Welcome

This is an online version of a presentation given by Dr Keith Merritt. Its purpose is to give a balanced review of the risks, benefits and alternative treatments for the changes and symptoms of female menopause. We hope you find it helpful.

If you would like bypass the presentation for the summary, right click on your mouse and go to slide # 138 . Enjoy

Depression, Hot Flashes, Insomnia

Are there safe treatment options for symptomatic midlife women?

The Basics

Common Abbreviations

- HRT- Hormone Replacement Therapy
- CHD- Coronary Heart Disease
- HERS- Heart Estrogen/Progesterone Replacement Study
- WHI- Women's Health Initiative (Study)
- mcgm- micrograms

Common Terms

- **Premarin**- a mixture of estrogens isolated from the urine of pregnant mares. The most well studied estrogen HRT
- **Provera**- a synthetic progesterone. Again, the most well studied progesterone HRT
- **Estradiol**- the form of estrogen that actually acts in the body. All types of estrogen HRT are eventually converted to this by the body before they act on the body's estrogen receptors.

Common Terms

- **DVT**- deep vein thrombosis
  -a blood clot forming in a deep vein
- **Thromboembolism**- a blood clot either forming in or breaking free from a clot in a deep vein and flowing to an artery in the lungs

What is Menopause?

Menopause is

- A natural transition
- The end of fertility
- A loss of estrogen production by the ovaries
- A change in the estrogen dependant parts of a woman's body

Menopause is Not

- A disease
- An estrogen deficient state that requires replacement to prevent illness

Postmenopausal

When there has been no menstrual flow for one year

What is a Hormone?

- A chemical messenger

  -Secreted by one body part

  -Directs the function of other body parts

Hormones Affected by Menopause

- Estrogen
- Progesterone
- Testosterone

Estrogen

- The hormone whose loss at menopause is most associated with the symptoms of menopause
- Symptoms are caused more by blood level fluctuations than by the actual levels
- Body changes of menopause are due to the actual levels
- Majority is made by the ovaries
- Some is produced by conversion of male type hormones, made by the ovary and adrenal gland, to weak estrogens by the body's fatty tissue

