WHY DOES MENOPAUSE HAPPEN & WHAT IS ITS SIGNIFICANCE?

Felice L. Gersh, M.D.

Medical Director

Integrative Medical Group of Irvine

Faculty, Fellowship in Integrative Medicine

University of Arizona School of Medicine

What's Going On During Menopause?

Menopause

- Occurs between the ages of 45 and 55
- The cessation of menstrual periods
- Loss of reproductive function of the ovaries
- Extensive alterations throughout the female body

Brotman et al. Association between the vaginal microbiota, menopause status, and signs of vulvovaginal atrophy. Menopause. 2014;21:450-458.

Leeners et al. Ovarian hormones and obesity. Hum Reprod Update. 2017;23:300-321.

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

Because nature is not always kind.

Menopause is not just the loss of fertility and periods…

It is the beginning of a major metabolic shift

The unique health issues faced by women are often minimized and overlooked; perhaps the most egregious example is menopause…

Common symptoms associated with Menopause:

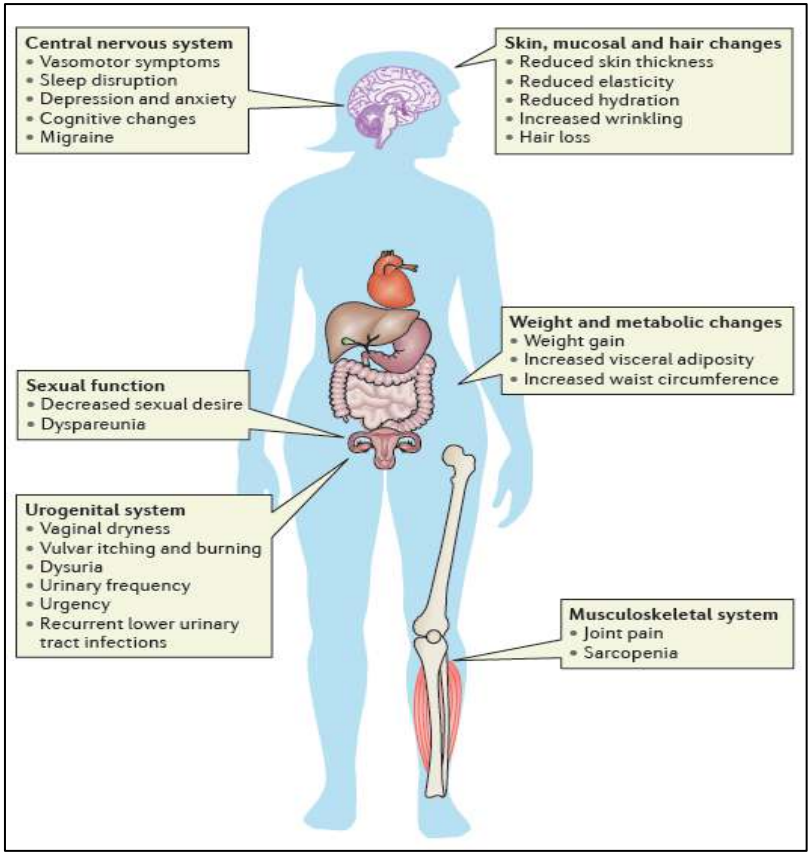
- Hot flashes
- Cold or night sweats
- Low energy
- Sleep disturbances
- Palpitations
- Weight gain
- Mood disturbances
- Inability to concentrate
- Vaginal dryness

It's estimated that 90% of women will seek support during the menopausal transition.

We can support the comfort of women through the menopausal transition!

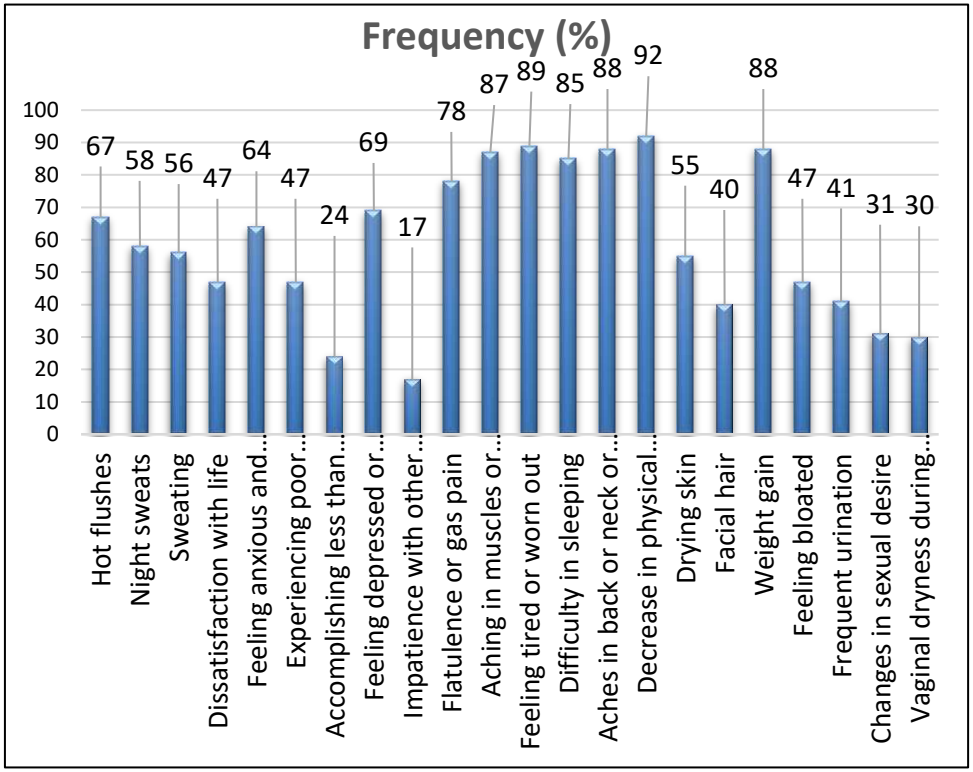
Guthrie JR, Dennerstein L, Taffe JR, Donnelly V. Climacteric 2003;6:112–117

Symptoms & Prevalence of Symptoms Overall – Poor Quality of Life



Overview of menopausal symptoms[1]

The prevalence of menopausal symptoms (*n*=140)[2]



1 Nat Rev Endocrinol. 2018 Apr;14(4):199-215.
2. Ganapathy T, Al Furaikh SS. Health-related quality of life among menopausal women. Arch Med Health Sci 2018;6:16-23.

