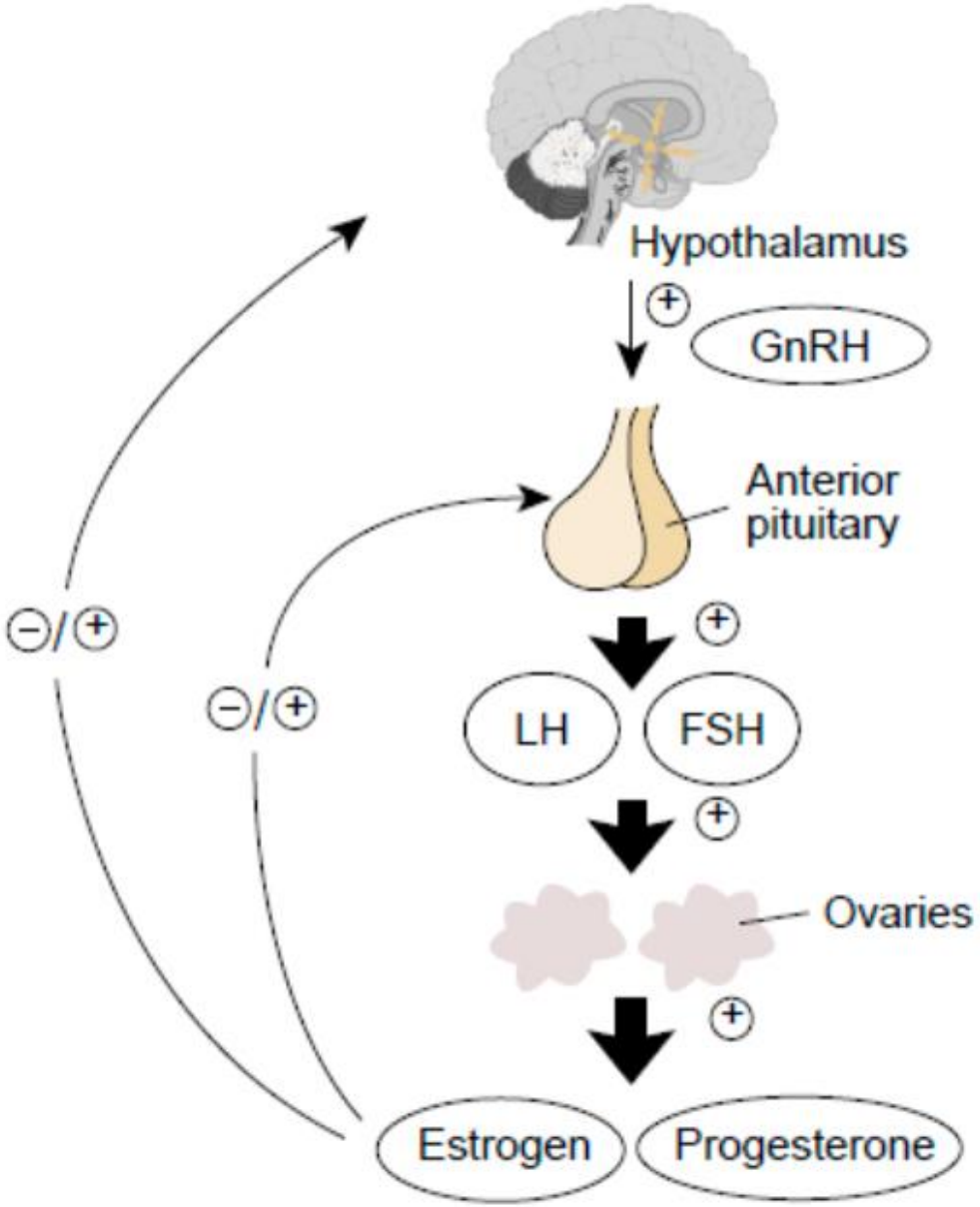
MENARCHE

- Definition: age at first occurrence of menstruation
- Onset of cyclic ovarian function
- Increased endogenous estradiol secretion and exposure

Lee J. et al., 2019

NEUROHORMONAL CHANGES

Hypothalamic-Pituitary-Gonadal Axis in Females



Kong et al., 2014.

WOMEN'S ISCHEMIA SYNDROME EVALUATION (WISE)

- Followed 648 women who underwent natural menopause for 6 years (average)
- Undergoing coronary angiography for suspected ischemia
- MACE:
  - 1st occurrence of all-cause death
  - Nonfatal MI
  - Nonfatal stroke
  - Heart failure hospitalization
- Self reported age of menarche ($\leq 10, 11, 12, 13, 14, \geq 15$ years of age)
- **Early & late menarche associated with higher risk of adverse cardiovascular outcomes**

Lee J. et al., 2019

OUTLINE

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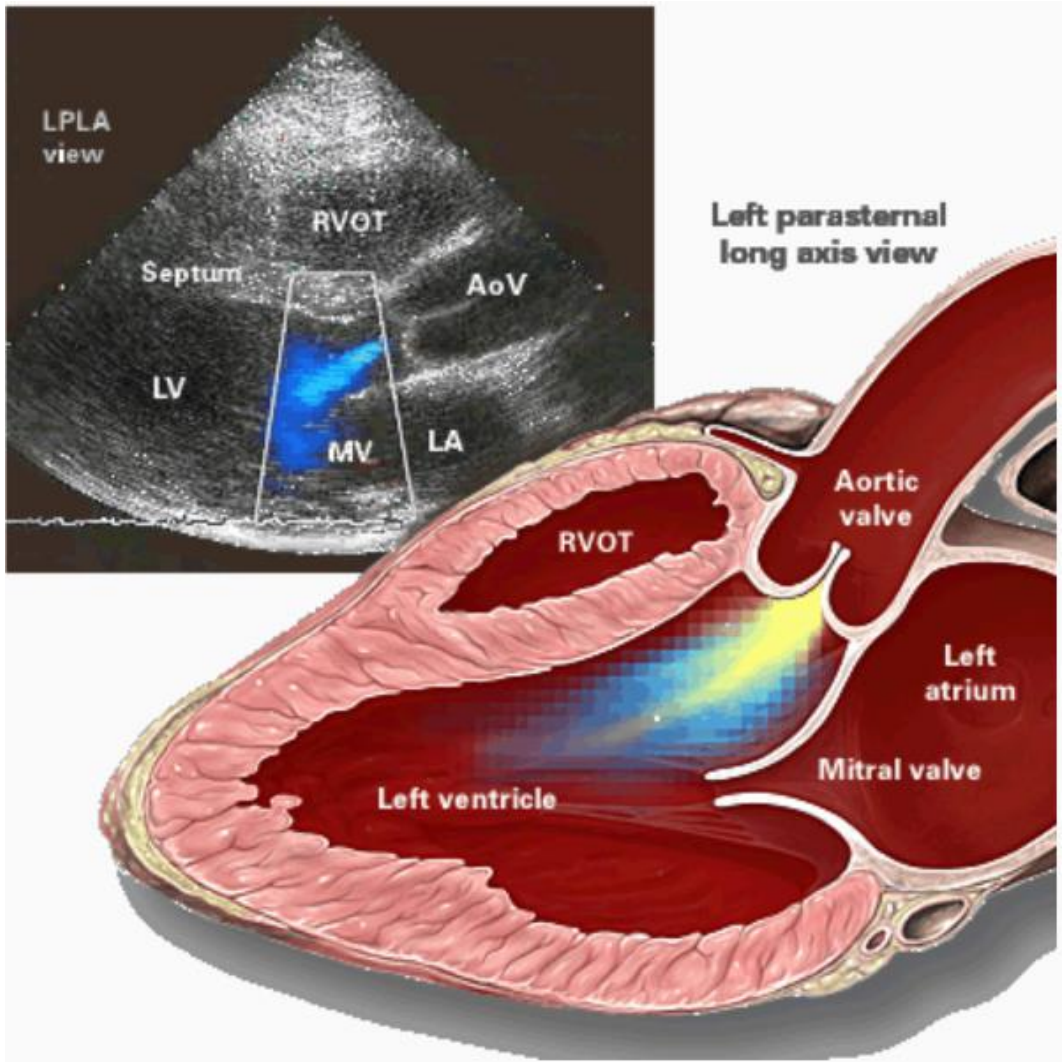
CASE #1: HISTORY OF ENDOCARDITIS

- 26 year old with a remote history of aortic valve endocarditis resulting in moderate aortic regurgitation and stroke
- Active smoker
- History of IV drug abuse, currently in remission
- Normal biventricular function
- Interested in pregnancy in the future but currently interested in contraception



CASE #1: HISTORY OF ENDOCARDITIS

1) What are her risks of pregnancy in the future?
2) What contraceptive would you recommend?

PRE-PREGNANCY COUNSELING

- Rise in US maternal morbidity and mortality over the past few decades
- Cardiovascular disease is the leading cause of pregnancy related deaths
- Potential explanations:
  - Older mothers
  - More cardiovascular risk factors
  - More complex cardiac disease at the time of first birth
- The field of cardio-obstetrics has emerged in response

PRE-PREGNANCY RISK STRATIFICATION

1) Cardiovascular risk:
   - **Modified World Health Organization classification**
   - **CARPREG II (Cardiac Disease in pregnancy study)**
   - ZAHARA (Pregnancy in Women with Congenital Heart Disease)
2) Maternal obstetric risk
3) Fetal and neonatal risk

MODIFIED WHO- CLASS I

- No higher risk than the general population
- Uncomplicated, small or mild lesions:
  - Pulmonary stenosis
  - Ventricular septal defect
  - Patent ductus arteriosus
  - Mitral prolapse with no more than trivial mitral regurgitation
- Successful repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous drainage)
- Isolated PVCs and PACs

Regitz-Zagrosek V et al., 2018

MODIFIED WHO- CLASS II

- Small increased risk of maternal morbidity and mortality
- Unoperated atrial septal defect
- Repaired tetralogy of Fallot
- Most arrhythmias
- Coarctation of the aorta w/out significant gradient or aneurysm (repaired or unrepaired)
- Long QT syndrome

Regitz-Zagrosek V et al., 2018

MODIFIED WHO- CLASS II TO III

- Intermediate increased risk of maternal mortality, moderate to severe increase in morbidity
- Mild left ventricular Impairment
- Hypertrophic cardiomyopathy
- Heart transplant
- Native or tissue valve disease not considered WHO class I or IV
- Marfan syndrome without aortic dilation
- Bicuspid aortic valve without aortic dilatation

Regitz-Zagrosek V et al., 2018

MODIFIED WHO- CLASS III

- Significant risk of maternal morbidity and mortality
- Systemic right ventricle, post-Fontan operation, cyanotic heart disease
- Other complex congenital heart repair
- Mechanical valve
- Aortic dilation without known fibrinogen disease
- Coarctation of aorta with residual gradient or aneurysm (repaired or unrepaired)
- Marfan syndrome with aortic root dilation < 45 mm or s/p aortic replacement
- Bicuspid aortic valve with aortic root dilation 45 to 50 mm

Regitz-Zagrosek V et al., 2018

MODIFIED WHO- CLASS IV

- Pregnancy contraindicated (predicted maternal cardiac event rate: 40-100%)
- Pulmonary arterial hypertension of any cause
- Severe left ventricular dysfunction (LVEF <30% or NYHA functional class III to IV)
- Previous peripartum cardiomyopathy with any residual impairment of LV function
- Severe left heart obstruction: severe aortic stenosis or severe mitral stenosis
- Marfan syndrome with aortic dilation > 45 mm
- Bicuspid aortic valve with aortic dilation > 50 mm

Regitz-Zagrosek V et al., 2018

CARPREG II RISK PREDICTION MODEL

CARPREG II Predictors	Points
Prior cardiac event or arrhythmia	3
Baseline NYHA functional class III or IV or cyanosis	3
Mechanical valve	3
Ventricular dysfunction s	2
High risk left sided valve disease/LVOT obstruction	2
Pulmonary hypertension	2
Coronary artery disease	2
High risk aortopathy	2
No prior cardiac intervention	1
Late pregnancy assessment	1

Silversides CK et al.,2018.

CARPREG II SCORE

CARPREG II Score	Predicted Risk %
0 to 1	5
2	10
3	15
4	22
>4	41

Primary cardiac outcomes:

- Maternal cardiac death
- Cardiac arrest
- Sustained arrhythmia
- Left sided heart failure (pulmonary edema)
- Right sided heart failure
- Stroke or TIA
- Cardiac thromboembolism
- Myocardial infarction
- Vascular dissection

Silversides CK et al., 2018.

CASE #1: HISTORY OF ENDOCARDITIS

26 year old smoker with a remote history of aortic valve endocarditis resulting in moderate aortic regurgitation and stroke

Normal biventricular function

What are her risks of pregnancy in the future?