Progesterone

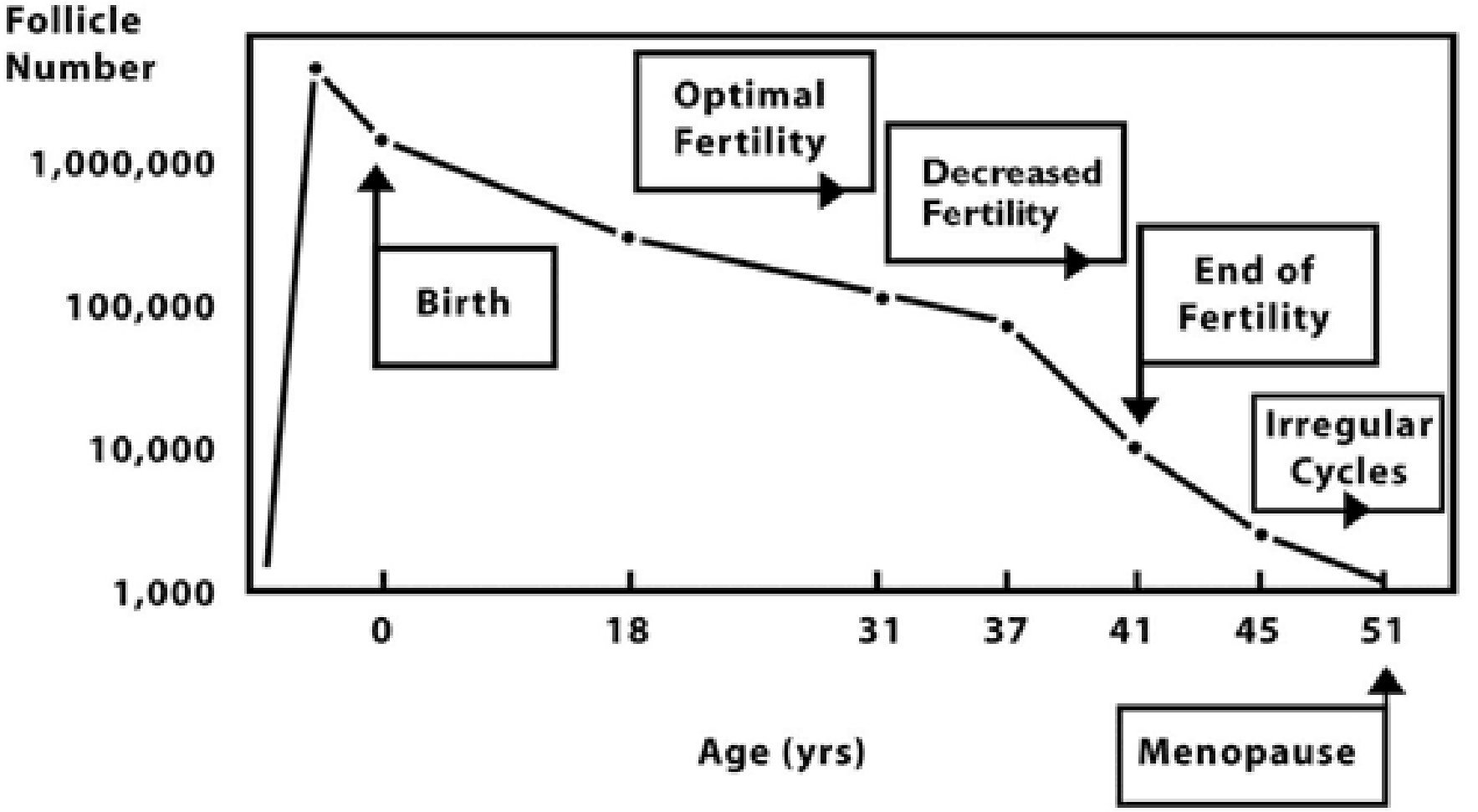
- Produced by the ovaries during each monthly cycle after the egg is released
- Purpose is to work with estrogen to provide a healthy lining in the uterus for implantation of a fertilized egg
- Replacement may help some menopausal symptoms
- Not given as part of hormone replacement in women who have had a hysterectomy
- Required as part of hormone replacement regimen in women with a uterus to prevent the estrogen replacement from causing cancer of the uterine lining (endometrial cancer)

Testosterone

- Responsible for a woman's libido
- 50% is made by the ovaries
- Blood levels peak each month with ovulation
- Ovarian production typically continues until age 65 years
- May or may not be an issue in those who have their ovaries surgically removed

The Ovary

- Analogous to a man's testicle
- Contain around 1 million eggs at birth
- During fertile years a small number of eggs are recruited each month for ovulation
- One dominant egg is then released each month
- In the late 30's, there is a very large increase in number of eggs recruited for each cycle
- Eggs are depleted in the early 50's- menopause



E.R. TE VELDE ET AL., 1998

The ovary is driven by the brain

- Glands in the brain produce hormones that direct hormone secretion by the ovary
- Ovarian hormones then feedback and mediate the brains hormone secretions
- The hypothalamus, the part of the brain that controls both body temperature and most hormone secretions, is affected by changes in ovarian hormone levels

Ovarian hormones act on the uterus over a 28 day cycle

- During the first half of the cycle, the ovary produces estrogen which thickens the lining of the uterus (endometrium)
- An egg is released around mid-cycle
- After an egg is released, the ovary makes both estrogen and progesterone
- Progesterone organizes the thickened lining in preparation for a fertilized egg to implant

If the uterine lining is exposed to estrogen without any progesterone exposure for a prolonged period of time it may develop endometrial hyperplasia (uncontrolled growth) which can in time progress to cancer- the reason all abnormal bleeding requires a biopsy

