WOMEN & CARDIOVASCULAR HEALTH

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Learning Objectives:

- Recognize the link between reproduction and cardiometabolic health, acknowledging the powerful role of estrogen
- Discuss the impact of estrogen directly and indirectly on all cardiovascular structures and the negative effects of menopause on female cardiovascular wellbeing
- Summarize the inter-relationship of estrogen, the gut, the immune system, and the Circadian Rhythm and their combined impact on female cardiometabolic status
- Describe how to implement effective strategies to help menopausal women maintain cardiovascular wellness and metabolic homeostasis by utilizing hormonal therapy, nutritional medicine, time restricted eating, stress reduction, and sleep hygiene

Prime Directive of Life:

Reproduction and survival and then to repeat the process

It is all about the process of making and raising babies!



The Menstrual Cycle – New Ways to Understand it



Introducing Estrogen



Functions of Estrogen: Critical roles in all extra-gonadal tissues

- Gut and Liver
- Heart
- Muscle
- Bone, cartilage, joints
- Endothelium-arteries
- Epithelium-skin
- Hematopoietic cells
- Immune cells/mitochondria
- Bladder
- Lungs
- Brain



Physiologic responses

Estrogen Basics: An Overview

ER alpha → Regulates genes & membrane receptors

Primarily expressed in the *gonadal* organs: Reproductive organs, breasts, bone, cardiovascular system, liver, adipose tissue, brain - hypothalamus, immune cells

ER beta → Regulates genes & membrane receptors

Primarily expressed in *non-gonadal* tissues: G tract, colon, bone marrow, vascular endothelium, lung, bladder, B cells, brain, lung

Membrane-associated ER → No effect on genes, but rapid effects on cellular signaling



Paterni et al. Estrogen Receptors Alpha and Beta. Steroids. 2014.

Dahlman-Wright et al. International Union of Pharmacology. LXIV. Estrogen Receptors. Aspet PharmacologicalReviews.2006:

Modulated by Estradiol ...

Vasodilation and vasoconstriction

- Endothelial NO synthase
- Prostacyclin cyclooxygenase
- Prostacyclin synthase
- Renin and angiotensin
- Endothelin-1

Lipid Metabolism

- Lipoprotein lipase
- Apo-lipoproteins
- Leptin
- PON 1
- LDL receptors
- HMG-CoAR activity

Immune activity

- Vascular-cell adhesion molecule
- Cytokines (IL1, IL6, TNFα)
- Cytokine receptors
- Superoxide Dismutase

Coagulation

- Fibrinogen
- Coagulation factors
- Protein S

Angiogenesis

- Matrix metalloproteinase
- Vascular endothelial growth factor

Non-Genomic Effects

Fast-acting actions such as NO facilitated vasodilation

Menopause is a universal and natural event for women... Why address it?





Menopause is not just

the loss of fertility and

periods...

It is the beginning

of a major

metabolic shift

What's Going On During Menopause?



Menopause is about estrogen loss – Major overlooked factor in women's health

What are the Estrogens?

- Steroid hormones produced primarily by the ovaries and peripherally from cholesterol-derived precursors
- Regulate multiple functions across organs, cells, and genes
- Typically bind to receptors (ERs) to perform their functions
- Alternative ways exist for E2 to impact cell function





Paterni et al. Receptors Alpha and Beta: Subtype Selective Ligands and Clinical Potential, Steroids, 2014; 0:13-29

Estrogen Basics Remembered:

Steroid hormones - bind to receptors throughout the body - regulate a multiplicity of functions



Cardiometabolic Health

- Reproductive Health
- •Immune Health
- Cognitive & Emotional Health
- Musculoskeletal Health
- Gastrointestinal Health
- •Skin Health

Estrogen Related Receptor (ERR) Isoforms Expressed in Myocardium

Members of steroid hormone superfamilyregulate expression of genes for energy metabolism, mitochondrial biogenesis, fatty acid oxidation, oxidative phosphorylation

ERRa and \gamma – share target genes in myocardium

ERRB – maintains proper oxygen consumption rates in myocardium

Cunningham et al. Estrogen-Related Receptor α (ERRα) is required for adaptive increases in PGC-1 isoform expression during electrically stimulated contraction of adult cardiomyocytes in sustained hypoxic conditions. *Am J Cardiovasc Dis.* 2016;6(2):46-54