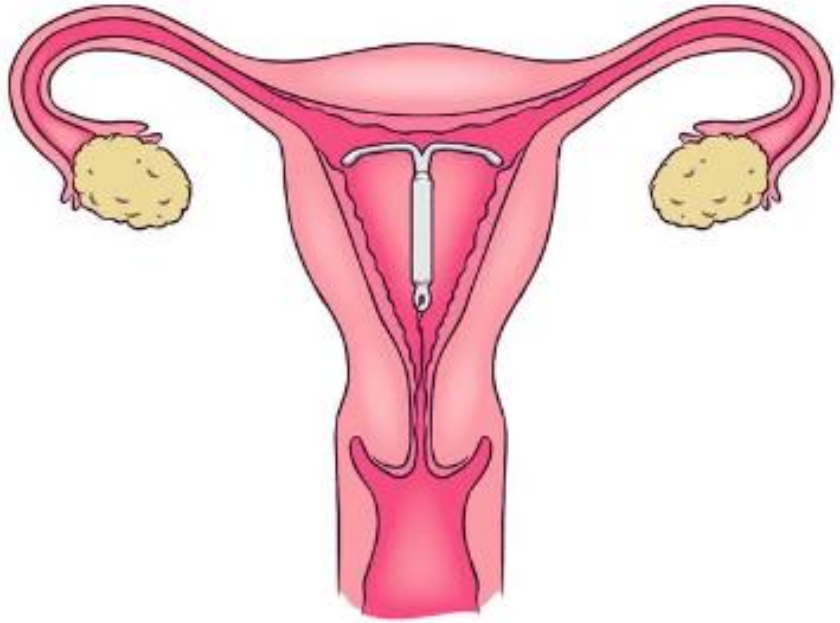
1) mWHO class would be class II to III: known valvular regurgitation
2) CARPREG II risk score: 3 points (prior cardiac event)
   ~15% risk of maternal cardiovascular event

CONTRACEPTION

- Increase in childbearing age women with congenital or acquired CVD in the US
  - Improved pediatric cardiac surgical care
  - Increasing rates of cardiovascular risk factors in young women
- Prevalence of CVD is ~ 11.5% in women 20-29 years old (Benjamin et al 2018)
  - Coronary heart disease
  - Heart failure
  - Stroke
  - Hypertension

Kathryn & Teal, 2022.

CONTRACEPTION



- Contraceptive choice considerations:
  - Risks and benefits of the method
  - Patient's personal preference
  - Relative importance of avoiding pregnancy with patient's underlying cardiovascular condition

Kathryn & Teal, 2022.

SAFETY CONCERNS WITH HORMONAL CONTRACEPTIVES

- Combined hormonal contraceptives: estrogen + progestin (CHC):
  - Increased risk of venous thromboembolism: 7-10/100,000 in healthy patients
  - Mild increase in blood pressure
  - **Avoid estrogen methods with acquired/congenital CV conditions**

- **Progestin-only methods preferred**
  - No effect on blood pressure, cholesterol, or coagulation factors

Kathryn & Teal, 2022.

ABSOLUTE CONTRAINDICATIONS TO CHC

- Acute DVT/PE or history at high risk of recurrence
- Major surgery with prolonged immobilization
- Poorly controlled hypertension
- Ischemic heart disease
- Known thrombogenic mutation
- Multiple risk factors for ASCVD
- Acute peripartum cardiomyopathy
- Moderate to severe left ventricular dysfunction
- Tobacco use in women ages ≥35
- Complicated heart transplant
- History of stroke
- Pulmonary hypertension
- Atrial fibrillation
- Endocarditis

Consider progestin-only or nonhormonal methods (copper IUD, permanent contraception, or barrier methods)

Kathryn & Teal, 2022.

RELATIVE CONTRAINDICATIONS TO CHC

- History of DVT at low risk of recurrence
- Well controlled hypertension
- History of PPCM (normal or mildly reduced LV systolic function)
- Tobacco use <15 cigarettes/day in women ≥35
- Mechanical heart valve
- Dilated left atrium
- Previous coronary arteritis
- Cyanosis
- Potentially reversible left to right shunt
- Post Fontan operation

Consider progestin-only or nonhormonal methods (copper IUD, permanent contraception, or barrier methods)

Kathryn & Teal, 2022.

Hormonal IUD	Copper IUD	Subdermal Implant	Tubal Sterilization	Male Sterilization
• **Amenorrhea** • **Irregular bleeding** • **Lighter menses** • No increased risk of VTE	• **Increased** amount and duration of **menstrual bleeding,** cramping • No increased risk of VTE	• Deep insertion could require surgical removal • **Irregular bleeding and spotting** • No increased risk VTE	• Requires anesthesia • **Not reversible** • No impact on bleeding pattern	• **Requires monogamy**

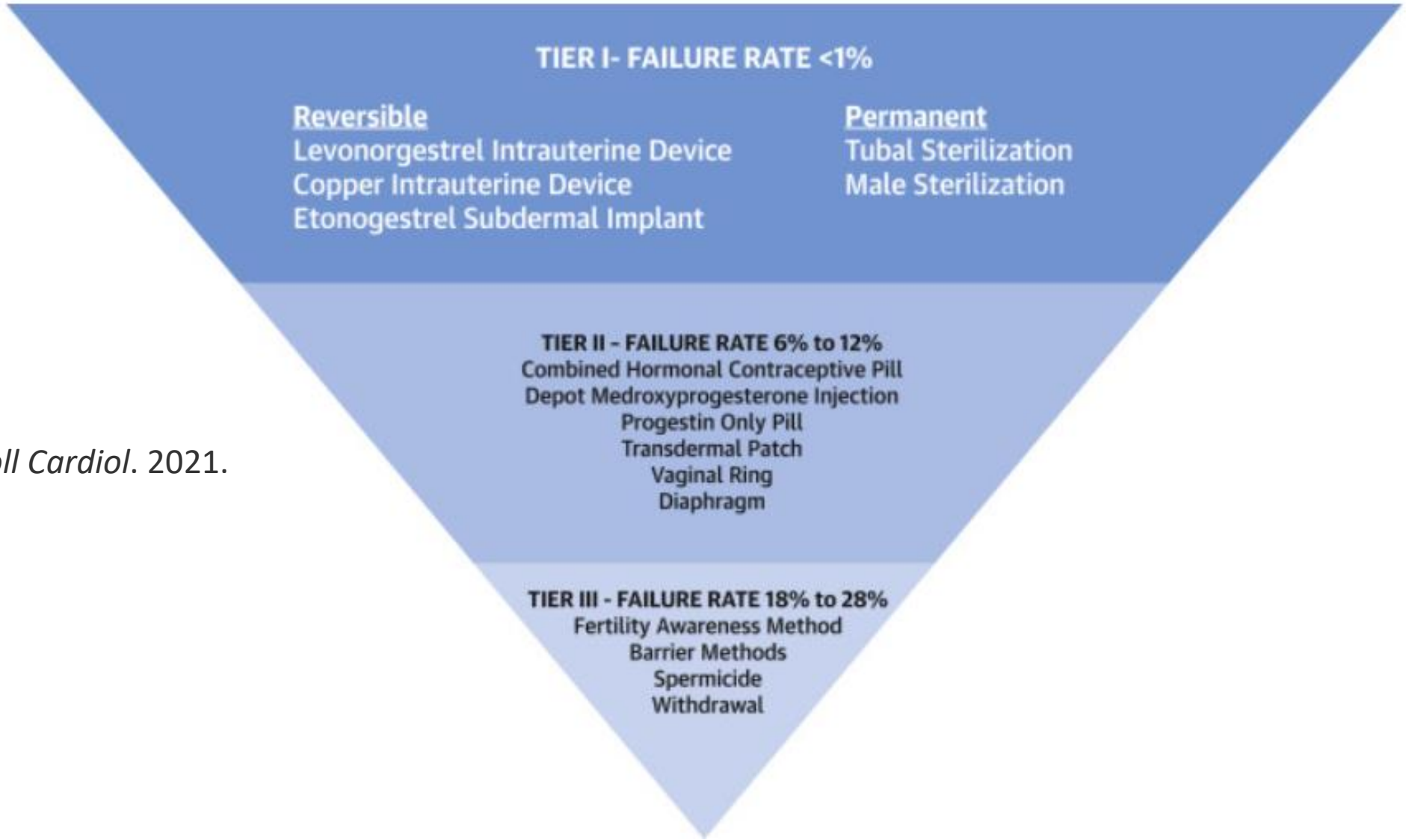
TIER 1 INTERVENTIONS

Lindley et al., 2021.

CHC/Transdermal patch/Vaginal Ring	Progestin Only Pill	DMPA (injection)	Diaphragm
• **Increased risk of VTE** • Irregular bleeding • More predictable, lighter bleeding • Decreased cramping	• **Requires strict adherence** • Irregular bleeding • **No increased risk of VTE** • **More predictable, lighter bleeding** • Decreased cramping	• **Possible increased risk of VTE** • Irregular bleeding • **Weight gain** • **Reversible bone loss** • **Delayed return to fertility** • Lighter menses • Decreased cramping	• **Requires correct use with each act of intercourse** • **Increased risk of UTI, allergic reaction, TSS** • No effect on hormones or breastfeeding

TIER 2 INTERVENTIONS

Lindley et al., 2021.



Lindley et al. *J Am Coll Cardiol*. 2021.

1 YEAR FAILURE RATES OF CONTRACEPTIVES

CASE #1: HISTORY OF ENDOCARDITIS

26 year old with history of aortic valve endocarditis resulting in moderate aortic regurgitation and stroke. She is an active 2PPD smoker.

Normal biventricular function

What contraceptive would you recommend?

- History of stroke and tobacco (relative contraindication) use put her at increased risk of thromboembolism
- Avoid estrogen containing contraceptive.
- Options: IUD (hormonal or copper), subdermal implant, or progestin pill

CASE #1 REVISED: HISTORY OF ENDOCARDITIS AND REDUCED LVEF

26 year old with a history of aortic valve endocarditis resulting in moderate aortic regurgitation and stroke. She smokes 2 PPD. She has severely reduced LVEF of 25%.

Now how would you counsel this patient regarding pregnancy and contraception?

CONTRAINDICATIONS TO PREGNANCY

- High or exceptionally high risk of cardiovascular complications during pregnancy (modified WHO risk III or IV)

- Need potentially teratogenic medications that might put fetus at risk
  - ACE-I/ARB
  - Spironolactone
  - Warfarin
  - Endothelin receptor blockers
  - Amiodarone

- **Recommend long-acting reversible contraceptives or permanent contraception**
  - **Annual failure rates <1 unintended pregnancy/100 users**

Kathryn & Teal, 2022.

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PHYSIOLOGIC CHANGES IN PREGNANCY

- Numerous physiological changes during normal pregnancy
- Allow for growth and development of the fetus
- Prepare for labor
- Almost every organ system is involved, including the cardiovascular system

INCREASE IN BLOOD PRODUCTION

- Increase in red blood cell mass (20-30%)
- Increase in plasma volume (30-50%)
- Increase in total blood volume with relative anemia
- Oxygen use increases up to 30% with pregnancy