Historical Views of HRT

- 1930's- expensive miracle
- 1960's- critical to remaining feminine
- 1970's- endometrial cancer scare
- 1980's- hormones keep your bones strong
- 1990's- hormones prevent heart attacks
- 2000's- hormones will kill you
- 2014 - Perhaps a more balanced, informed view

2014 Common View

During menopause, I have only two options

1- Stay off hormones and want to die

2- Take hormones and die

Makes one feel a bit like a squirrel caught in the middle of the road

History of Hormone Replacement

- 1930's- estrogen therapy began
  -isolated originally from the urine of pregnant women
  -later pregnant mares were, and continue to be, used for conjugated estrogens (premarin)

- 1960's- rapid expansion of use

“Feminine Forever”

- Dr Robert Wilson

- 1966 best seller
- Nationwide lecture tour
- “menopause is completely preventable”
- “every woman alive today has the option to remain feminine forever”

Dr Robert Wilson

Financed by a major pharmaceutical company (guess what they made)

Women's Health Advocates

- 1950's- began raising safety questions
- 1970's- linked to endometrial cancer
  -reason why pro(gesterone) is in prempro

"Women and the Crisis in Sex Hormones"

-Barbara Seaman

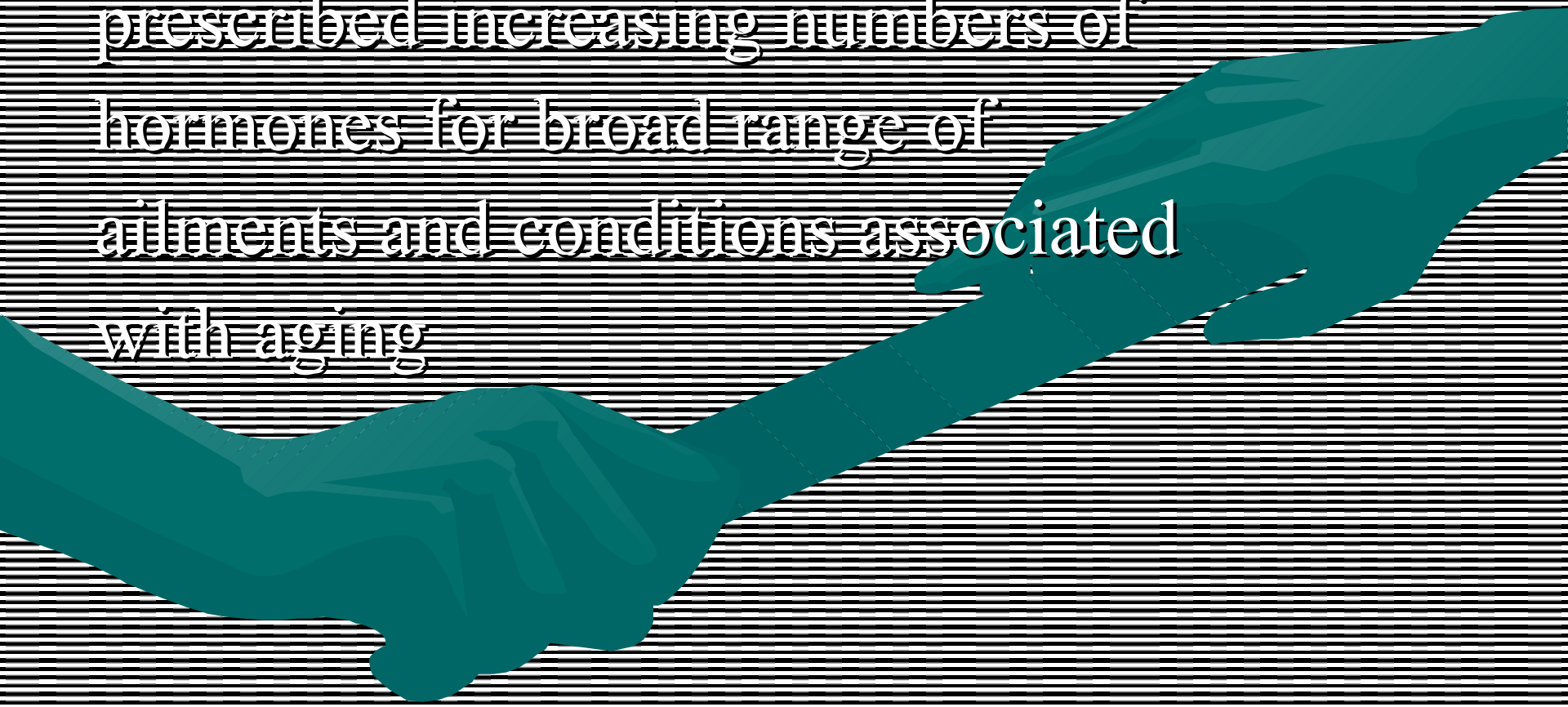
- 1977 bestseller
- Raised questions about risk of HRT
  -Breast cancer, blood clots, stroke
- Warned against over-promotion