Estrogen Metabolite – 2 Methoxy Estradiol

Impact on CV health – not always via estrogen receptors

- Down regulates synthesis of Angiotensin Type 1 Receptor in liver epithelial cells
- Down regulates Endothelin 1 in coronary artery endothelial cells
- Inhibits cell growth in human aortic smooth muscle cells by decreasing ERK1/2 phosphorylation – inhibits neo-intima formation and smooth muscles cell growth

Kigabti et al. Eur J Pharmacol. 2014. 723, 131-40 Dubey et al. Hypertension, 2001, 37:640-644 Barchiesi et al. Circ Res. 2006; 99(3): 266-74

Age-Dependent Shift in Estrogen Levels = Pro-inflammaging



Hidden Risks of Menopause

Estrogen receptors are everywhere and play vital roles in regulating countless physiologic functions

Cardiovascular Health & Atherosclerosis

- Obesity & Increased Visceral Fat
- Metabolic Syndrome & Diabetes
- Musculoskeletal effects, including Osteoporosis & Osteoarthritis
- Alzheimer's Disease & Neuro-inflammation
- Cellular Health (breast, colon)
- Autoimmune disease
- Fatty Liver
- GI Disorders: Colon Cancer, GERD, Malabsorption & Motility

The Significance of Cardiovascular Health

Coronary artery disease (CAD) is the number one cause of death in women in the world

More than cancer, diabetes, Alzheimer's & pneumonia



Center for Disease Control and Prevention Ramachandran H, Wu V, Kowitlawakul Y, Wang W. *Heart & Lung*. 2016; 45: 173-185

Impact of Menopause: Endothelial Function

85% of all women in the US are hypertensive by the age of 75

- Typically expressed as systolic hypertension
- Often develops around menopause
- Attributed to the decline in estrogen
- Risk factor for CAD and other cardiometabolic events



Negative Effects of Estrogen Deficiency on Metabolism

Inflammation Underlies Cardiovascular Events



INFLAMMATION

 endothelium damage
 leukocytes chemotaxis
 cytokines, growth and adhesion factors synthesis
 free radicals induction, low density lipoproteins oxidation





Bergmann et al. Biochem Med. 2011; 21(3):210-8

Cardio-Renal-Vascular-Metabolic Syndrome



Guanghong et al. Prog Mol Biol Transl Sci. 2014;127: 229-249

Estradiol + Renal Angiotensin Aldosterone System (RAAS)







Estradiol & the Heart -Overview

Estrogen Alleviates Diastolic Dysfunction

Variable	Time point	Oestradiol	Placebo	p Value
Vel E (cm/s)	Baseline (T1)	66 (19)	63 (11)	NS
	90 minutes (T2)	68 (20)	61 (13)	NS
	12 weeks (T3)	74 (22)	61 (16)	NS
Vel A (cm/s)	Baseline (T1)	81 (21)	79 (14)	NS
	90 minutes (T2)	81 (21)	76 (11)	NS
	12 weeks (T3)	75 (23)*	73 (13)*	NS
E/A ratio	Baseline (T1)	0.8 (0.2)	0.8 (0.1)	NS
	90 minutes (T2)	0.9 (0.2)	0.8 (0.1)	NS
	12 weeks (T3)	1.0 (0.2)†	0.8 (0.2)	0.04
DTE (ms)	Baseline (T1)	260 (42)	254 (22)	NS
	90 minutes (T2)	248 (40)	245 (20)	NS
	12 weeks (T3)	238 (20)*	274 (42)*	0.01
IVRT (ms)	Baseline (T1)	127 (23)	121 (15)	NS
	90 minutes (T2)	121 (17)	120 (16)	NS
	12 weeks (T3)	106 (16)†	121 (16)	0.01

The values are expressed as mean (SD).

*p < 0.05 (T1 v T3) in the same group.

p<0.001 (T1 v T3) in the same group.

DTE, deceleration time of mitral E wave; E/A, the ratio between the peak velocity of mitral E and A wave; IVRT, isovolumic relaxation time; Vel A, peak velocity of mitral A wave; Vel E, peak velocity of mitral E wave.