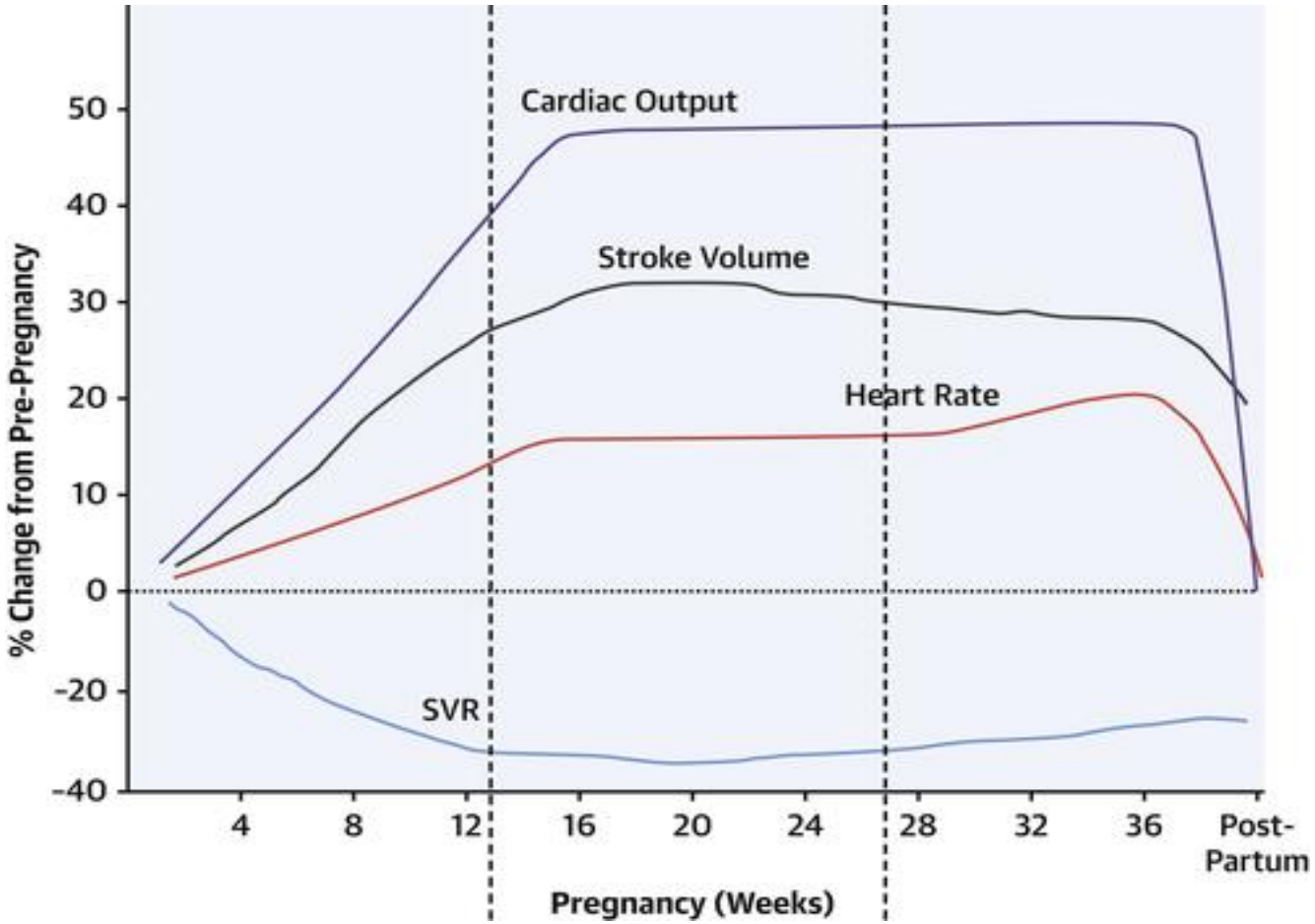
Mayo Clinic Cardiology Concise Textbook, 4th Edition. Pregnancy and the Heart. Heidi Connolly

HEMODYNAMICS

- Decrease in pulmonary and systemic vascular resistance
- Maternal heart rate rises by 10 beats/min
- Cardiac output = volume of blood pumped each beat × heart rate
  - Increases by 30-50% above baseline during pregnancy
  - Peak around 32nd week of pregnancy
  - Pregnant uterus can require almost 20% of the cardiac output

Mayo Clinic Cardiology Concise Textbook, 4th Edition. Pregnancy and the Heart. Heidi Connolly

Hemodynamic Changes of Pregnancy

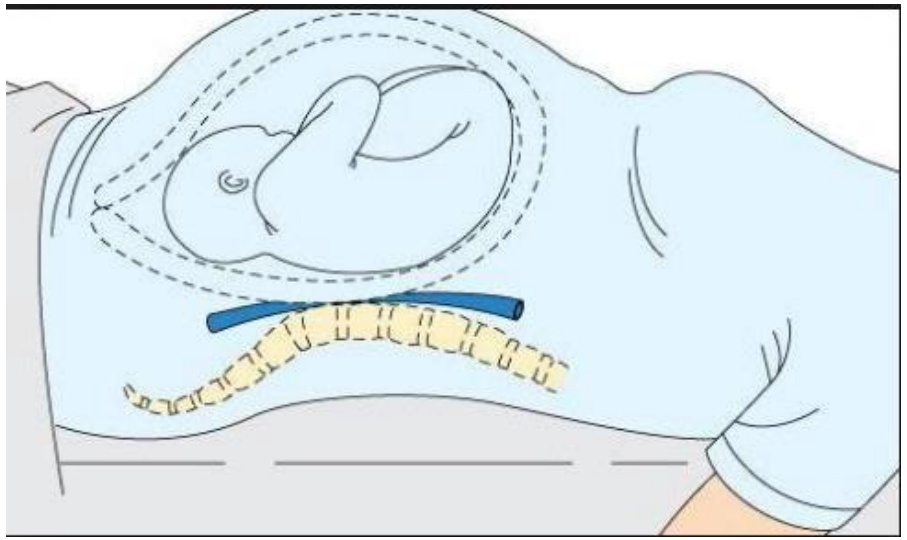


Melinda B. Davis et al. *J Am Coll Cardiol* 2021; 77:1763-1777.

JACC JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

BLOOD FLOW THROUGH THE BODY

- Blood volume depends on positioning during second half of pregnancy
- Enlarging uterus decreases blood return from veins in legs
  - Lying on back decreases blood return
  - Lying on left side allows for more blood return
- Supine hypotension syndrome:
  - Sweating
  - Low blood pressure
  - Low heart rate
  - Nausea/vomiting



CLOTTING

- Increased hypercoagulability during pregnancy
- Helps prevent significant blood loss at delivery
- 1-2/1000 pregnancies are complicated by VTE
- Antenatal:
  - Risk is 5-fold higher than in non-pregnant women
  - Deep venous thrombosis is more common
- Postnatal:
  - Risk is 20-fold higher than in non-pregnant women
  - Pulmonary embolism is more common

Greer IA, 2012.

LABOR AND DELIVERY

- Uterus contraction: 300-500 mL of blood is pushed back into the circulation
- Blood pressure and heart rate increase
- Cardiac output increases by as much as 80% of pre-pregnancy level (up to 9 L/min)
- Up to 500 mL of blood is lost during vaginal delivery
- Up to 1L of blood is lost during normal cesarean section

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CASE #2- HIGH BLOOD PRESSURE

- 32 year old woman who is 36 weeks pregnant who has developed frequent headaches for the last 2 weeks…
- At her doctor's office, she is noted to have a blood pressure of 180/90 mm Hg and leg swelling.
- A urine test shows that she has proteinuria.
- **What is the diagnosis in this case?**

HYPERTENSIVE DISORDERS OF PREGNANCY(HDP)

- 2nd leading cause of global maternal death
- Complicates ~11% of pregnancies
- Hypertension in pregnancy: $\geq \frac{140}{90}$ mm Hg

Chronic Hypertension

Gestational Hypertension

Preeclampsia

Eclampsia

Preeclampsia Superimposed on Hypertension

Garovic et al., 2022.

DEFINITIONS

Chronic Hypertension	• SBP $\geq$ 140 mm Hg or DBP $\geq$ 90 mm Hg • Before 20 weeks gestation • OR persists at least 12 weeks postpartum
Gestational Hypertension	• SBP $\geq$ 140 mm Hg or DBP $\geq$ 90 mm Hg • After 20 weeks gestation • Previously normal blood pressure
Severe Hypertension	• SBP $\geq$160 and/or DBP 110 mm Hg

Garovic et al. *Hypertension,* 2022.

PREECLAMPSIA

- SBP ≥140 mm Hg or DBP ≥ 90 mm Hg
  - two occasions at least 4 hours apart
  - after 20 weeks of gestation
  - previously normal blood pressure
- SBP ≥160 mm Hg or DBP ≥ 110 mm Hg
- Proteinuria
  - ≥ 300 mg/24 hour urine collection
  - Protein/creatinine ratio of ≥ 0.3

Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. June 2020.

PREECLAMPSIA (CONTINUED)

Any of the following w/out proteinuria:

- Thrombocytopenia
- Renal insufficiency
- Impaired liver function
- New-onset headache

HIGHEST RISK FOR PREECLAMPSIA

- Previous pregnancy with preeclampsia
- Multi-fetal gestation
- Renal disease
- Autoimmune disease
- Type 1 or 2 DM
- Chronic hypertension

Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. June 2020.

ECLAMPSIA/HELLP SYNDROME

- Generalized seizure in a patient with preeclampsia
- HELLP Syndrome:
  - **H**emolysis
  - **E**levated **L**iver enzymes
  - **L**ow **P**latelets
  - Hypertension may be present

Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. June 2020.

IMMEDIATE COMPLICATIONS OF HDP

	Mortality	MI	Stroke	Peripartum CM	SCAD
Chronic HTN	↑	↑	↑	↑	
Preeclampsia	↑	↑	↑	↑	↑
Gestational HTN		↑	↑	↑	
Preeclampsia on Chronic HTN	↑	↑	↑	↑	
Eclampsia			↑		

Parikh N. et al., 2021

FETAL/NEONATAL OUTCOMES

	SGA (birth weight <10th centile)	Stillbirth	Preterm delivery (<37 wks)	Preterm delivery (<34 wks)	Placental Abruption	Postpartum Hemorrhage
Severe HTN	↑		↑	↑		
Preeclampsia	↑	↑	↑	↑	↑	↑
Chronic HTN		↑	↑		↑	↑
Preeclampsia on chronic HTN		↑	↑		↑	↑
Gestational HTN					↑	↑

Parikh N. et al., 2021

LONG TERM MATERNAL COMPLICATIONS OF HDP

- Hypertension (≥140/90 mm Hg)
- Type 2 DM
- Hyperlipidemia
- Coronary heart disease
- Heart failure
- Atrial fibrillation
- Stroke
- Ischemic/Intracerebral/Subarachnoid hemorrhage
- Vascular dementia
- Chronic kidney disease
- Venous thromboembolism

Parikh N. et al., 2021

PREVENTION OF PREECLAMPSIA

- Low dose aspirin (81-150 mg daily):
  - Started at 12-16 weeks of gestation
  - Patients with $\geq$ 1 high risk factor (history of preeclampsia, chronic HTN, multifetal pregnancy, autoimmune disease, DM, chronic kidney disease)
  - OR $\geq$ 2 moderate risk factors
- Treatment of chronic hypertension (Tita A, et al. 2022)
- Exercise may be helpful

Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. June 2020.

TREATMENT

- Eclampsia/Preeclampsia/Severe HTN: Delivery is the treatment of choice
- Observation appropriate if <37 weeks
  - Gestational hypertension
  - Preeclampsia without severe features
- Delivery with gestational hypertension/preeclampsia with severe features >34 weeks
- Seizures or seizure prophylaxis: magnesium, lorazepam
- Blood pressure management

Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. June 2020.

ANTIHYPERTENSIVE THERAPY

- Persistent acute-onset severe HTN (>15 minutes)
  - Treatment as soon as possible, within 30-60 minutes
  - IV hydralazine, labetalol, or oral nifedipine
  - Attempt to reduce MAP by no more than 25% over 2 hours
  - Goal 130-150/80-100 mm Hg

- Mild chronic hypertension:
  - Treatment debated
  - Chronic hypertension and pregnancy (CHAP) project

Tita, A et al, 2022.

CASE #2- HIGH BLOOD PRESSURE

- 32 year old woman who is 36 weeks pregnant who has developed frequent headaches for the last 2 weeks…
- At her doctor's office, she is noted to have a blood pressure of 180/90 mm Hg and leg swelling.
- A urine test shows that she has proteinuria.
- **What is the diagnosis in this case?**

CASE #2- HIGH BLOOD PRESSURE

What is the diagnosis in this case?