But

One book was no match for a multimillion dollar drug industry

Decades that followed

Drug companies pushed & doctors prescribed increasing numbers of hormones for broad range of ailments and conditions associated with aging



FDA Approved Uses

- Initially only for treatment of symptoms
  -not disease prevention

- 1986- approved for osteoporosis prevention

- 1990- concluded- evidence did not support use for CHD prevention

But then, who really cares what the FDA thinks?

Seriously

Who really cares what the FDA thinks?

Against a backdrop of multiple small, poor quality studies with conflicting results, hormones became the most widely prescribed drugs in the world

1980's & 1990's

Widespread belief within medical community that postmenopausal women absolutely needed hormones to prevent heart attacks

The momentum behind this belief was the observation that very few women had heart attacks until after menopause. After menopause they then rapidly began approaching the rates of heart attacks in men.

1998- HERS Trial

- Well designed trial
- Intention was to show that HRT reduced heart attacks in women with known coronary heart disease

1998- HERS Trial Result

- Women with heart disease who took hormones had no change in risk
- Critics of study countered that the study did not apply to healthy women
- Results did not impact hormone use

2002- WHI Trial

- Well designed trial
- Intended to show that HRT reduced risk of developing coronary heart disease in healthy postmenopausal women

2002- WHI Trial Results

- Hormone use increased risk of
  -breast cancer
  -heart attack
  -stroke
  -blood clots