The Hidden Risks of Menopause

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

Adapted from Exper Rev Endocrinol Metab® 2011 Expert Reviews Ltd

Obesity and Increased Visceral Fat

Metabolic Syndrome and Diabetes

Musculoskeletal effects, including Osteoporosis and Osteoarthritis

Cardiovascular Health and Atherosclerosis

Alzheimer's Disease and Neuro-inflammation

Cellular Health (breast, colon)

Autoimmune disease (Rheumatoid Arthritis)

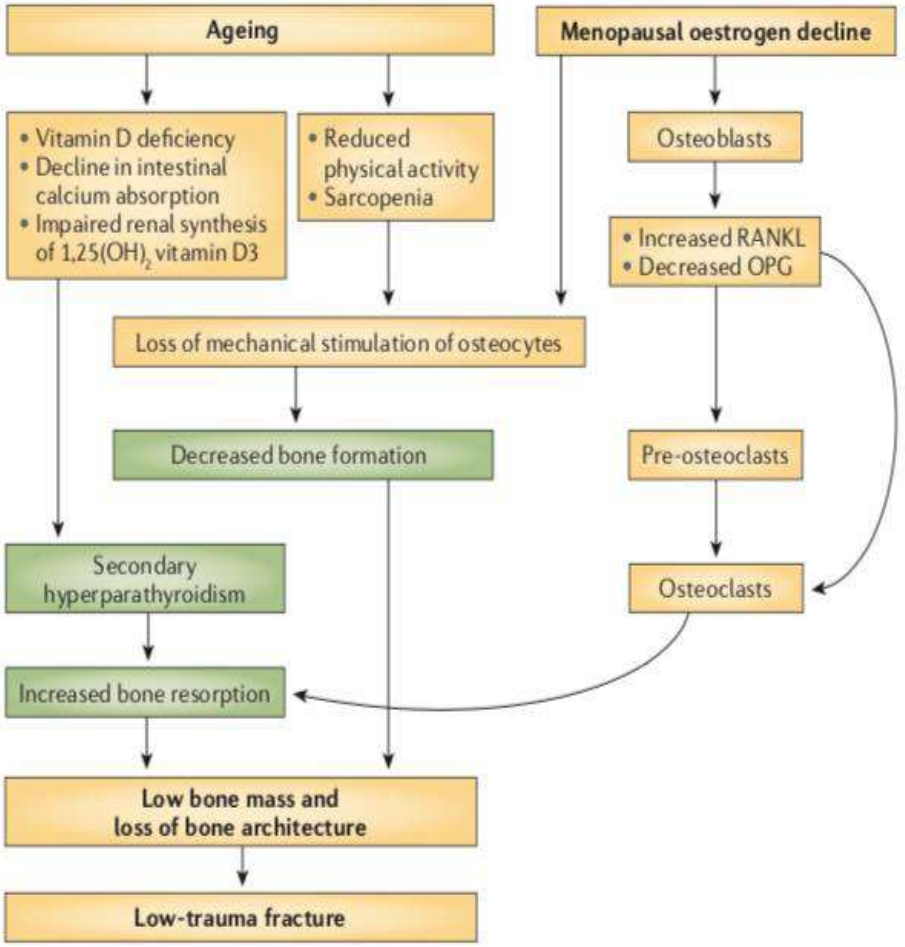
Fatty Liver

GI Disorders: GERD, Malabsorption and Motility

Menopause Increases the Risk of Osteoporosis

Woman can lose up to 20% of their bone density during the five-seven years following menopause

Reduced estrogen production results in increased receptor activator of nuclear factor-κB ligand (RANKL) levels, which leads to osteoclast activation and increased bone resorption.



Davis, S., Lambrinoudaki, I., Lumsden, M. *et al.* Menopause. *Nat Rev Dis Primers* **1,** 15004 (2015).
National Osteoporosis Foundation. What Women Need to Know. Accessed June 2021.

THERE IS A NEED FOR EFFECTIVE AND SAFE THERAPIES FOR THE MANAGEMENT OF THE MENOPAUSE

Let's start at the beginning: What is a hormone?

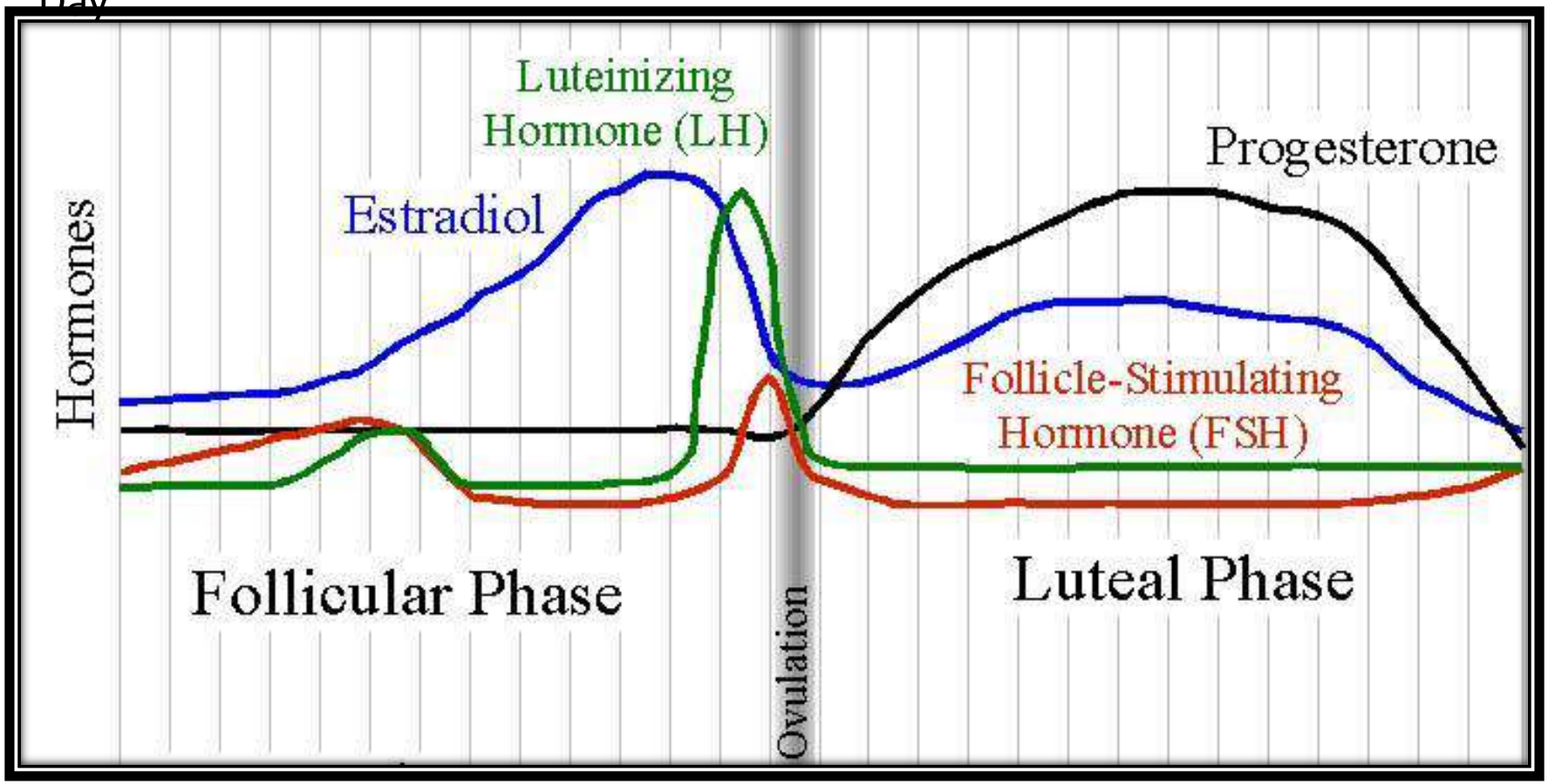
A hormone is any member of a class of signaling molecules produced by glands in multicellular organisms that are transported by the circulatory system to target distant organs to regulate physiology and behavior.