- This patient has preeclampsia with severe features
- Treatment with IV antihypertensives (labetalol or hydralazine)
- Admit with plan for delivery

PERIPARTUM CARDIOMYOPATHY (PPCM)

- Definition:
  - Maternal heart failure with systolic dysfunction (LVEF < 45%)
  - Develops in the last month of pregnancy or the first 5 months after delivery
  - Absence of known preexisting cardiac dysfunction

- Complicates approximately 1 in 2000 births worldwide (Viljoen C. 2023)

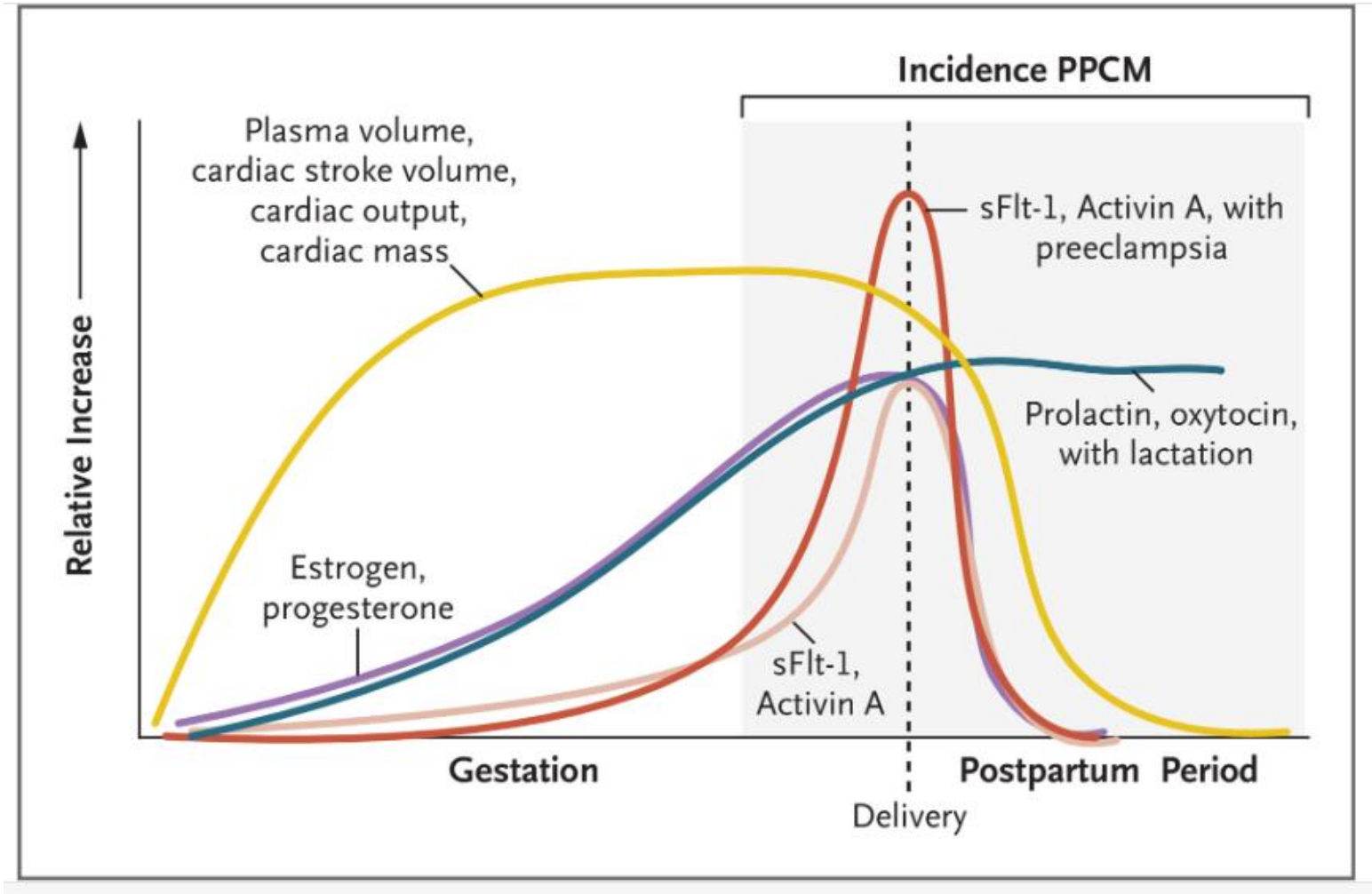
RISK FACTORS FOR PPCM

- African descent
- Hypertensive diseases of pregnancy
- Multiple gestations
- Advanced maternal age
- Anemia
- Maternal cocaine abuse
- Long term (>4 weeks) oral tocolytic therapy
- Parity≥4

PPCM PATHOGENESIS

Hormones released peripartum:

- Pituitary gland:
  - Prolactin
  - Oxytocin
- Placenta:
  - Fms-like tyrosine kinase
  - Activin A

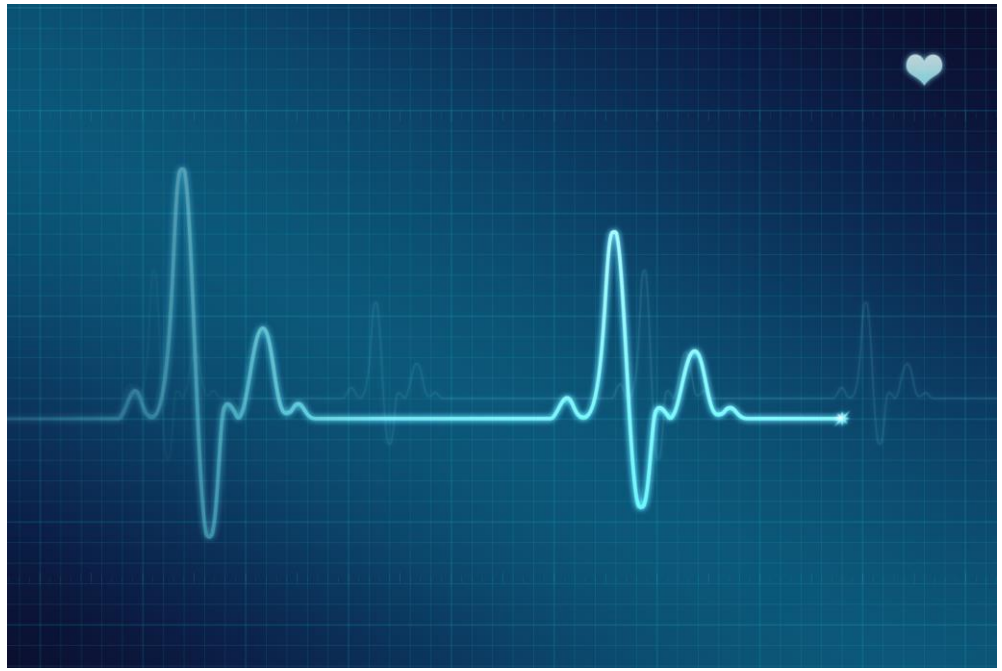


Arany, Z. *NEJM.* Jan 2024.

CLINICAL PRESENTATION OF PPCM

- Signs and symptoms of heart failure:
  - Dyspnea
  - Orthopnea
  - Elevated jugular venous pressure
  - Pulmonary rales
  - Edema
- Potential cardiogenic shock, arrhythmia, thromboembolism
- Can mimic normal symptoms of pregnancy

WORK-UP



- Thorough history
- Electrocardiogram
- BNP
- Echocardiogram
  - Systolic dysfunction, often dilated left ventricle
  - Absence of other structural heart disease
- Genetic testing: approximately 15% have heterozygous loss of function genetic variants associated with NICM

Zoltan A, 2024.

MANAGEMENT

- Based on guideline directed medical treatment for nonischemic cardiomyopathy
- Diuretics and nitrates for volume control
- ACE-I, ARBs, sacubitril-valsartan, aldosterone receptor antagonists
  - Contraindicated before delivery
  - ACE-I can be used while breastfeeding
- Hydralazine/isosorbide dinitrate for afterload reduction during pregnancy
- Beta-blockers are considered safe during pregnancy and breastfeeding
- SGLT2 inhibitors: Avoid during pregnancy and breastfeeding (not studied)

Zoltan A, 2024.

CONTROVERSIAL TREATMENTS

- Bromocriptine:
  - Blocks release of prolactin from the pituitary gland
  - Inadequate trials evaluating safety and efficacy
  - Stops breastmilk production

- Anticoagulation:
  - Traditional risk factors (atrial fibrillation, LV thrombus)
  - Use of bromocriptine
  - More aggressive approach: LVEF < 30-35%

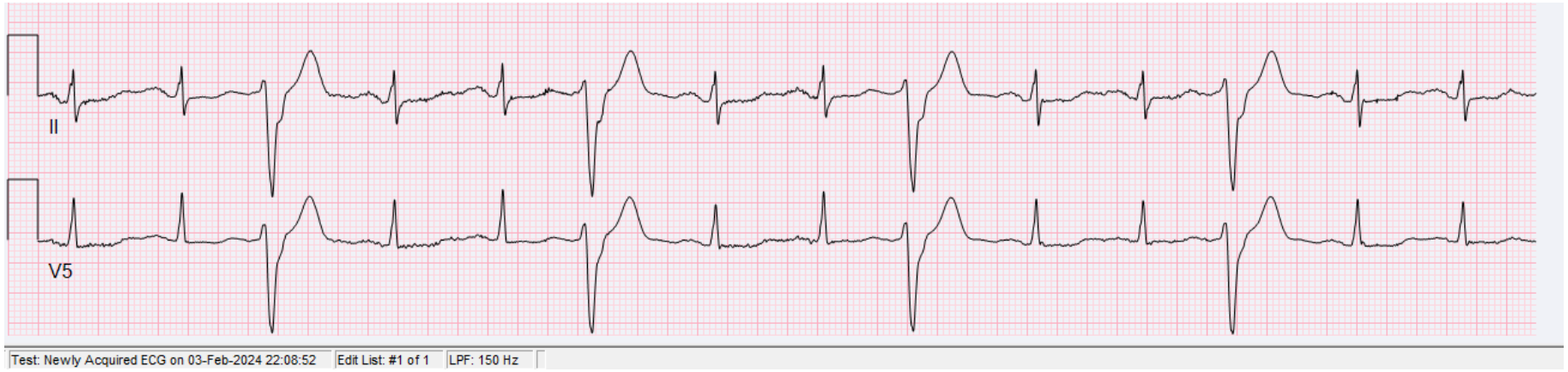
Zoltan A., 2024.

OUTCOMES

- LVEF typically increases to > 50% within 6 months of diagnosis (McNamara DM, 2015)
- Lower LVEF at presentation correlates with persistent systolic dysfunction
- LVADs and cardiac transplants occasionally required
- **Recurs in 20-50% of subsequent pregnancies (Elkayum U, 2014)**
- **Mortality: ~4% of patients died at 1 year (McNamara DM, 2015)**

ARRHYTHMIAS IN PREGNANCY

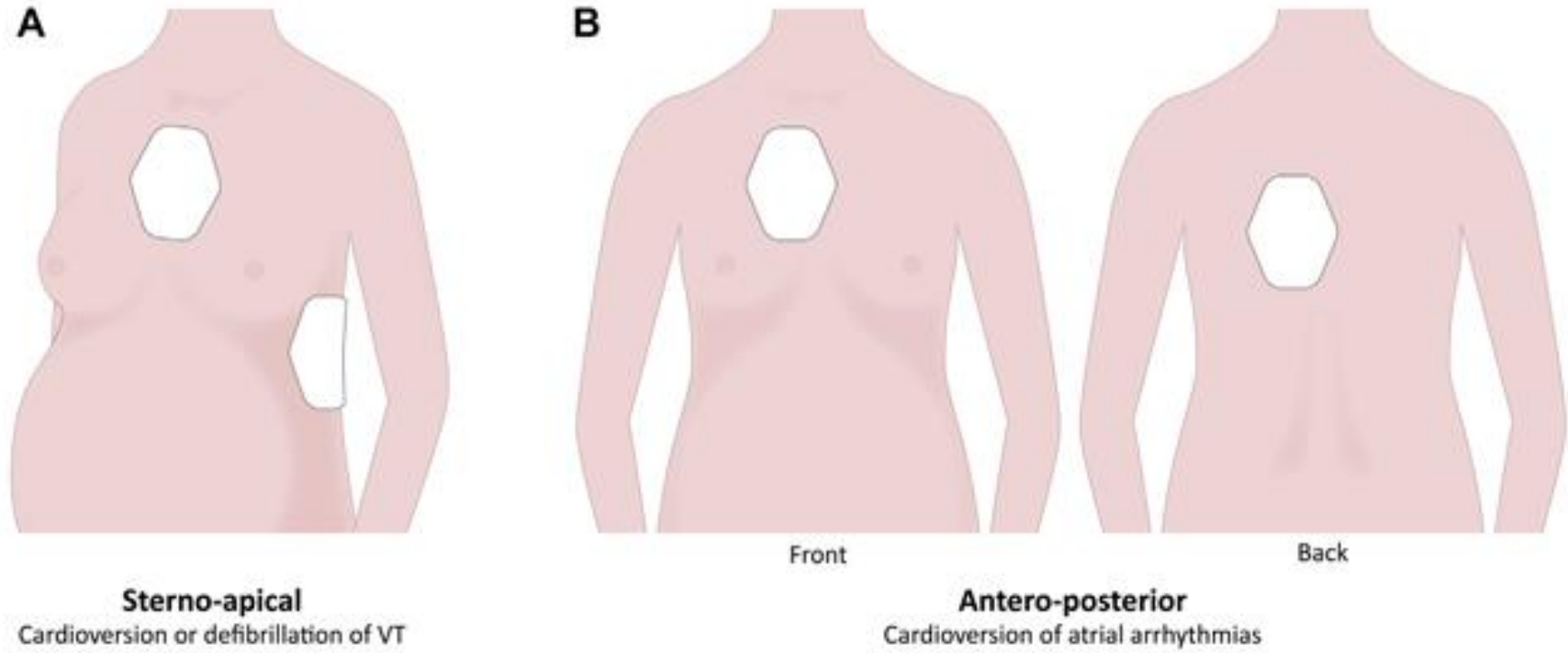
- Most common: premature ventricular and atrial ectopic beats
- Increased rates of atrial fibrillation and ventricular tachycardia
- Bradycardia is unusual



Shotan A et al., 1997.