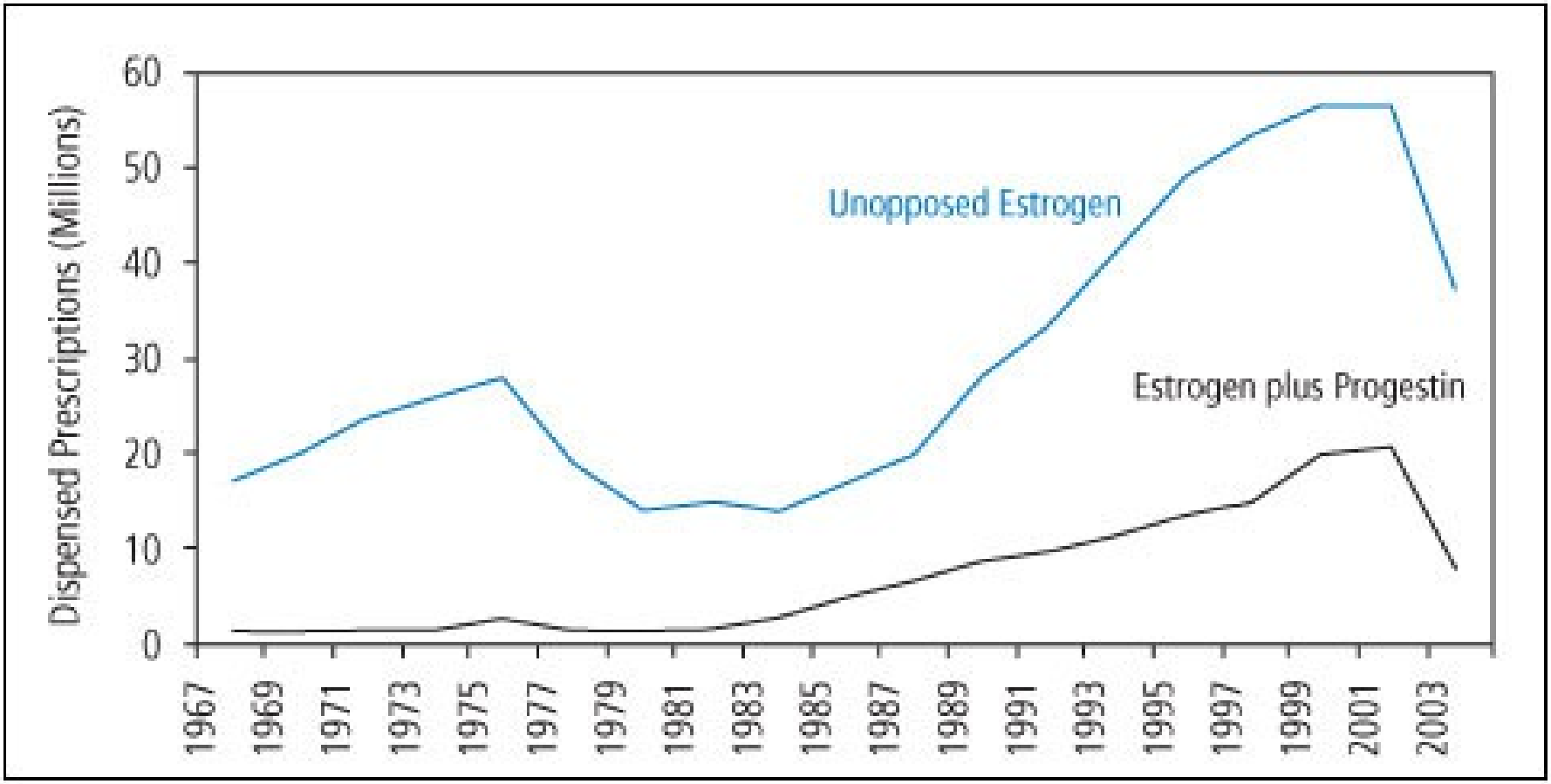


Figure 1. Trends in menopausal hormone therapy use in the U.S.A., 1967–2003. (Adapted from Beral V, et al. 1999 and Hersch AL, et al. 2004)