Hormones deliver important information to cells

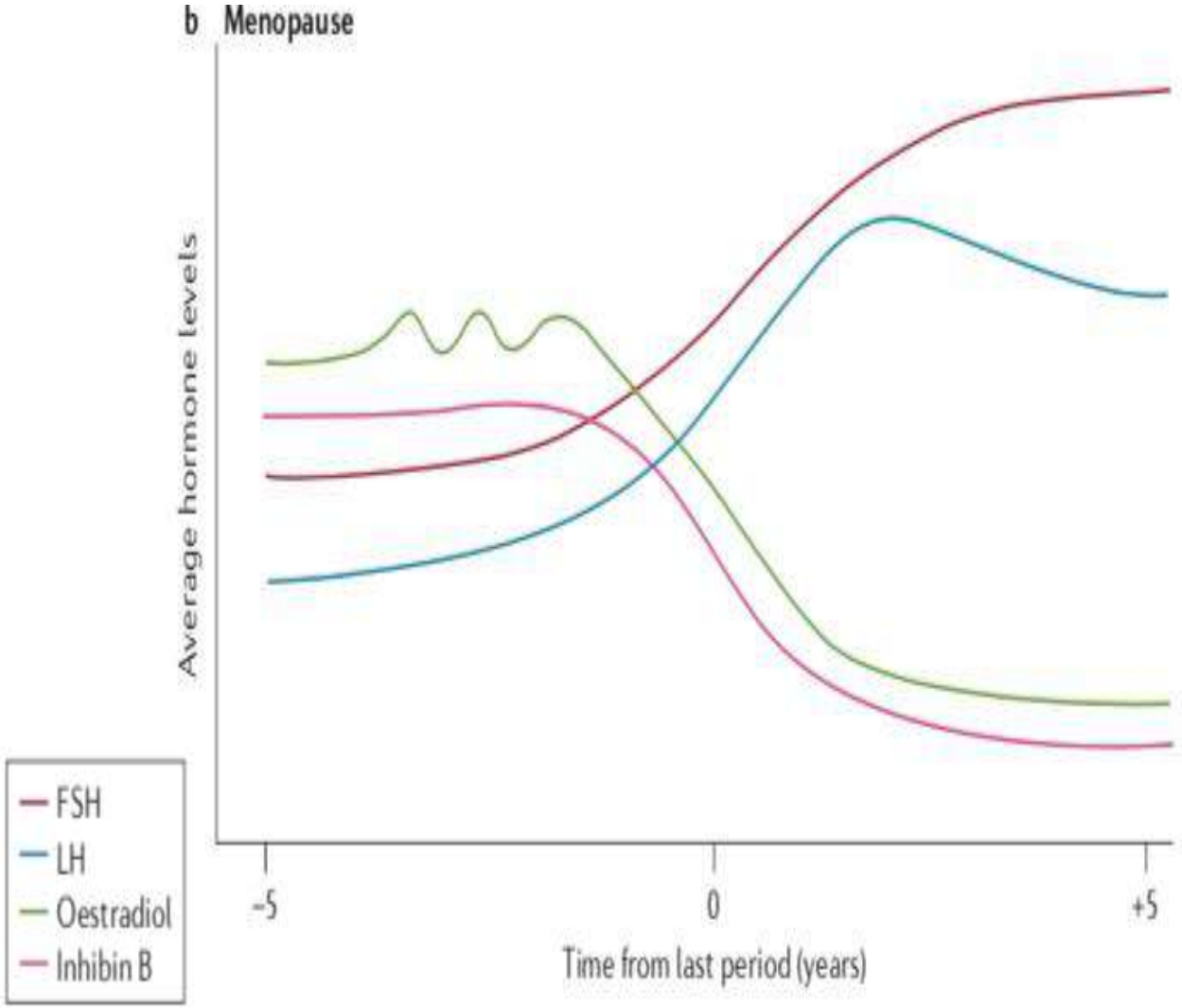
THE LONGER YOU KEEP THEM – THE BETTER!

and best to have human identical hormones

Introducing the Menstrual Cycle



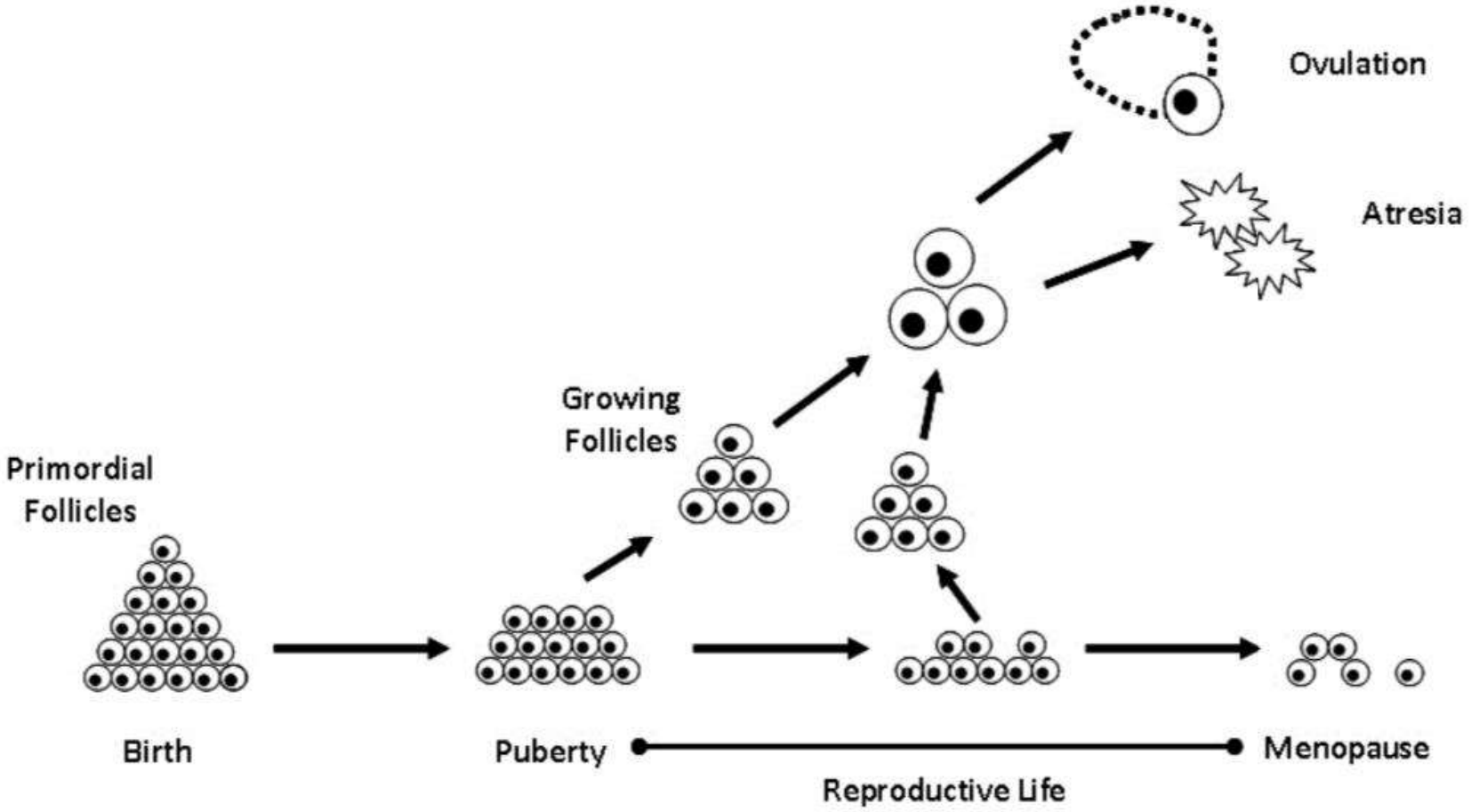
Fluctuations & Changes in Hormones



Lambrinoudaki, I., Lumsden, M. *et al.* Menopause. *Nat Rev Dis Primers* **1,** 15004 (2015).