CARDIOVERSION DURING PREGNANCY

- Goal to restore a perfusing rhythm
- Rapid VT or unstable SVT with significant hemodynamic compromise



Joglar et al. *Heart Rhythm*, 2023.

SYNCOPE DURING PREGNANCY

- Occurs in approximately 1% of pregnancies (Chatur S. J Am Heart Assoc. 2019)

- Causes classified similarly to general population:
  - Neurally mediated: vasovagal, situational, carotid sinus syndrome
  - Orthostatic hypotension: volume depletion, drug induced, neurogenic
  - Cardiac syncope: **arrhythmia,** structural disease
  - **Supine orthostatic hypotension and syncope**
  - Psychogenic pseudosyncope

Joglar et al. HRS Management of Arrhythmias During Pregnancy, 2023.

PREGNANCY ASSOCIATED MYOCARDIAL INFARCTION (PAMI)

- Myocardial infarction during pregnancy or the postpartum period (6-12 weeks postpartum)
- Accounts for over 20% of maternal cardiac deaths (Pregnancy Mortality Surveillance System, 2020)
- PAMI occurs in about 3-8/100,000 deliveries (Smilowitz NR et al., 2018)
- Majority of cases occur postpartum in the US (Smilowitz NR et al, 2018)
- In 150 case reports of PAMI, 75% of cases presented with STEMI (Elkayam U et al., 2014)

PAMI CAUSES

- Majority of cases due to obstructive coronary disease and spontaneous coronary artery dissection
- In-situ thrombosis or embolus
- Coronary vasospasm
- MI with nonobstructive (<50% stenosis) coronary artery disease
  - Coronary plaque disruption with thrombosis and spontaneous thrombolysis
  - Coronary vasospasm with resolution
  - Microvascular dysfunction

Elkayam U. et al., 2014

TREATMENT

- Can receive aspirin, heparin, clopidogrel, nitrates, beta-blockers
  - May need to hold P2Y12 inhibitor for neuraxial anesthesia
- No statin, ACE-I or ARB, aldosterone antagonist while pregnant
- Ionizing radiation from coronary angiography and PCI is considered acceptable
- Cardiac rehab
- Blood pressure control, tobacco cessation, healthy diet, exercise, lipid management

Tweet M et al., Nov 2020.

DELIVERY PLAN

- Delivery plans created by 20-28 weeks gestation
- Consider induction for stable cardiac patients at 39 weeks
- Earlier delivery possible for high-risk conditions:
  - Serious cardiac complications
  - Hemodynamic instability

Regitz-Zagrosek V et al., 2011

VAGINAL DELIVERY WITH CVD

- *Preferred method of delivery with a few exceptions*

- Associated with fewer maternal complications with adequate analgesia
  - Shortened hospital stay
  - Reduced risk of sudden death
  - Peripartum infections
  - Hemorrhage

Regitz-Zagrosek V et al., 2011

WHEN C-SECTIONS PREFERRED

- Marfan with dilated aorta > 45 mm
- Some other high risk aortopathies: history of acute or chronic aortic dissection
- Women who receive therapeutic anticoagulation with vitamin K antagonists
- Severe pulmonary arterial hypertension
- Women in acute decompensated heart failure requiring urgent delivery
- Severe aortic or mitral stenosis

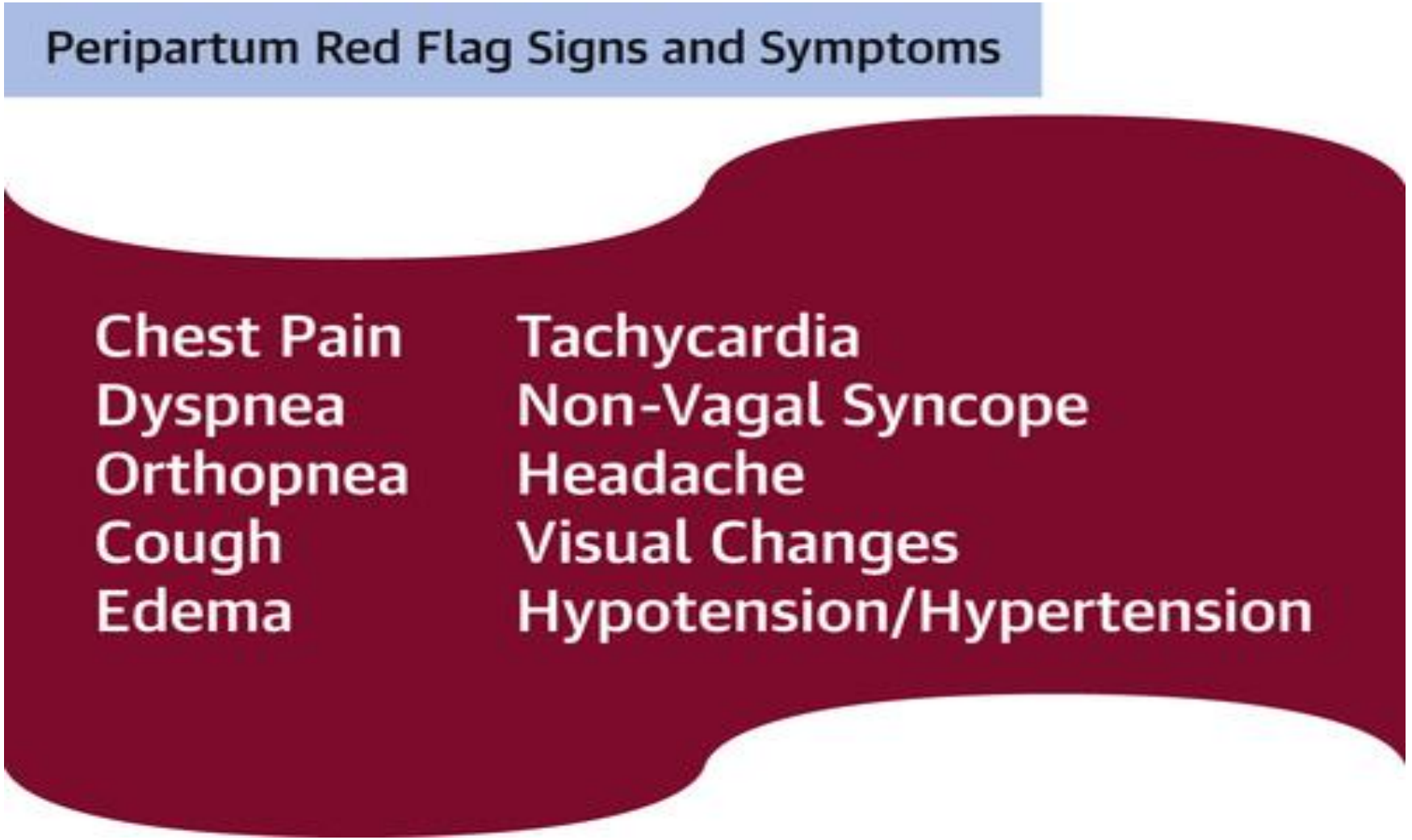
Regitz-Zagrosek V et al., 2011.

OUTLINE

- Reproductive years
  - Menarche
  - Pregnancy counseling and contraception
  - Physiologic changes of pregnancy
  - Cardiac complications of pregnancy
  - **Postpartum**
- Menopause
  - Impact on cardiovascular risk
  - Hormonal therapy

THE FOURTH TRIMESTER

- Period following delivery through the first 12 weeks postpartum
- Cardiac complications are common in the first days to months postpartum
- Readmission within 6 weeks postpartum (Lima F et al, 2019):
  - Heart failure
  - Arrhythmias
  - Hypertensive syndromes
  - Pregnancy complications (i.e hemorrhage, infection)
- **Over half of pregnancy related deaths occur days 7-365 postpartum (Trost SL et al, 2022)**



Melinda B. Davis et al. *J Am Coll Cardiol* 2021; 77:1763-1777.

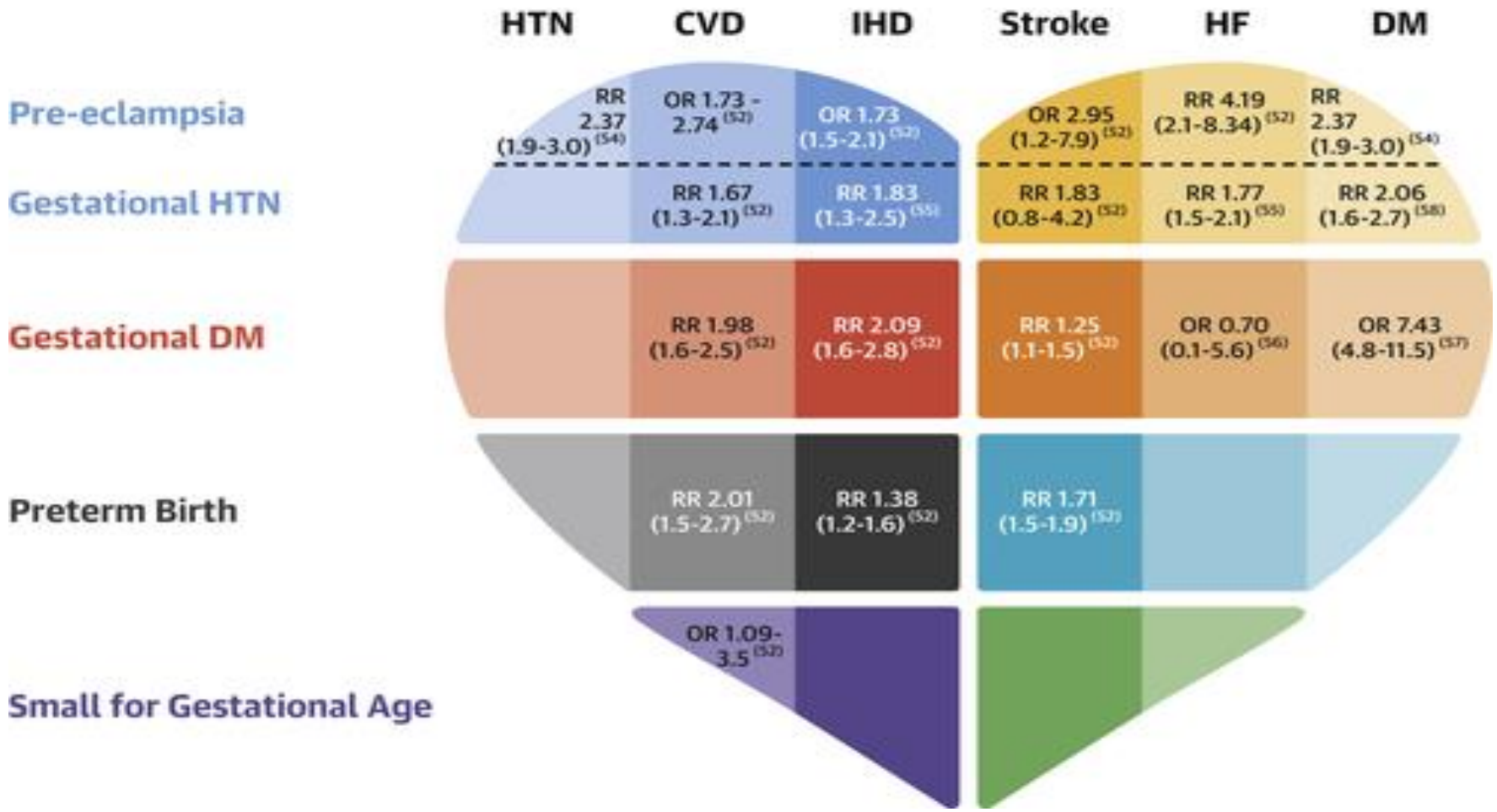
POSTPARTUM HTN AND PREECLAMPSIA

- Pre-eclampsia can develop de novo postpartum

- Other causes of postpartum hypertension
  - Persistence of gestational hypertension
  - Chronic hypertension

- Any woman with hypertensive disorder:
  - BP check 7-10 days postpartum
  - Severe hypertension patients should be seen within 72 hours