Symptoms of Menopause

Vasomotor Instability

Hot Flashes

Night Sweats

Insomnia

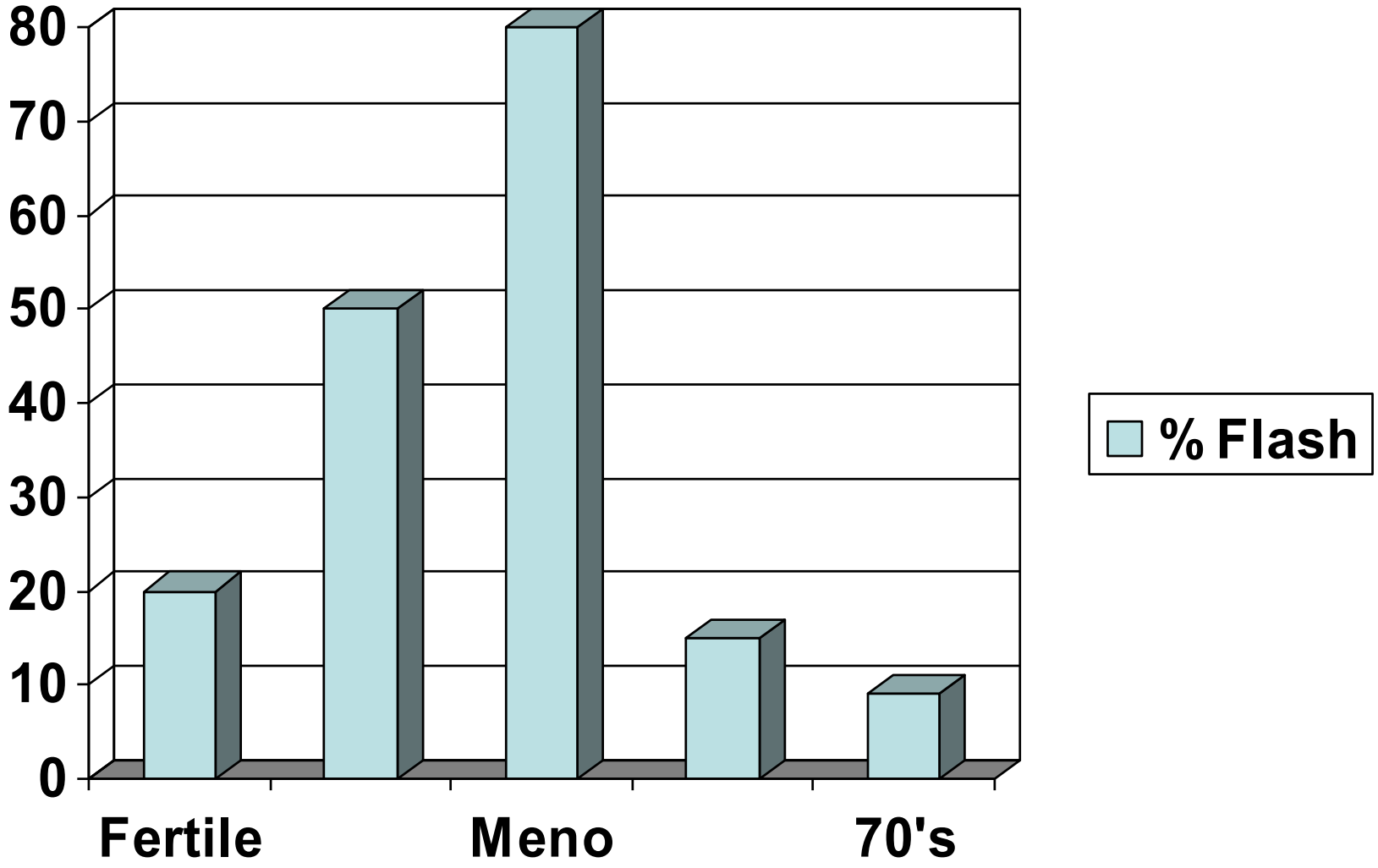
- **Vasomotor instability** (hot flashes) is caused by a malfunction of the bodies thermostat.

- This **thermostat** is located in the **hypothalamus**- a small part of the mammalian brain layer that controls multiple critical body functions.

- The hypothalamus monitors the body's core temperature and will alter blood flow to the skin to either conserve heat or radiate heat off.

- The hypothalamus will allow a certain range in core body temperature without intervening.
- When estrogen levels are not stable, the hypothalamus allows a much smaller rise in core temperature before it acts by increasing blood flow to the skin.
- This creates the flash and sweating followed by chills as the core body temperature then drops.