Why must menopause occur and what is the process?

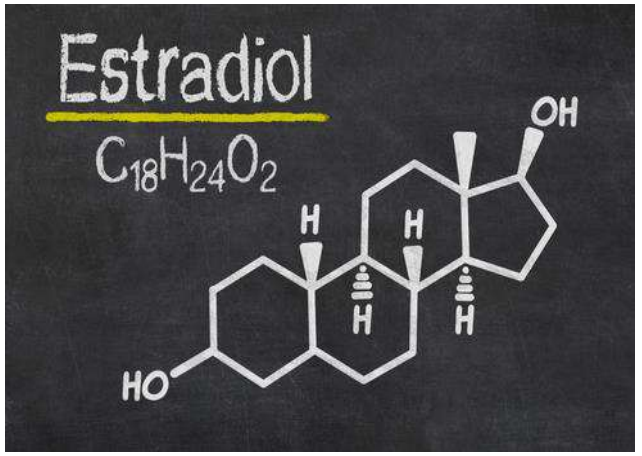
The Aging Process and the Path of Ovarian Follicles



Menopause is about the loss of estrogen – A major overlooked factor in women's health

What are Estrogens?

- **Steroid hormones produced primarily by the ovaries and peripherally from cholesterol-derived precursors**
- **Regulate multiple functions across organs, cells, and genes**
- **Must bind to receptors (ERs) to perform their functions**



Balthazart and Ball, 2006

In the Beginning … Estrogen was all about Metabolism

Ancestral ER existed in invertebrates lacking sexual reproductive capabilities-played an important role in energy metabolism and survival

All members of the steroid receptor family descend from a single ancestral receptor, which separated from the rest of the nuclear receptor family early in animal evolution, 500 million years ago

Mol Cell Endocrinol. Evolution of steroid receptors.2011;334:31-38

ESTROGEN IS THE "MOTHER HORMONE" THE MASTER OF METABOLIC HOMEOSTASIS

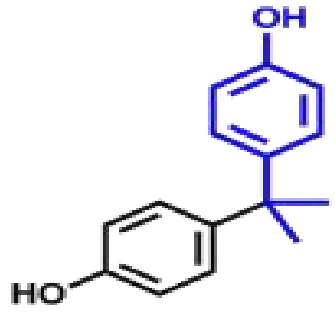
Risks to Ovarian Health and Longevity

- Overweight and underweight
- Poor nutrition
- Smoking – oxidative damage
- Alcohol
- Toxins – heavy metals, air pollution, car exhaust, pesticides, endocrine disruptors
- Emotional stress and PMS, Depression

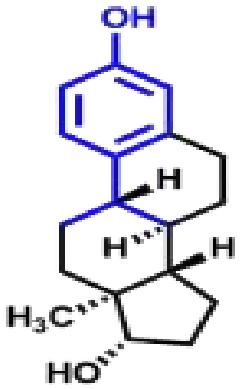
Anwar et al. Women's Health and Gynecology.2016;2(6)

Endocrine disruptors

Similar in structure to E2-can bind to multiple targets inside and outside the nucleus



Bisphenol-A (BPA)

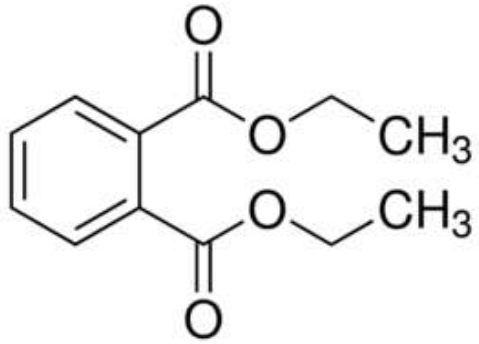


Estradiol

Optimize hormones: Reduce toxins

Major Endocrine Disruptors:

- Phthalates
- Alkylphenolic compounds
- Polychlorinated bisphenols
- Polychlorinated dibenzodioxins
- Organochlorine pesticides
- Bisphenol A
- Lead
- Mercury
- Cadmium



Phthalate

Endocrine disruptors:
Be aware of “hormonal” contraception

Oral contraceptives – Birth control pills

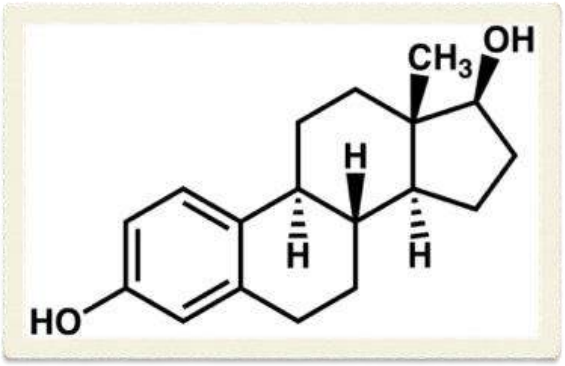
Rings, patches – similar to BCPs

Progestin IUD (Levonorgestrel)