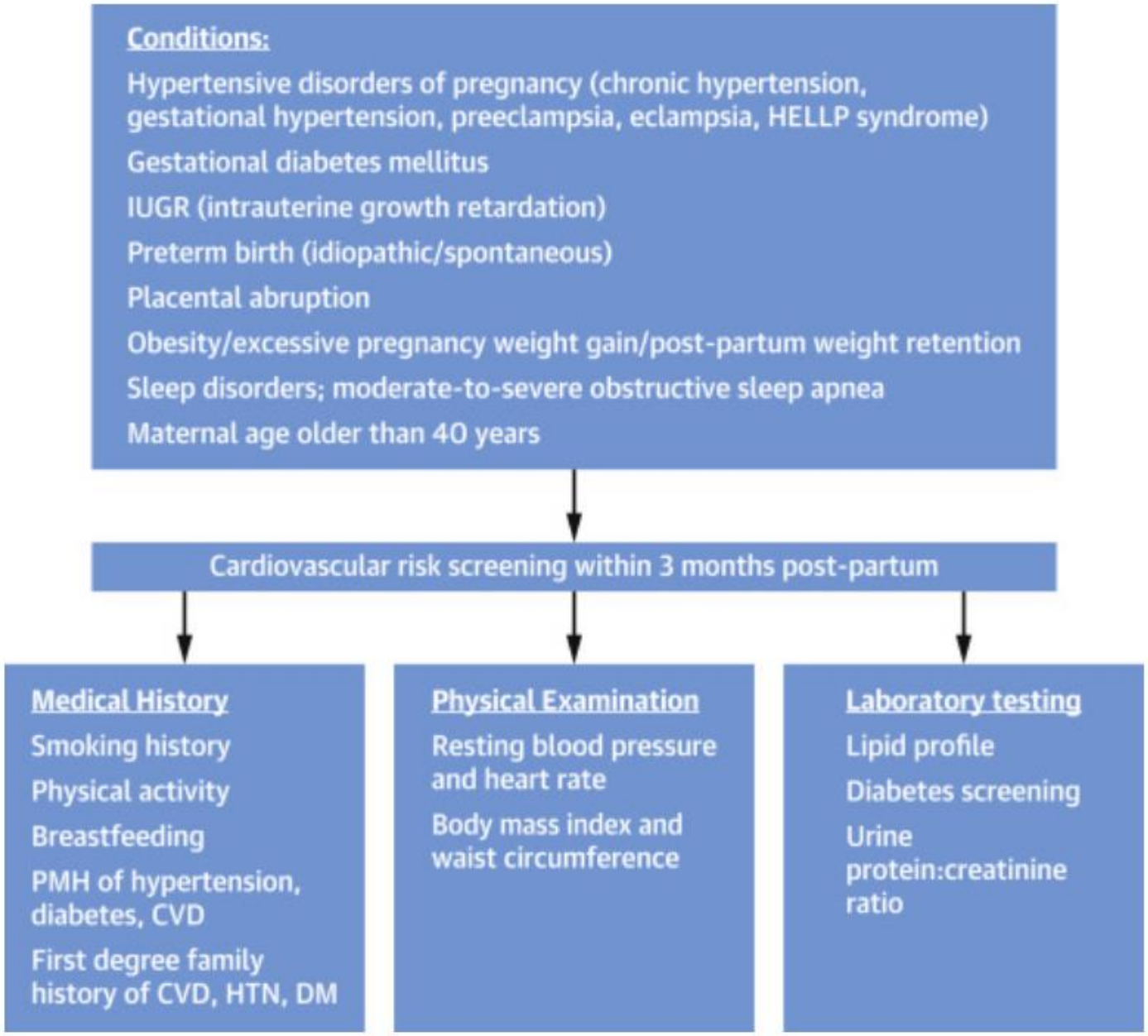
ADVERSE PREGNANCY OUTCOMES AND FUTURE CARDIOVASCULAR RISK



Melinda B. Davis et al. *J Am Coll Cardiol* 2021; 77:1763-1777.

JACC JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

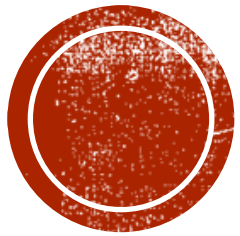
CVD RISK SCREENING AFTER ADVERSE PREGNANCY OUTCOME



Cho L. et al. 2020

REPRODUCTIVE YEARS: TAKE HOME POINTS

- Pregnancy is a form of a stress test
- Discuss pregnancy plans with cardiovascular patients
- Cardiovascular disease and several risk factors are contraindications for combined oral contraceptives
- Obstetric history can predict cardiovascular risk



QUESTIONS

OUTLINE

- Reproductive years
  - Menarche
  - Pregnancy counseling and contraception
  - Physiologic changes of pregnancy
  - Cardiac complications of pregnancy
  - Postpartum
- **Menopause**
  - Impact on cardiovascular risk
  - Hormonal therapy

CASE #3: HOT FLASHES

- A 48 year old female veteran presents with worsening hot flashes.

- Past Medical History:
  - Hypertension
  - Paroxysmal atrial fibrillation (diagnosed 2019)- on Apixaban, bisoprolol, diltiazem
  - Obesity, BMI: 35
  - Obstructive sleep apnea on CPAP
  - Anxiety

- Tobacco: former smoker (quit 2007), ½ PPD x4 years

- Pertinent family history: Father- MI in his 40s s/p angioplasty

- Physical Exam: BP: 125/60 mm Hg, P: 70 bpm, obese but otherwise unremarkable

CASE #3: HOT FLASHES

1. What is the treatment for hot flashes with menopause?
2. Is it safe for this patient to be on treatment?
3. What is the best treatment for her?

OUTLINE

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  - **Impact on cardiovascular risk**
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MENOPAUSE DEFINITION

- Permanent cessation of ovarian function
- Transition to a nonreproductive phase of life
- Median age of menopause is 51
  - Premature: before age 40
  - Early: 40-45 years old
- Natural menopause: 12 consecutive months of amenorrhea

MENOPAUSE TRANSITION

- Time preceding final menstrual period (FMP)
- Average of 4 years in the menopause transition
- Changes in bleeding pattern and hormone profiles
- Four primary hormones:
  - Follicle stimulating hormone (FSH)
  - Anti-Mullerian hormone (AMH)
  - Inhibin B
  - Estradiol

STAGES OF REPRODUCTIVE AGING

Stages	Reproductive			Menopause/Transition		Postmenopause		
Terminology	Early	Peak	Late	Early	Late	Early		Late
Menstrual Cycles	Variable to regular	Regular	Regular	Variable (>7 days different from normal)	>2 skipped cycles and an interval of amenorrhea (>60 day)	Amenorrhea~12 months	None	None

[**Perimenopause**]

Harlow et al. *Menopause.* 2012.

REPRODUCTIVE AGING AND HORMONES

	Peak Reproductive	Late Reproductive	Early MT	Late MT	FMP Post-menopause
FSH	Normal	↑	↑	↑	↑
AMH	Normal/↓	↓	↓	Undetectable	Undetectable
Inhibin B	Normal	↓	↓	Undetectable	Undetectable
Estradiol	Normal	Normal	Normal	↓	↓

Su & Freeman, Nov 2013.

MENOPAUSE SYMPTOMS

- Hot flashes- approximately 85% of women
- Sleep disturbances
- Depression
- Joint aches
- Genitourinary syndrome

IMPACTS OF MENOPAUSE

- Central adiposity
- Atherogenic dyslipidemia during transition:
  - Increase in total cholesterol, low-density cholesterol, triglycerides
  - Decrease in high density lipoprotein cholesterol
- Glucose intolerance
- Hypertension
- Non-alcoholic fatty liver disease
- Lower estrogen alters vascular function

Anagnostis P et al., 2019

DOES MENOPAUSE INCREASE CARDIOVASCULAR DISEASE RISK?

- Women develop ischemic heart disease about a decade after men (Kannel et al, 1976)
- Increase in coronary heart disease around the time of menopause transition
- Difficult to distinguish from the effects of aging

- **Early menopause (<40 years old) and premature ovarian insufficiency**
  - Associated with increased cardiovascular morbidity and mortality
  - Primarily ischemic heart disease

Muka T et al., 2016

HEALTHY LIFESTYLE IN MENOPAUSE

- Heart healthy diet
- Regular exercise
- Smoking cessation
- Not recommended: routine use of aspirin and statin

OUTLINE

- Reproductive years
  - Menarche
  - Pregnancy counseling and contraception
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- Menopause
  - Impact on cardiovascular risk
  - **Hormonal therapy**

REASONS FOR MENOPAUSAL HORMONE THERAPY (MHT) PRESCRIPTION

- **Hot flashes (vasomotor symptoms)**
- Sleep disturbances
- Mood lability/depression
- Joint aches and pains
- Genitourinary syndrome of menopause

TREATMENT OPTIONS

- Menopausal hormone therapy (MHT): Estrogen +/- progestin
- Non-hormonal therapies:
  - SNRIs
  - SSRIs
  - Gabapentinoids
  - Clonidine
  - Oxybutinin

MHT: ESTROGEN

- **Unopposed estrogen (ET) for women who have undergone hysterectomy**
- Estrogens:
  - Oral
  - Transdermal
  - Topical gels/lotions
  - Vaginal rings
  - Subcutaneous implant
- Dose: goal to use the lowest effective dose
- **Lower rate of VTE and stroke with transdermal compared to oral (Scarabin P.Y et al, 2003)**

MHT: ESTROGEN + PROGESTIN

- Combined estrogen-progestin (EPT) for women with a uterus
  - Progestin to prevent estrogen-associated endometrial hyperplasia
- Progestins: typically oral micronized progesterone
  - 200 mg/day for 12 days/month(cyclic)
  - 100 mg daily (continuous)
  - Take at bedtime to minimize potential associated somnolence
- **Micronized progesterone may be less thrombogenic than synthetic progestins**

WOMEN'S HEALTH INITIATIVE (WHI)

- Randomized, placebo-controlled study of healthy postmenopausal women 50-79 (mean age 63)
- 16,608 women with a uterus randomized: oral CEE + MPA vs placebo
- 10,739 women with hysterectomy randomized: oral CEE vs placebo
- Primary efficacy outcome: coronary artery disease mortality or non-fatal MI
- Primary safety outcome: invasive breast cancer

Rousseau, JE et al., 2002; Anderson, JL et al., 2004

WHI OUTCOMES

- Oral estrogen + progestin:
  - **Higher rate of coronary artery disease mortality and non-fatal MI**
  - Higher rates of invasive breast cancer
  - Higher rates of VTE and strokes
  - Fewer skeletal fractures

- Oral estrogen alone:
  - **No increase in coronary artery disease mortality and non-fatal MI**
  - Increased risk of stroke and venous thrombosis
  - Decreased hip fractures and diabetes

Rousseau, JE et al., 2002; Anderson, JL et al., 2004

TIMING HYPOTHESIS

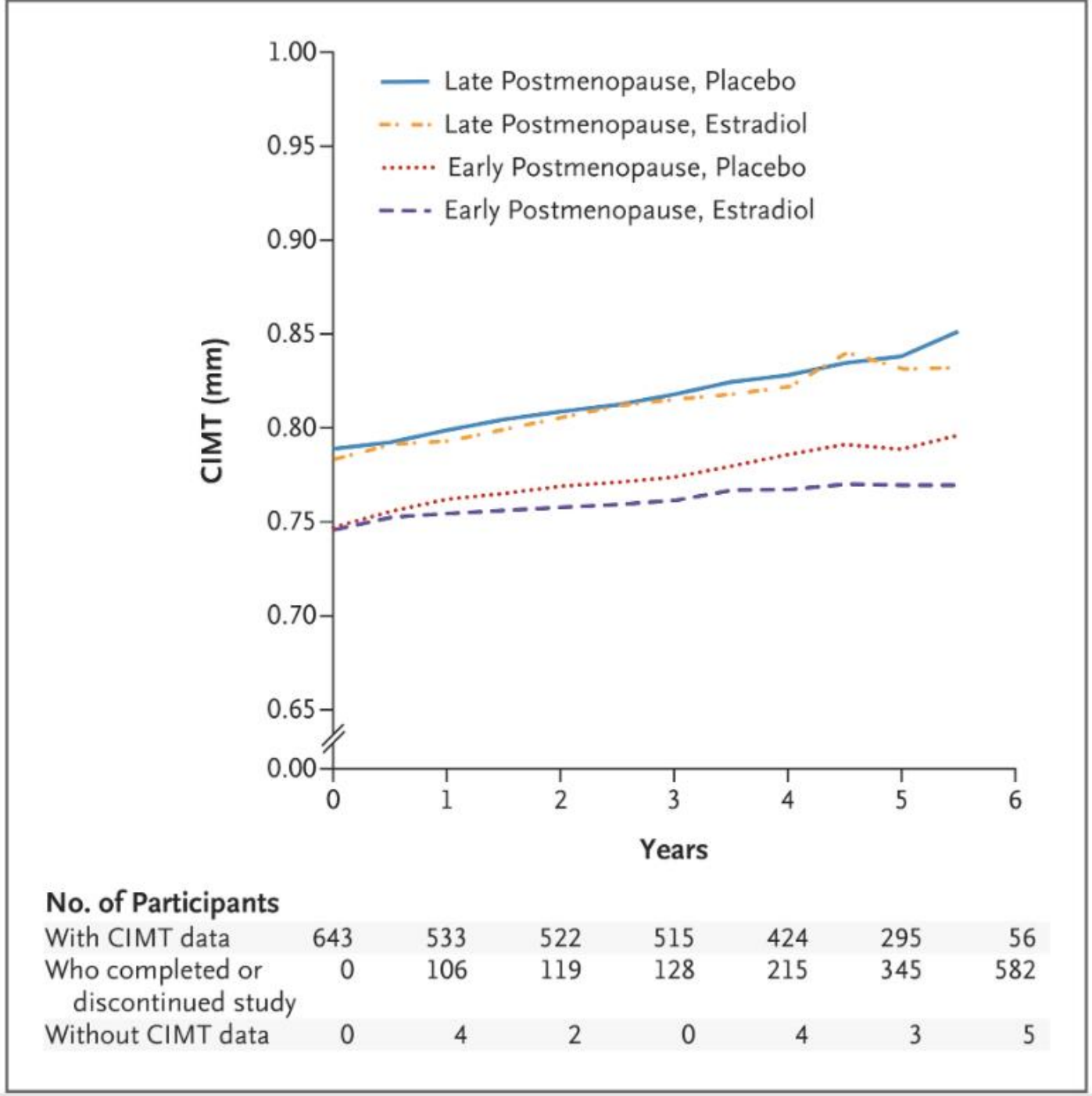
- MHT may provide coronary artery disease benefit in younger women
- Estrogen may protect against development of atherosclerosis
- Increased disease complications when coronary disease already present
- Supported by combined analysis of the two WHI MHT trials