3 Cardiovascular Benefits of Estradiol (E₂)



Estrogen Supports Mitochondrial Health

There is a growing understanding of the role which E2 plays in metabolism via its regulation of mitochondrial function



Duckles et al. Molecular Interventions, 2006;Vol 6, No1, pp26-35 Wang et al. J Neurochemistry, 2001; Vol 77, No.3; pp 804-11

Estrogen-Mitochondria-SIRT3 Link



Estrogen Supports Insulin Sensitivity

- Supports glucose transporter (GLUT3, GLUT4) function
- Enhances glucose-stimulated insulin biosynthesis
- Promotes β cell survival



Lipid Metabolism: Cholesterol

- Compared to men, during reproductive years, women have:
- Lower LDL levels
- Higher HDL levels
- Lower total lipid levels
- Estradiol upregulates the expression of:
- Apolipoprotein A1
- LDL receptors responsible for the uptake of lipoprotein

• Estradiol decreases:

- Lipoprotein lipase
- HMG-CoA Reductase activity

Saltiki, K and Alevizaki M. Coronary heart disease in postmenopausal women; the role of endogenous estrogens and their receptors. Hormones. 2007; 6(1): 9-24

Estrogen Supports a Healthy Lipid Profile

- Supports HDL levels by promoting apolipoprotein A-I and moderating hepatic lipase activity
- Moderates LDL levels by promoting levels of hepatic LDL receptors



Knowlton A and Lee A. *Pharmacology & Therapeutics*. 2012; 135,(1): 54-70 Feingold K, Brinton E and Grunfeld C. EndoText.com , 2000.

Estrogen and Paraoxonase (PON 1)

- Oxidized low-density lipoproteins (oxLDL) involved in initiation of atherosclerosis
- PON 1 located on HDL protects against oxidation of HDL and LDL by hydrolysing lipid peroxides
- Oxidative status reduces PON 1 activity, increases oxLDL

Estrogen increases PON 1 activity

Topcuoglu et al. The effect of hormone replacement therapy on oxidized low density lipoprotein levels and paraoxonase activity in postmenopausal women. *J Exp Med*. 2005;205(1): 79-86

Estradiol Promotes Prostacyclin Expression

Produced by endothelial and vascular smooth muscle cells

- Major anti-atherogenic prostanoid
- Counter effects thromboxane important balance in cardiovascular homeostasis

E2 promotes vasodilation through release of prostanoids (and others)

 E2 binds to ERα to up-regulate (Cyclooxygenases and PGI Synthase and PGI expression



Estradiol and Arterial Health – Production of Nitric Oxide



lorga et al. Biol Sex Differ. 2017; 8: 33.

Nitric Oxide Maintains Endothelial Health



Progression with Age: a NO Perspective



Adapted from: Celermajer DS et al. *J Am Coll Cardiol.* 1994; 24 (2):471-476

Importance of the Circadian Rhythm



Menopause-Circadian-Metabolic Triad:





Redefining Menopause:

It's like living a life of jetlag – and that is a major challenge!!

Lifestyle Approaches to Optimize Pardiovascular Health

Coordination of Reproduction & Metabolism: Optimal Health





Sirtuin-dependent control of the circadian clock in the brain and periphery



Chrono-nutrition

- (1) Clock regulation
 - ex. High-fat diet (HFD), Caffeine
- (2) Meal-time effects
 - ex. Skipping breakfast (SB) Nocturnal eating (NE)



Current Nutrition Reports.2014; 3(3): 204–212

Poor diet + Estrogen Deficiency *drives Dysbiosis*

Dysbiosis → Systemic Inflammation

High fat/high sugar diet leads to gut dysbiosis

& Circadian Rhythm Dysfunction

Guinane CM et al. Tole of the gut microbiota inhealth and chronic gastrointestinal disease. Therp Adv Gastroenterol 2013; 6: 295-308 Turnbaugh PJ et al. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. Cell Host Microbe 2008; 3: 213-223

Healthy Microbiome Supports all Systems



Metabolic Health

Reproductive Health

Mental Health

Immune Health

Downloaded from http://pmj.bmj.com/ on February 29, 2016 - Published by group.bmj.com

Review

Healthy Gut Microbiota

Composition Bacteroidetes : Firmicutes



IEC differentiation Tight junction function Intestinal barrier integrity Energy harvest Vitamin K synthesis SCFA production