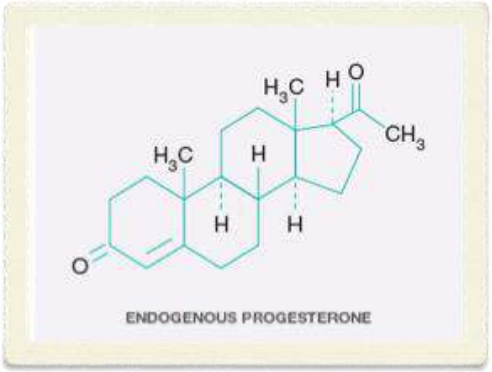
Implantables

Injections

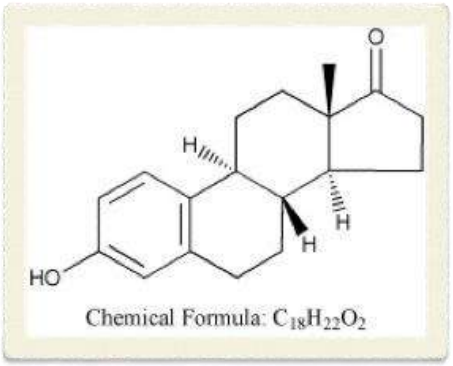
Difference in Molecules



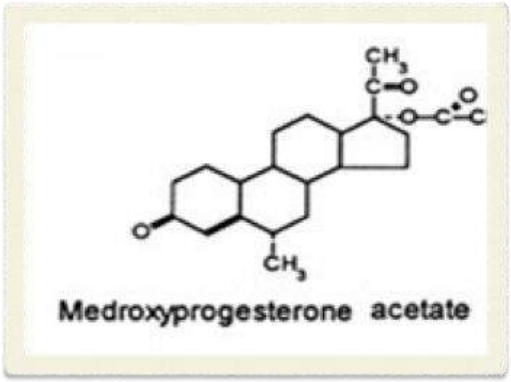
Estradiol



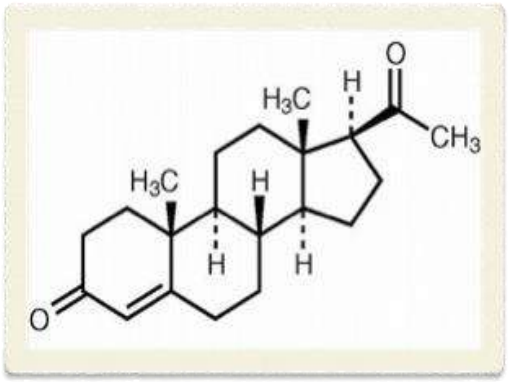
Progesterone



Premarin



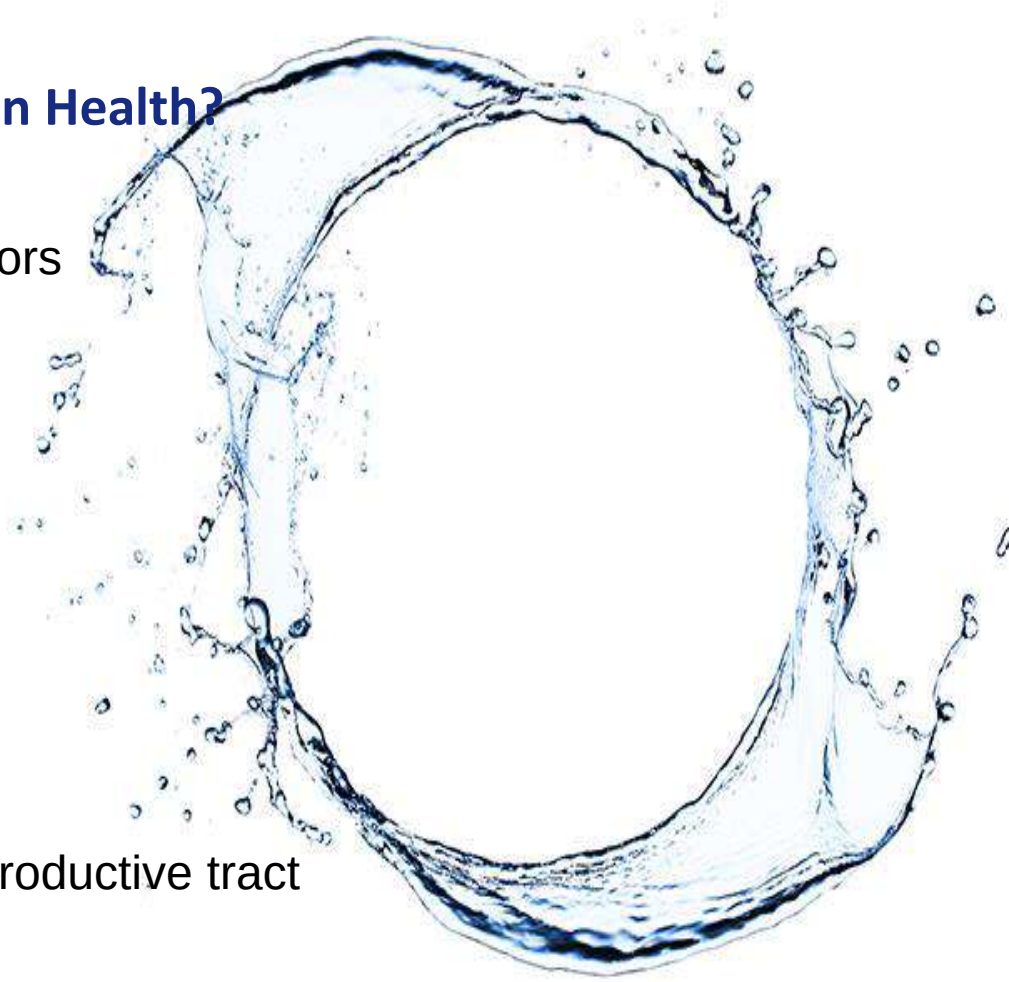
Provera



Prometrium

What Can We do to Enhance Ovarian Health?

- Limit exposure to endocrine disruptors
- Healthy diet
- Support hormone metabolism
- Support detoxification pathways
- Support our Circadian Rhythm
- Support the gut microbiome
- Support the microbiomes of the reproductive tract



So-called Sex Hormones Began Long Before Human-Style Sex!

Sex Hormones have:

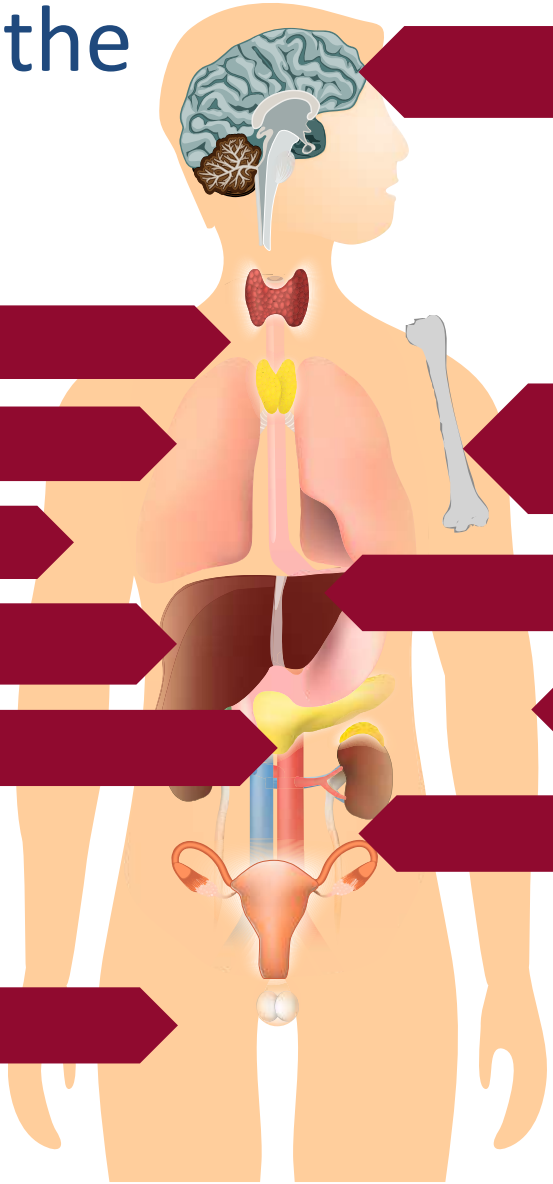
Numerous receptors all over the body

Lots to do with biological systems unrelated to reproduction or sex

REPRODUCTION AND SURVIVAL

If you're going to reproduce and survive – you'd best be smart & metabolically well

Estrogen Receptors Throughout the Body



- Central nervous system
- Lungs
- Breast
- Endothelium
- Liver
- Bladder/Prostate
- Bone/Joints/Muscle/ Immune Cells
- Gastrointestinal Tract
- Skin
- Ovary/Uterus
- Mitochondria