Roussouw, JE. et al., 2007

EARLY VS. LATE POSTMENOPAUSAL TREATMENT WITH ESTRADIOL (ELITE)

- Randomized 643 women to two timing groups:
  - Early: less than 6 years from menopause
  - Late: over 10 years since menopause
- Oral 17-beta estradiol 1 mg /d + progesterone vaginal gel 45 mg for 10 to 30 days
- Follow-up: vitals, biomarkers, CIMT every 6 months, CAC at baseline and 5 years

Hodis HN et al., 2016



No. of Participants							
With CIMT data	643	533	522	515	424	295	56
Who completed or discontinued study	0	106	119	128	215	345	582
Without CIMT data	0	4	2	0	4	3	5

CIMT PROGRESSION ACCORDING TO STUDY GROUP AND POSTMENOPAUSAL STRATUM

Hodis HN et al., 2016

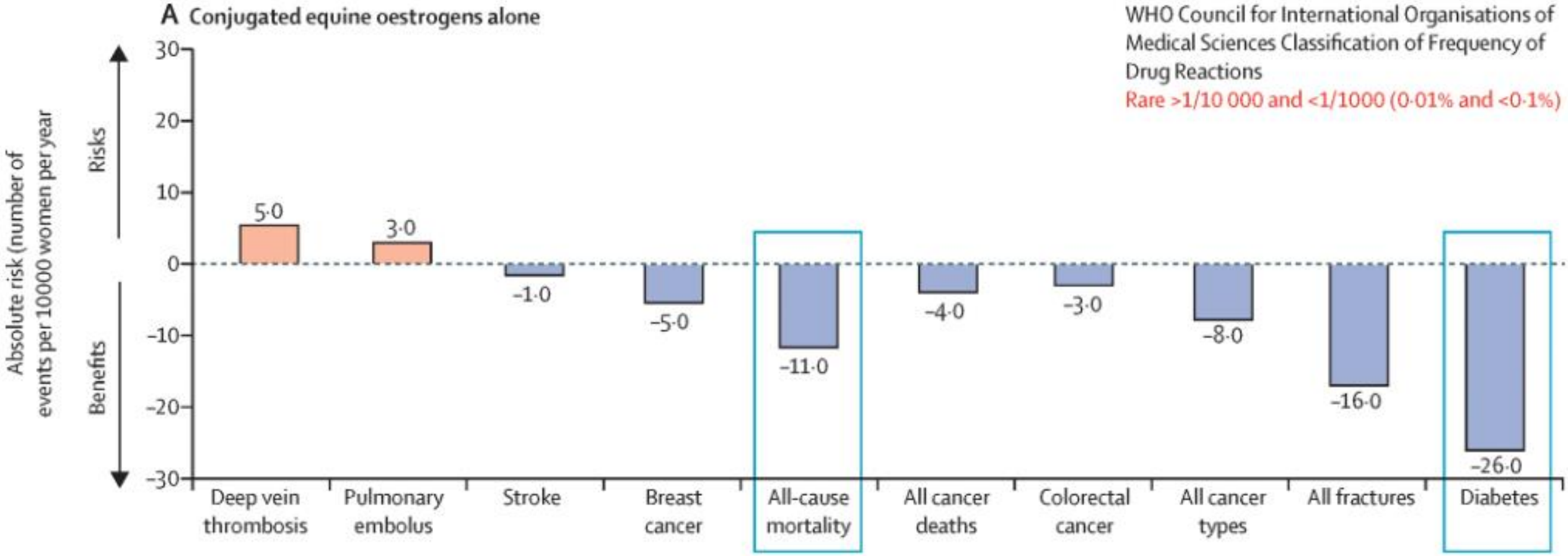
HORMONE THERAPY AND CVD RISK

- Two meta-analyses by Salpeter, et al in 2004 and 2006:
  - MHT in <60 years of age and/or <10 years-since-menopause compared to placebo
  - Reduced all-cause mortality and coronary heart disease by >30%

- Danish Osteoporosis Prevention Study (Schierbeck LL et al, 2012):
  - 1000 women in early post menopause randomized to oral estradiol +/- progestin vs. no treatment
  - MHT reduced composite endpoint of MI, death or hospitalization for heart failure

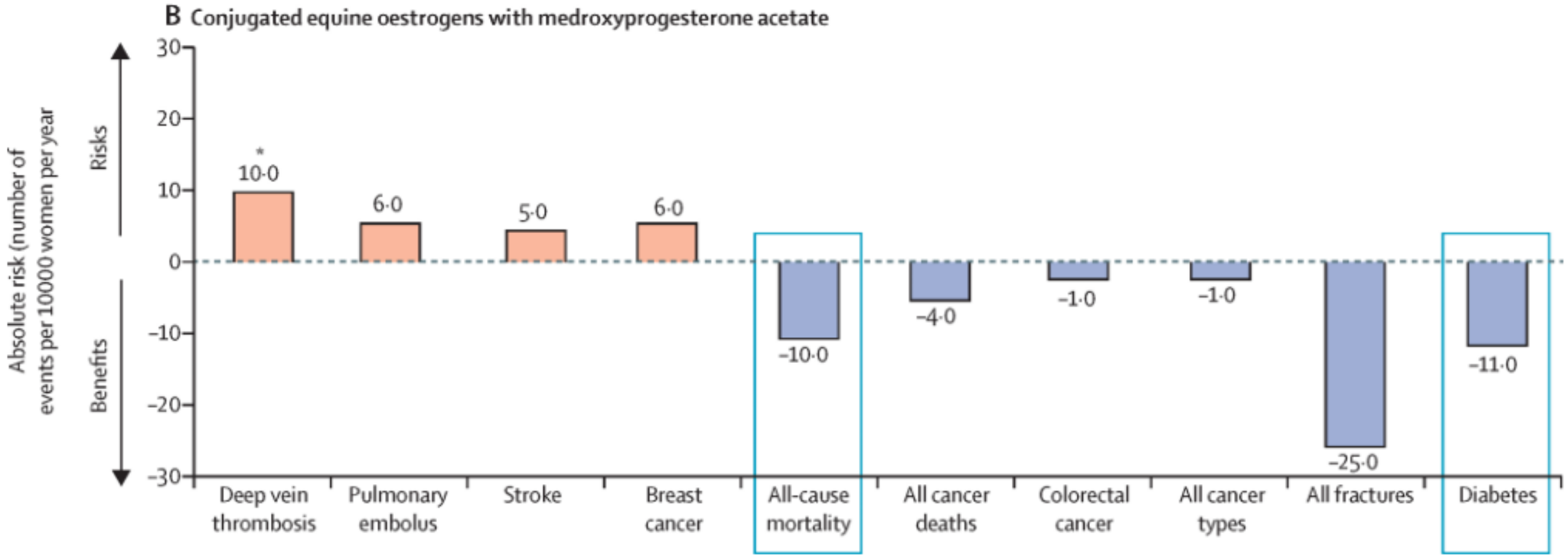
- **MHT considered safe for healthy (low CVD disease risk) women if:**
  - **Under 60 years old**
  - **Less than 10 years since the onset of menopause**

WHI ESTROGEN ALONE



Manson, JE 2017; Lobo & Gompel. 2022

WHI ESTROGEN+PROGESTIN



Manson, JE 2017; Lobo & Gompel. 2022

MHT: RISK OF STROKE, VTE, AND PE

- A 2015 Cochrane Database (Boardman HM et al) showed MHT was associated with:
  - Additional 6 strokes per 10,000 women
  - Additional 8 cases of VTE per 10,000 women
  - Additional 4 cases of pulmonary embolism per 10,000 women

- Transdermal MHT:
  - Less risk of stroke
  - No increased risk of VTE

RISK ASSESSMENT FOR MHT

Higher Risk/Avoid MHT	Definite Risk for CVD/Caution with MHT	Lower Risk/Acceptable for MHT
Known ASCVD/CAD/PAD Known VTE or PE Known Stroke/TIA or MI Known clotting disorder Known breast cancer 10 year ASCVD risk >= 7.5%	Diabetes Smoking Uncontrolled HTN Obesity/Sedentary/Limited mobility SLE/RA/Migraine with aura High TG or Uncontrolled Cholesterol Levels 10 year ASCVD risk ≥ 5-7.4%	Recent Menopause Normal weight Normal blood pressure Active female 10 year ASCVD risk ≤ 5 %

Lundberg & Wenger, 2019

TREATMENT CONSIDERATIONS

- High cardiovascular risk: Nonhormonal therapies
- Moderate cardiovascular risk:
  - Transdermal estrogen preferred over oral
  - Women with a uterus: micronized progesterone preferred to synthetics
- Moderate to high risk for breast cancer: Nonhormonal therapies

Stuenkel CA et al., 2015

MHT SUMMARY

- Do not use for primary or secondary prevention of coronary heart disease
- Indicated for symptoms of menopause
- Individualized cardiovascular risk assessment
- Young age+ early menopause + good cardiovascular health = low CVD risk with MHT
- Encourage heart healthy lifestyles to reduce cardiovascular risk
- Duration of therapy is individualized

ACOG Committee Opinion No.565: Hormone therapy and heart disease, 2013

CASE #3: HOT FLASHES

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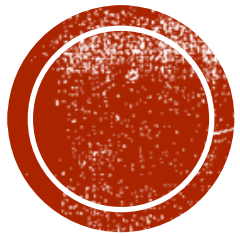
- Physical Exam: BP: 125/60 mm Hg, P: 70 bpm, obese but otherwise unremarkable

CASE #3: HOT FLASHES

1. What is the treatment for hot flashes with menopause?
   - MHT or non-hormonal therapies such as SNRIs and SSRIs

2. Is it safe for this patient to be on treatment?
   - Potential risk factors:
     - Obesity
     - Atrial fibrillation on AC (CHADS2VASC: 1)
     - 10 year estimated risk of a major cardiovascular event: 1.6%
     - Moderate cardiac risk patient