Prevalence of Hot Flashes



Non-HRT Treatment of Hot Flashes

- Effexor XR- low dose effective in 70%
- Other SSRI antidepressants- effective
- Clonidine- effective in 40%
- Neurontin- effective in 40%
- Lifestyle alterations

Lifestyle Alterations

- Hot shower before bedtime- depletes flashes
- Loose clothing
- Avoid
  -hot drinks
  -alcohol
  -spicy foods

Other Causes of Hot Flashes

- Hyperthyroidism
- Malignancy
- Infection
- Drug therapies
- Alcohol
- Emotional distress

Mood Instability

- Common- easy irritability & depression
- May have rapid swings in mood
- Estrogen replacement very effective
- Common to see women on antidepressants without HRT with little relief

Vaginal Atrophy

Loss of caliber and depth

Dryness

Loss of lubrication

Loss of sensation

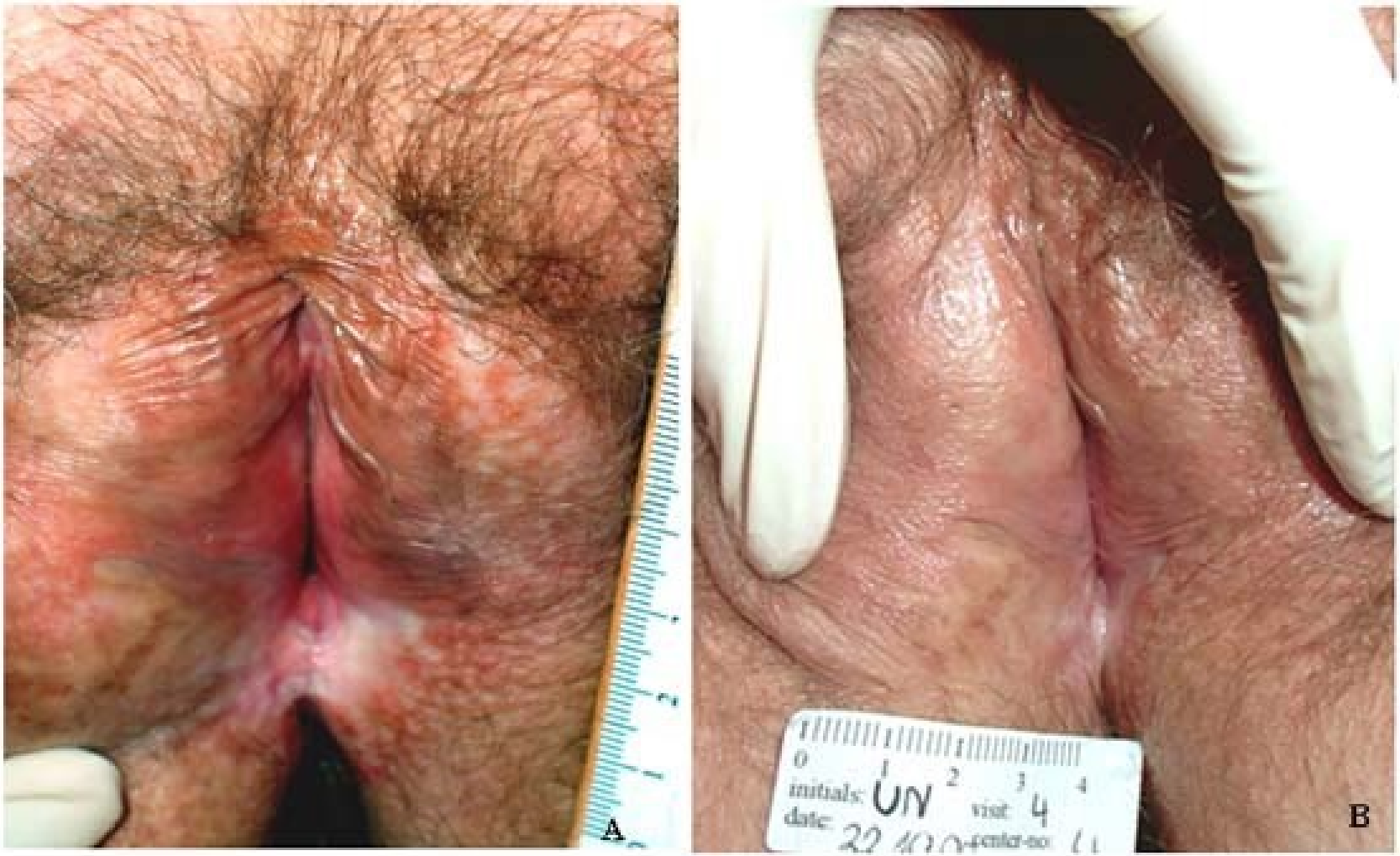
Irritation

Itching

- All vaginal tissues, including the skin lining the vagina, and the surrounding support tissues require estrogen to remain healthy.
- With the loss of estrogen at menopause, all of these tissues thin, weaken and become more fragile.
- Blood flow and sensation are diminished.

- The result is often prolapse of pelvic organs, urinary incontinence, pain with intercourse, decreased sensation during intercourse, dryness, frequent bladder infections, itching and irritation.

- These changes can either be prevented or stabilized and reversed by simply applying a small amount of estrogen into the vagina two times each week.



Significant inflammation, atrophy, and sclerosis can be seen on the vulvar entrance to the vagina (A). All signs except the sclerosis disappeared after 6 weeks of treatment (B).

Vaginal Atrophy and Estrogen

- Compared to direct application into vagina
  -systemic estrogen(ex- pills) gives only 25% as much benefit

- Low dose systemic estrogen (pills) may not have any impact on the vagina

Types of Vaginal Estrogen

- All have similar efficacy

  - creams, pills, rings

- Choices

  -Estring, Phadia

  -Femring- (provides systemic estrogen)

  -Vagifem

  -Creams- Premarin & Estrace