Estrogen Basics

ESTRADIOL

ESTRONE

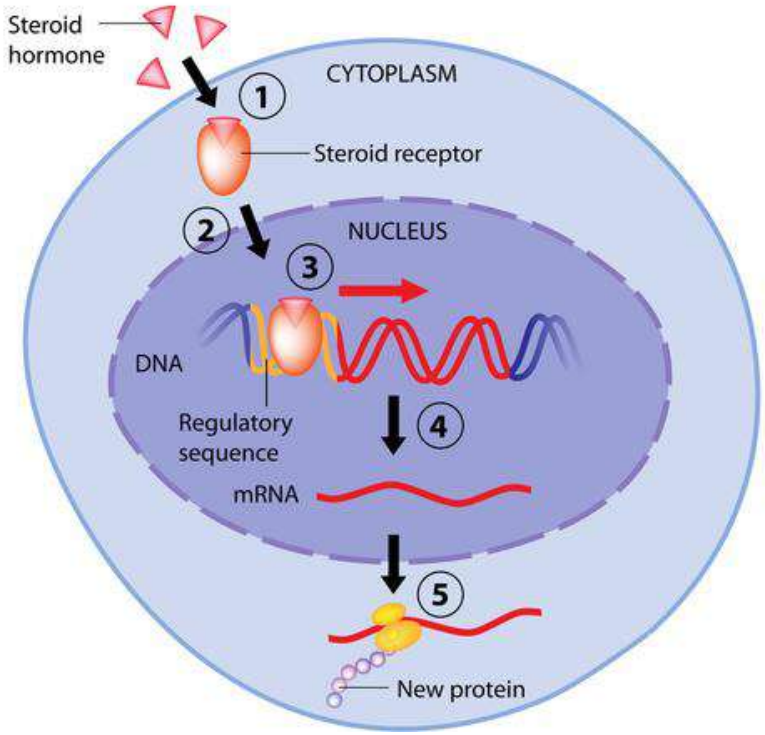
ESTRIOL

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

Physiologic & rhythmic levels of estrogens support:

1. Reproduction
2. Metabolic homeostasis and the Circadian Rhythm
3. Immune health
4. Musculoskeletal, gut, skin, emotional cardiovascular, neurological … everything

Estradiol Receptors (ER)



ER alpha → Regulates genes and kinases

Primarily expressed in the gonadal organs: uterus, ovary, prostate, testes, and breast, and in the hypothalamus of the brain

ER beta → Regulates genes and kinases

Primarily expressed in *non-gonadal* tissues: GI tract, colon, bone marrow, vascular endothelium, lung, bladder, and brain

Membrane-associated ER →

no effect on genes, but rapid effects on cellular signaling

Mendelsohn ME, and Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med.* 1999: 340; 1801-1811
Dahlman-Wright et al. International Union of Pharmacology. LXIV. Estrogen Receptors. *Aspet Pharmacological* Reviews. 2006: 58 (4); 773-781

The many roles of estrogen

Increases lean body mass
Reduces abdominal fat
Improves insulin resistance
Decreases LDL/HDL ratio
Decreases blood pressure/improves endothelial health
Maintains bone density
Improves mood and sleep quality
Reduces skin wrinkling and hair loss
Maintains cognition
Controls the immune system
Maintains a healthy gut and gut microbiome

Diabetes Obes Metab.Meta-analysis:effect of hormone-replacement therapy. 2006;8:535-554

Protective roles of estrogen

- Heightens insulin sensitivity, glucose homeostasis
- Supports microbiome
- Supports adiponectin production
- Moderates appetite
- Supports restorative sleep
- Supports AMPK, a cellular sensor involved in maintaining metabolic health and circadian rhythms

Age-dependent shift in estrogen levels

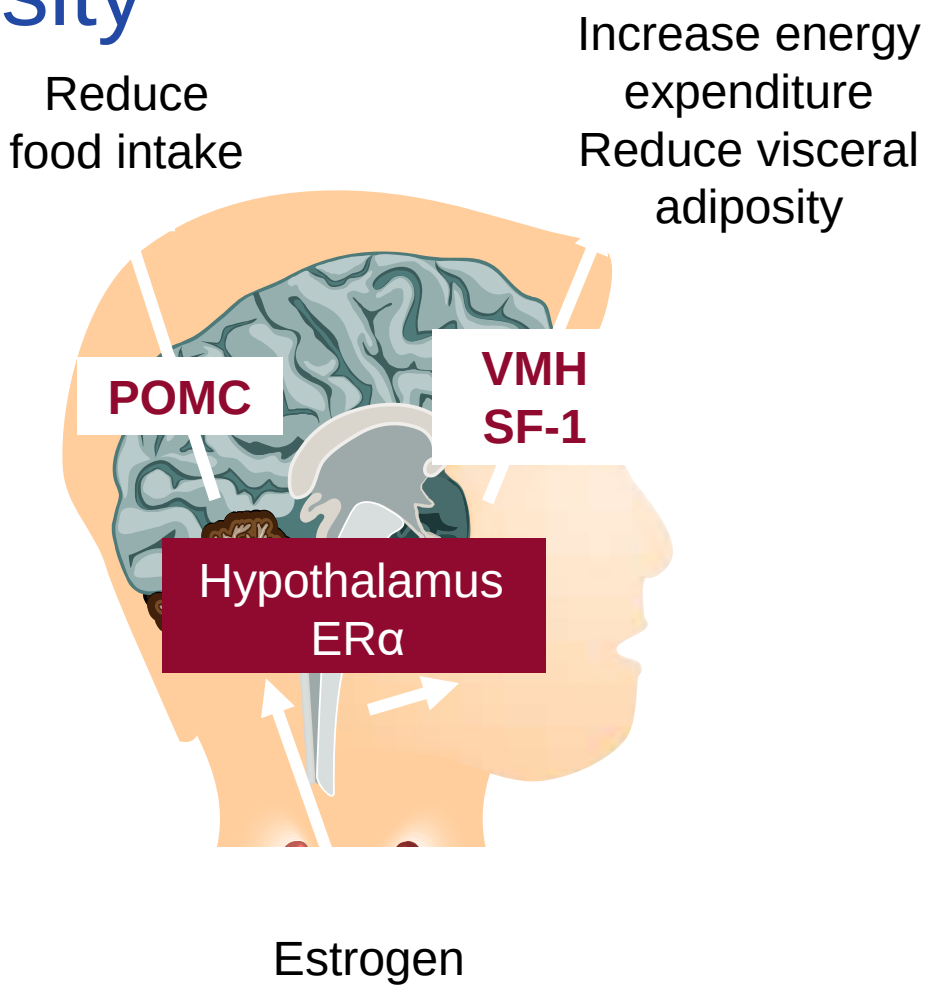
Post-menopausal women with estrogen deficiency are vulnerable to

- Obesity
- Metabolic Syndrome and Diabetes
- NAFLD
- Cancers (Breast, Colon, Hepatocellular)
- Osteoarthritis/Osteoporosis
- Atherosclerosis
- Alzheimer's Disease
- Neuro-Inflammatory Diseases
- Sleep Disturbance/Insomnia
- Systemic Inflammation & Immune Dysregulation