3. What is the best treatment for her?
   - Consider transdermal estrogen + progestin treatment



THANK YOU

references

- ACOG Committee Opinion No. 565: Hormone therapy and heart disease. Obstet Gynecol. 2013 Jun;121(6):1407-1410. doi: 10.1097/01.AOG.0000431053.33593.2d. PMID: 23812486.
- Anagnostis P, Paschou SA, Katsiki N, Krikidis D, Lambrinoudaki I, Goulis DG. Menopausal Hormone Therapy and Cardiovascular Risk: Where are we Now? *Curr Vasc Pharmacol.* 2019;17(6):564-572. doi: 10.2174/1570161116666180709095348. PMID: 29984659.
- Arany, Z. Peripartum Cardiomyopathy. *N Engl J Med.* Jan 2024; 390. 154-64. DOI: 10.1056/NEJMra2306667.
- Benjamin et al. American Heart Association Council on Epidemiology and Prevention: Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics- 2019 update; a report form the American Heart Association. *Circulation.* 2019; 139: e56-528.
- Boardman HM, Hartley L, Eisinga A, et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women. Cochrane Dababase Syst Rev 2015: CD002229.
- Carrasquilla GD, Frumento P, Berglund A, Borgfeldt C, Bottai M, Chiavenna C, Eliasson M, Engström G, Hallmans G, Jansson JH, Magnusson PK, Nilsson PM, Pedersen NL, Wolk A, Leander K. Postmenopausal hormone therapy and risk of stroke: A pooled analysis of data from population-based cohort studies. PLoS Med. 2017 Nov 17;14(11):e1002445. doi: 10.1371/journal.pmed.1002445. PMID: 29149179; PMCID: PMC5693286.
- Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death 1999–2018 on CDC WONDER Online Database, released in 2020.http://wonder.cdc.gov/ucd-icd10.html. Accessed April 28, 2020.
- Chatur S, Islam S, Moore L.E., Sandhu R.K., Sheldon R.S., Kaul P. Incidence of syncope during pregnancy: temporal trends and outcomes.*J Am Heart Assoc.* 2019; 8e011608

References, Continued

- Cho L. et al. Summary of Updated Recommendations for Primary Prevention of Cardiovascular Disease in Women. *JACC.* Vol 75 No. 20, 2020
- Davenport MH, Ruchat SM, Poitras VJ, Jaramillo Garcia A, Gray CE, Barrowman N, Skow RJ, Meah VL, Riske L, Sobierajski F, et al. Prenatal exercise for the prevention of gestational diabetes mellitus and hypertensive disorders of pregnancy: a systematic review and meta-analysis. *Br J Sports Med.* 2018; 52:1367–1375.
- Davis, M, Arendt, K, Bello, N. et al. Team-Based Care of Women With Cardiovascular Disease From Pre-Conception Through Pregnancy and Postpartum: JACC Focus Seminar 1/5. *J Am Coll Cardiol.* 2021 Apr, 77 (14) 1763–1777.
- Elkayam U, Jalnapurkar S, Barakkat MN, Khatri N, Kealey AJ, Mehra A, Roth A. Pregnancy-associated acute myocardial infarction: a review of contemporary experience in 150 cases between 2006 and 2011. *Circulation*. 2014;129:1695–1702.
- Elkayam U. Risk of subsequent pregnancy in women with a history of peripartum cardiomyopathy. *J Am Coll Cardiol.* 2014; *64*:1629–1636.
- Garovic VD, Dechend R, Easterling T, Karumanchi SA, McMurtry Baird S, Magee LA, Rana S, Vermunt JV, August P; on behalf of the American Heart Association Council on Hypertension; Council on the Kidney in Cardiovascular Disease, Kidney in Heart Disease Science Committee; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Lifestyle and Cardiometabolic Health; Council on Peripheral Vascular Disease; and Stroke Council. Hypertension in pregnancy: diagnosis, blood pressure goals, and pharmacotherapy: a scientific statement from the American Heart Association. *Hypertension.* 2022;79:e21–e41.

References, continued

- Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. Obstetrics & Gynecology 135(6):p e237-e260, June 2020.
- Greer IA. Thrombosis in pregnancy: updates in diagnosis and management. *Hematology (Am Soc Hematol Educ Program)* 2012; 2012: 203–207.
- Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, Sherman S, Sluss PM, de Villiers TJ; STRAW 10 Collaborative Group. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. *Menopause.* 2012 Apr;19(4):387-95. doi: 10.1097/gme.0b013e31824d8f40. PMID: 22343510; PMCID: PMC3340903.
- Harman SM, Black DM, Naftolin F, et al. Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: a randomized trial. *Ann Intern Med* 2014; 161(4): 249-260
- Hodis, HN, Mack WJ, Henderson VW, Shoupe D, Budoff MJ, Hwang-Levine J, Li Y, Feng M, Dusin L, Kono N; et al. Vascular effects of early vs. late postmenopausal treatment with estradiol. *NEJM.* 2016, 374, 1221-1231.
- Hoevelmann J, Engel ME, Muller E, et al. A global perspective on the management and outcomes of peripartum cardiomyopathy: a systemic review and meta-analysis. *Eur J Heart Fail* 2022; 24: 1719-36.
- Hsia J, Langer RD, Manson JE, Kuller L, Johnson KC, Hendrix SL, Pettinger M, Heckbert SR, Greep N, Crawford S, Eaton CB, Kostis JB, Caralis P, Prentice R; Women's Health Initiative Investigators. Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. *Arch Intern Med.* 2006 Feb 13;166(3):357-65. doi: 10.1001/archinte.166.3.357. Erratum in: Arch Intern Med. 2006 Apr 10;166(7):759. PMID: 16476878.
- Kannel WB, Hjortland MC, McNamara PM, Gordon T. Menopause and risk of cardiovascular disease: the Framingham study. *Ann Intern Med.* 1976; 85:447–452.

References, continued

- Kong L. et al. Nickel Nanoparticles Exposure and Reproductive Toxicity in Healthy Adult Rats. *International Journal of Molecular Sciences.* Nov 2014, 15 (11): 21253-21269.
- LÃ¸kkegaard E, Nielsen LH, Keiding N. Risk of Stroke with Various Types of Menopausal Hormone Therapies: A National Cohort Study. *Stroke.* 2017;48:2266-2269.
- Lee J. et al. Age of Menarche and Risk of Cardiovascular Disease Outcomes: Findings from the National Heart Lung and Blood Institute- Sponsored Women's Ischemia Syndrome Evaluation. *J Am Heart Assoc.* 2019 Jun 18; 8(12):e012406.doi:10.1161/JAHA.119.012406. Epub 2019 Jun 5. PMID: 31165670; PMCID: PMC6645646
- Lindley KJ, Bairey Merz CN, Davis MB, et al. Contraception and reproductive planning for women with cardiovascular disease. *J Am Coll Cardiol*. 2021;77(14):1823-1834.
- Lindley KJ, Bairey Merz CN, Asgar AW, et al. Management of women with congenital or inherited cardiovascular disease from pre-conception through pregnancy and postpartum. *J Am Coll Cardiol*. 2021;77(14):1778-1798.
- Lindley KJ, Teal SB. Contraception in women with cardiovascular disease. *JAMA* 2022 Aug 9; 328 (6): 577-578.
- Lundberg G, Wenger N. July 18,2019. Menopause Hormone Therapy: What a Cardiologist Needs to Know. American College of Cardiology. https://www.acc.org/latest-in-cardiology/articles/2019/07/17/11/56/menopause-hormone-therapy.
- Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, Anderson G, Howard BV, Thomson CA, LaCroix AZ, Wactawski-Wende J, Jackson RD, Limacher M, Margolis KL, Wassertheil-Smoller S, Beresford SA, Cauley JA, Eaton CB, Gass M, Hsia J, Johnson KC, Kooperberg C, Kuller LH, Lewis CE, Liu S, Martin LW, Ockene JK, O'Sullivan MJ, Powell LH, Simon MS, Van Horn L, Vitolins MZ, Wallace RB. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA.* 2013 Oct 2;310(13):1353-68. doi: 10.1001/jama.2013.278040. PMID: 24084921; PMCID: PMC3963523.

References, Continued

- McNamara DM, Elayam U, Alharethi R, et al. Clinical outcomes for peripartum cardiomyopathy in North America: results of the IPAC study (investigations of Pregnancy-Associated Cardiomyopathy), *J Am Coll Cardiol* 2015; 66: 905-14.
- Muka T, Oliver-Williams C, Kunutsor S, Laven JS, Fauser BC, Chowdhury R, Kavousi M, Franco OH. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. *JAMA Cardiology* 20161767–776. (10.1001/jamacardio.2016.2415)
- Murphy, Joseph G., and Margaret A. Lloyd (eds), *Mayo Clinic Cardiology: Concise Textbook*, 4 edn, Mayo Clinic Scientific Press (New York, 2012; online edn, Oxford Academic, 1 May 2013), https://doi.org/10.1093/med/9780199915712.001.0001, accessed 5 Feb. 2024.
- O'Keeffe LM, Kuh D, Fraser A, Howe LD, Lawlor D, Hardy R. Age at period cessation and trajectories of cardiovascular risk factors across mid and later life. *Heart* 2020;106:499–505.
- Parikh NI, Gonzalez JM, Anderson CAM, Judd SE, Rexrode KM, Hlatky MA, Gunderson EP, Stuart JJ, Vaidya D; on behalf of the American Heart Association Council on Epidemiology and Prevention; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; and the Stroke Council. 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–e916.
- Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J.* 2011 Dec;32(24):3147-97. doi: 10.1093/eurheartj/ehr218. Epub 2011 Aug 26. PMID: 21873418.
- Pregnancy Mortality Surveillance System. https://www.cdc.gov/reproductivehealth/maternal-mortality/pregnancy-mortality-surveillance-system.htm. Updated February 4, 2020. Accessed April 23, 2020.)

References, Continued

- Rasmusson K, Brunisholz K, Budge D, Horne BD, Alharethi R, Folsom J, Connolly JJ, Stehlik J, Kfoury A. Peripartum cardiomyopathy: post-transplant outcomes from the United Network for Organ Sharing Database.*J Heart Lung Transplant.* 2012; *31*:180–186.
- Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. *European Heart Journal.* 2018 Sep;39(34):3165-3241. DOI: 10.1093/eurheartj/ehy340. PMID: 30165544.
- Roberts JM, August PA, Bakris G, Barton JR, Bernstein IM, Druzin ML, Gaiser RR, Granger JP, Jeyabalan A, Johnson DD, et al. Hypertension in pregnancy: report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol.* 2013; 122:1122–1131.
- Roussouw JE, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial". *The Journal of American Medical Association.* 2002. 288 (3): 321-333.
- Roussouw JE; Prentice JL, Manson JE, Wu L, Barad D, Barnabei VM, Ko M, LaCroix AZ, Margolis KL, Stefanick ML, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years sine menopause. *JAMA* 2007, 297, 1465-1477.
- Salpeter SR, Walsh JM, Greyber E, Salpeter EE. Brief report: coronary heart disease events associated with hormone therapy in younger and older women. A meta-analysis. *J Gen Intern Med* 2006: 21:363-366.
- Scarabin, P.Y; Oger, E; Plu-Bureau, G; Estrogen Group, THRS. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. *Lancet* 2003, 362, 428-432.
- Schierbeck LL, Rejnmark L, Tofteng CL, Stifgren L, Eiken P, Mosekilde L, Kober L, Jensen JE. Effect of hormone replacement therapy on cardivoscular events in recently postmenopausal women: randomized trial. *BMJ* 2012; 345: e6409-e6409

References, Continued

- Shotan A, Ostrsega E, Mehra A et al. Incidence of arrhythmia in normal pregnancy and relation to palpitations, dizziness, and syncope. *Am J Cardiol* 1997;79:1061-1064.
- Silversides CK, Grewal J, Mason J, Sermer M, Kiess M, Rychel V, Wald RM, Colman JM, Siu SC. Pregnancy Outcomes in Women With Heart Disease: The CARPREG II Study*. J Am Coll Cardiol.* 2018 May 29;71(21):2419-2430. doi: 10.1016/j.jacc.2018.02.076. PMID: 29793631.
- Smilowitz NR, Gupta N, Guo Y, Zhong J, Weinberg CR, Reynolds HR, Bangalore S. Acute myocardial infarction during pregnancy and the puerperium in the United States. *Mayo Clin Proc*. 2018;93:1404–1414. doi: 10.1016/j.mayocp.2018.04.019)
- Stuenkel CA, Davis SR, Gompel A, et al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinic Practice Guideline. *J Clin. Endocrinol* Metab 2015; 100: 3975
- Su HI, Freeman EW. Hormone changes associated with the menopausal transition. *Minerva Ginecol.* 2009 Dec;61(6):483-9. PMID: 19942836; PMCID: PMC3823936.
- The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause* 24(7):p 728-753, July 2017
- Tita, A et al. Treatment for Mild Chronic Hypertension During Pregnancy*, NEJM.* May 12 2022. 386: 1781-1792. DOI: 10.1056/NEJMoa2201295

References, Continued

- Trost SL, Beauregard J, Njie F, et al. Pregnancy-Related Deaths: Data from Maternal Mortality Review Committees in 36 US States, 2017-2019. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services; 2022.
- Tweet M., Lewey J., Smilowitc N, Rose C, Best, P. Pregnancy Associated Myocardial Infarction. *Circulation.* Volume 13, Issue 11, Nov 2020.
- Viljoen C, Hoevelmann J, Sliwa K. Peripartum cardiomyopathy: risk factors and predictors of outcome. *Curr Opin Cardiol* 2023; 38:223-32.