Innate and adaptive immune response stimulation

Liver Acetate and propionate (Gluconeogenesis / lipogenesis)

Obese-Diabetic Microbiota

Bacteroidetes : Firmicutes



Circulatory System Metabolic endotoxemia (LPS)

> Lipogenesis Inflammation Oxidative stress Insulin resistance

Adipose Tissue Inflammation Oxidative stress Macrophage infiltration Insulin resistance

Figure 1 Compositional and functional alterations in the healthy gut microbiota versus the obese-diabetic microbiota. The metabolic processes in peripheral organs leading to increased adiposity, inflammation, oxidative stress, insulin resistance and lipogenesis are associated with the altered microbiota profile associated with the obese-diabetic phenotype. IEC, intestinal epithelial cell; LPS, lipopolysaccharide; SCFA, short chain fatty acid.

Your patient is menopausal ... NOW WHAT DO YOU DO??



Zhao Z et al. Role of estrogen in diastolic dysfunction. Am J Physiol Heart Circ Physiol. 2013; 306: H628-H640.

Motivation & Compliance

- Set the expectation: Accept "better"
- Each woman can set her own pace
- Help your patient make health a priority



Key Cardiovascular Testing Options

- ADMA
- Advanced lipid profile, Oxidized LDL
- Insulin and HbA1c
- Inflammatory markers: hsCRP, MPO, F2isoprostane, LpPLA2
- ApoE, MTHFR
- Hormones
- Thyroid
- Ferritin
- CBC, CMP

- Micronutrients
- Microalbumin
- Heavy metals
- Gut microbiome testing



7 Steps to Improve Women's Cardiometabolic Health

- 1.NUTRITION: SUPPORT GUT MICROBIOME & CELLULAR NEEDS
 2.EAT TO THE BEAT: TIME RESTRICTED EATING, FASTING
 3.STEP INTO THE LIGHT
 4.GET ADEQUATE REST & RESTORATIVE SLEEP
 5.EXERCISE ANY TIME POSSIBLE
 6.LIVE CLEAN & PURE
 7. DERSONALIZE THE PLAN: HORMONE THERAPY &
- 7.PERSONALIZE THE PLAN: HORMONE THERAPY & SUPPLEMENTS

Hormone Therapy Revisited: Hormones are Beneficial

- Estradiol patch or gel
- Oral micronized progesterone (preferably cyclic)
- Compounded Estradiol + progesterone creams



Estradiol



Progesterone

Estrogen: Concentration Matters

- "E2 has a bi-potential effect on monocytes and macrophages.
- Low doses enhance the production of pro-inflammatory cytokines while high doses reduce the production of these cytokines"

Modulating inflammation is a key function of ESTROGEN!

Supplements that May Support Cardiovascular Health



Supplements		Details	
	 Berberine Resveratrol 	Supports healthy insulin function and glucose homeostasis	
	• EPA & DHA rich fish oils	Supports healthy TGs and lipid metabolism, maintains healthy blood flow, and supports healthy platelet function	
	French maritime pine bark extract	A source proanthocyanidins support vascular endothelial integrity	
	 Hawthorn extract Cranberry and grape seed extract 	Supports healthy vascular relaxation and circulatory function for heart health	

Menopausal Metabolic & Cardiovascular Health



THANKS SO MUCH!



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Discover what happens to your body during the three stages of menopause

Up inderstanding the why and how of menopause empowers you to shape your own journey during this important transition. This book is an honest, accurate guide to menopause and how it impacts your body preparing you for what may lie ahead and helping you handle any health concerns you may have. Learn about 50 of the most common symptoms of menopause, why they occur, and the best ways to support yoursel as your body changes.

FIND AN INCLUSIVE AFPROACH Discover straightforward and practical guidance that gives you the tools to approach menopause in a way that's suthentic to you.

KNOW WHAT TO EXPECT Get to know the symptoms commonly experienced during each stage of menopause; perimenopause, early menopause, and late menopause.

LEARN THE SCIENCE. Find scientifically supported facts and concise advice to help you navigate the ups and downs of menopause



MENOPAUSE: 50

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Felice Gersh, MD, with Alexis Perella

MENOPAUSE:

50 Things You

Need to Know

What to Expect During the

Three Stages of Menopause