Adapted *from Exper Rev Endocrinol Metab* ® 2011 Expert Reviews Ltd

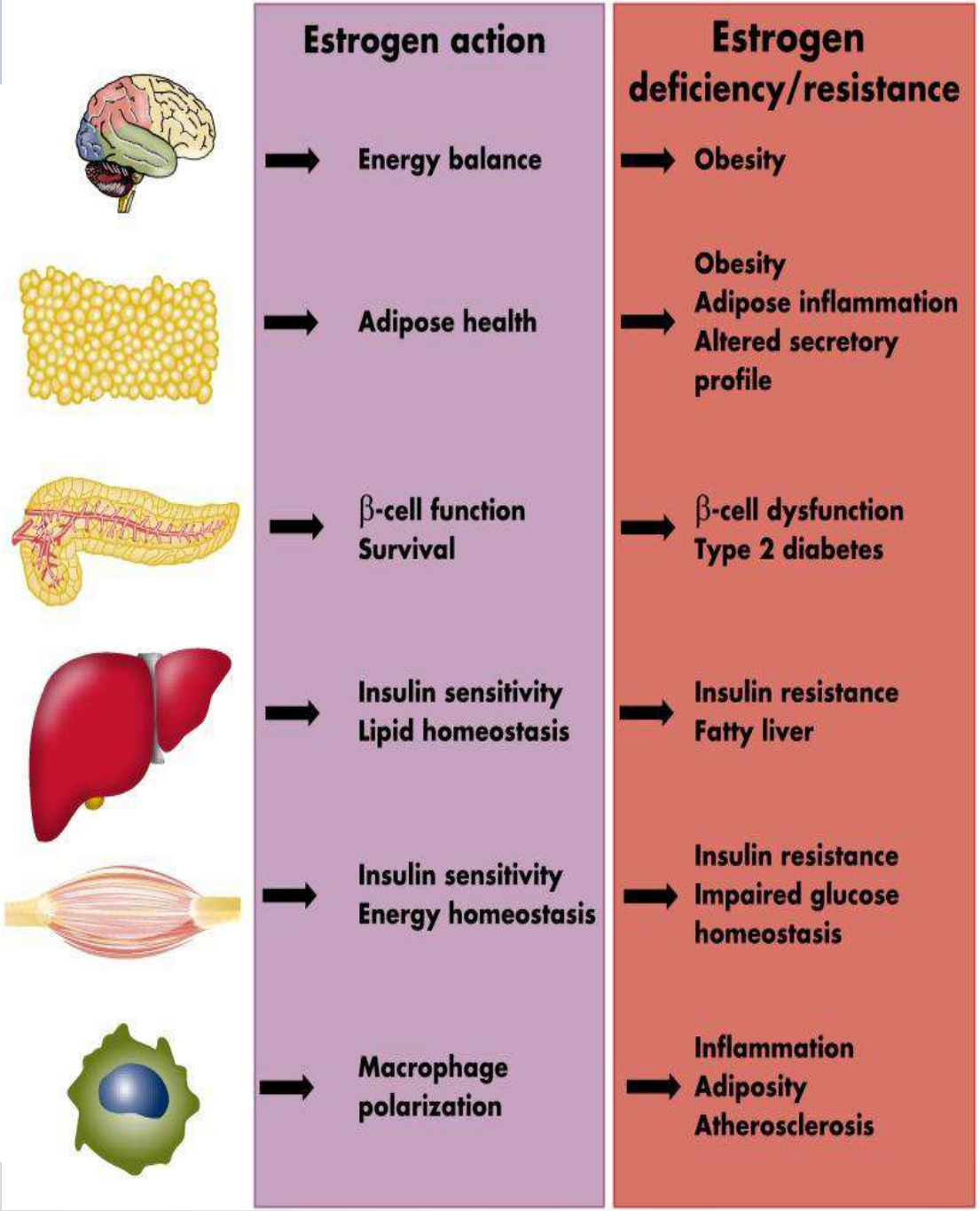
Estrogen's hypothalamic control of metabolism and obesity

- ERα in the brain regulates body weight in both males and females
- POMC neurons in ARC modulate food intake and energy expenditure



Cell Metabolism. Estrogens and obesity. 2011;14(4): 436-436

Estrogen and its Role in the Maintenance of Metabolic Homeostasis (Metabolic Health Linked to Reproductive Health



Endocr Rev. The role of estrogens in control of energy balance ... 309-338

Mol Cell Endocrinol. Evolution of steroid receptors from an estrogen-sensitive ancestral receptor 2011;334:31-38

Regulated by Estrogen

Vasodilation and vasoconstriction

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

Lipid Metabolism

- Lipoprotein lipase
- Apolipoproteins
- 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

Saltiki, K and Alevizaki M.. *Hormones*. 2007; 6(1): 9-24

Innate and Adaptive Immune System Genes Regulated by Estrogen

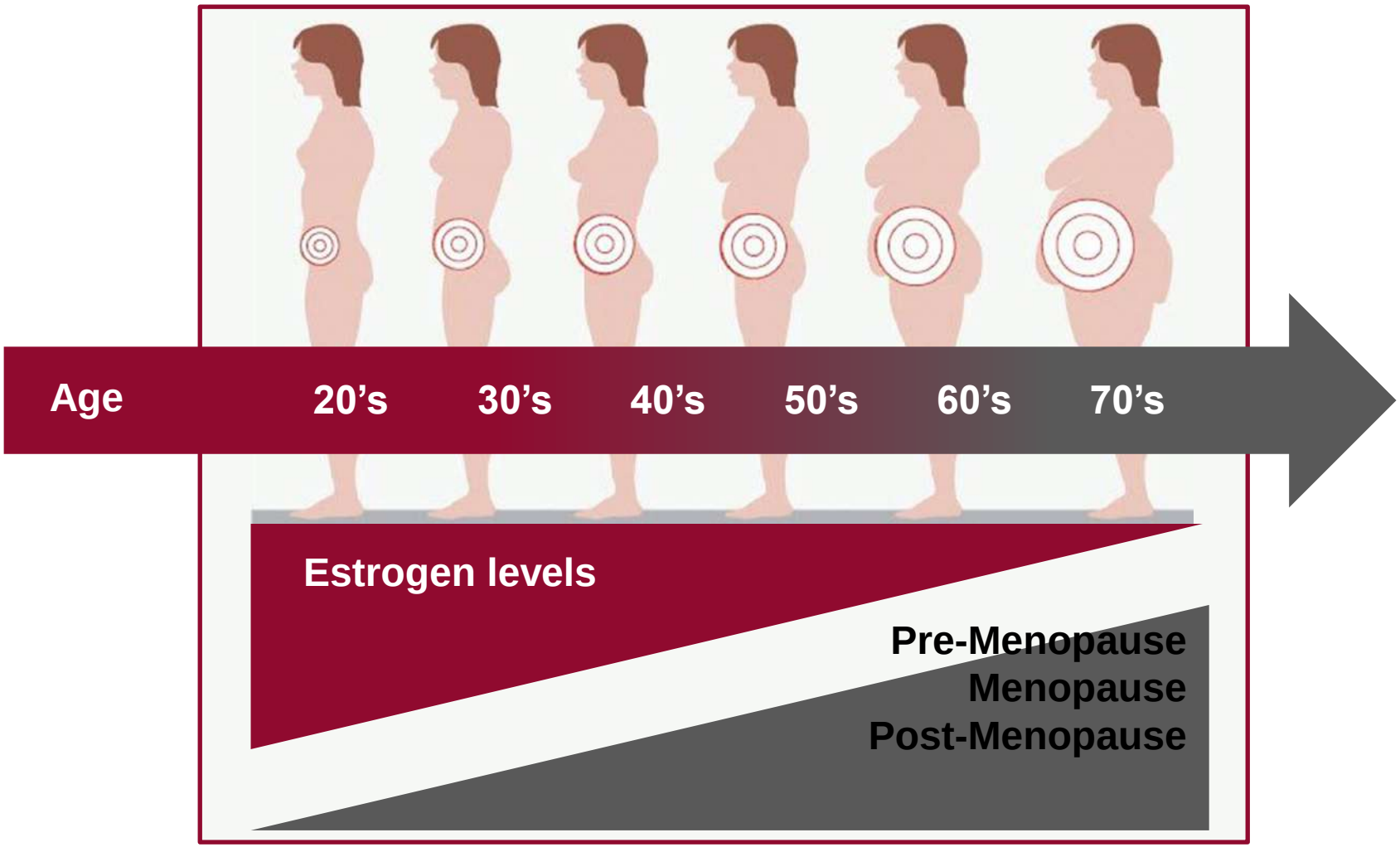
Key genes regulated by estrogen in cells of innate and adaptive immune system

Immune cell	List of genes
Neutrophil	CINC-1, CINC-2β, CINC-3, TNFα, IL-6, IL-1β
Macrophage	iNOS, NO, IL-6, TNFα
Dendritic cells	IL-6, IL-10, CXCL8, CCL2, TGFβ, IL-23, IL-12
Th1	IFNγ
Th2	IL-4
Tregs	FoxP3, PD-1, CTLA-4
B cells	Immunoglobulin, CD22, SHP-1, Bcl-2, VCAM-1

- **Effects on T cell activation vary based on different hormone concentrations— decrease MMP-9 expression**
- **Expression of iNOS is reduced and expression of nNOS and eNOS are increased**
- **Protective effect on mitochondria**

Drew et al. J. Neuroimmunol. 2000;111: 77-85
Kato et al.Science. 1995;270(524):1491-1494
Front Immuol.2015;6:635;Publishes online 2016

Age-dependent shift in estrogen levels



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Metabolic syndrome components during the menopausal transition

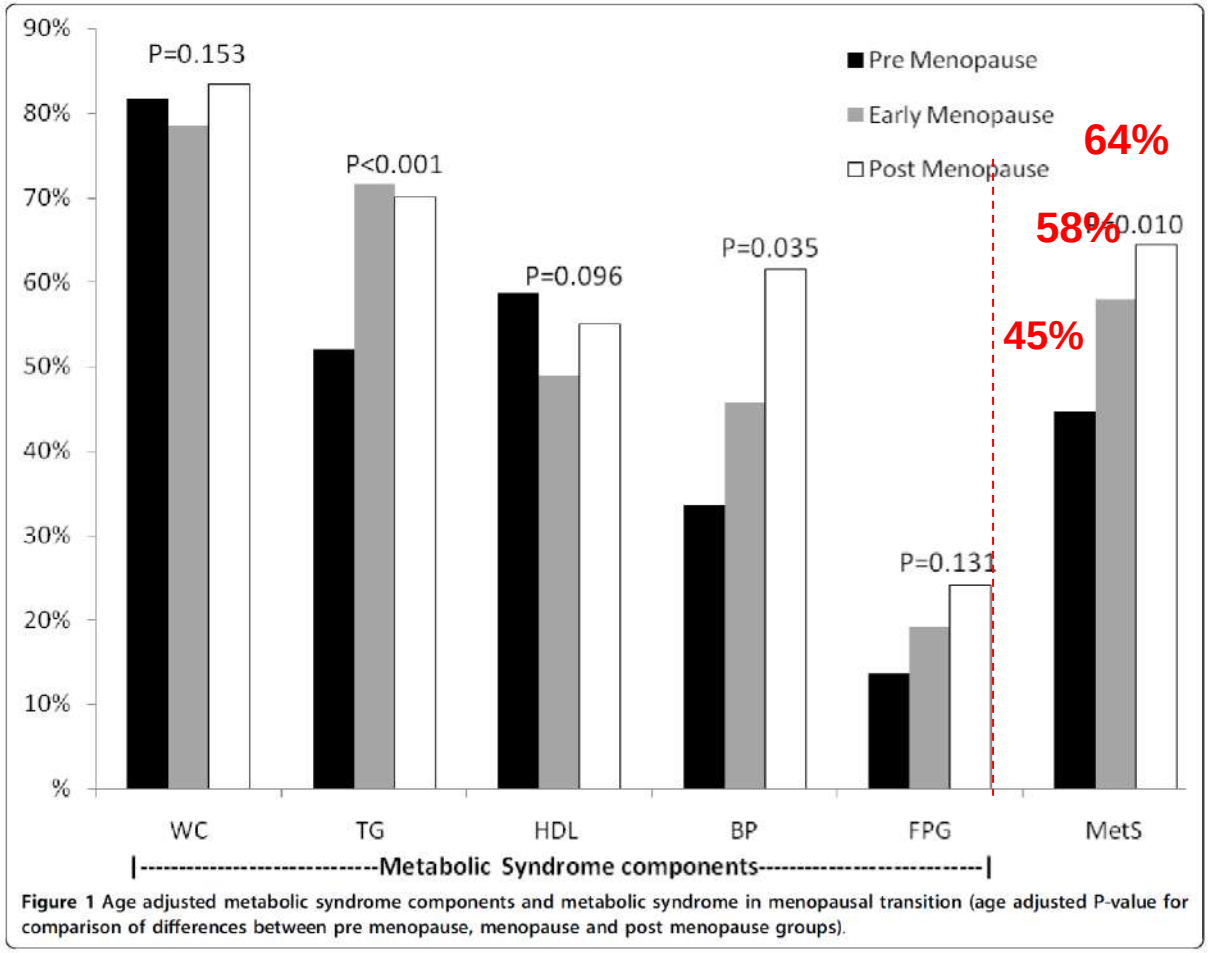

Figure 1 Age adjusted metabolic syndrome components and metabolic syndrome in menopausal transition (age adjusted P-value for comparison of differences between pre menopause, menopause and post menopause groups).

- **Cross-sectional study**
- **Isfahan Healthy Heart Program (IHHP) Samples**
- **1,596 women >45 y/o categorized into pre-menopause, menopause and post-menopause**

Heidari et al. *Diabetology & Metabolic Syndrome*. 2010; 2: 59

Progesterone: Endogenous steroid hormone

- Important role as a neuro-steroid in brain function
- Reduces sodium-retaining activity of aldosterone –natriuresis and reduction in extracellular fluid volume

Hallam et al. IOS Press. 2006; 69

Baulieu et al. Steroids. 2000;(10-11):605-12

Progesterone: A Neuro-steroid

- Neuroprotective and Neurogenic
- Regulates neurotransmission and myelination
- Protective effect on damaged brain tissue – lowers excitotoxicity; lowers apoptosis in neurons
- Enhances function of serotonin receptors in brain
- Fine tunes the GABA (A) receptor
- Acts as an anxiolytic, sedative, anticonvulsant

Espinoza et al. J of Head Trauma Rehab. 26(6):497-9

Progesterone Effects

- Anti tumor and anti-aging effects
- Improves bone strength
- Sustains stem cells by raising epidermal growth factor
- Relaxes smooth muscle – bronchi are widened and mucus regulated
- Anti-inflammatory agent - regulates immune response
- Normalizes blood clotting and vascular tone, zinc and copper level, cell oxygen levels, use of fat stores for energy
- Signaling of insulin release and pancreatic function – affects susceptibility to diabetes or gestational diabetes

Faivre et al. Mol and Cell Bio. 2006; 27(2):466-80

KEY TAKEAWAY:

Maintaining physiologic levels of ovarian hormones is a priority

Optimizing health in the years following ovarian senescence is essential to healthy longevity