Vaginal Estrogen Creams

- Applied 2 times each week into the vagina

- Can be a little messy but very effective & cheaper
  -one $150 prescription is enough for one year

- May adjust dose- recommended 0.5 gm- provides
  -Premarin- 30 mcgm of conjugate estrogens or
  -Estrace- 50 mcgm of estradiol

Vagifem

- Vaginal tablet inserted 2 times each week
- 25 mcgm estradiol per dose
- Minimal increase in systemic levels
- Less messy & lower dose than creams
- More expensive than creams

Estring (Phadia)

- Lowest dosing option for vaginal estrogen
- Flexible silastic ring self-inserted every 3 months
- Expensive
- 6-9 mcgm estradiol released daily
  -1/10 of amount produced in menstrual cycle
    -only 1/10 of this is absorbed systemically

Femring

- Provides both local & systemic estrogen
- 50 & 100 mcgm per day
- Not recommended for women needing only vaginal estrogen
- Requires progesterone if uterus is present

Systemic Absorption of Vaginal Estrogen

- Depends on degree of atrophy
  -higher when more atrophic
  -minimal when atrophy is reversed

- No systemic progesterone is needed except when Femring is used

- However, sufficient to reduce bone loss in study using 7.5 mcgm/day vaginal ring

Alternative Treatments

Continued sexual activity

-includes masturbation

-helps preserve vaginal elasticity & pliability

-related to increased androgens & gonadotropins

Water soluble lubricants aiding intercourse

- Astroglide
- K-Y lubricant

Alternative Treatments

Replens

- Must be used on regular basis
- Binds to vaginal epithelium
- Slowly releases purified water
- Not for use on an “as needed basis” before intercourse
- Does not slow or reverse vaginal atrophy

Alternative Treatments

Vitamin E vaginal suppositories

Vitamin E with coconut oil vaginal suppositories

Both are over the counter and can provide non-hormonal relief of dryness and itching

Other Clinical Symptoms of Menopause helped by HRT

- Irregular bleeding
- Joint pain
- Breast pain
- Skin changes
- Menstrual Migraines
- Loss of balance
- Sexual dysfunction

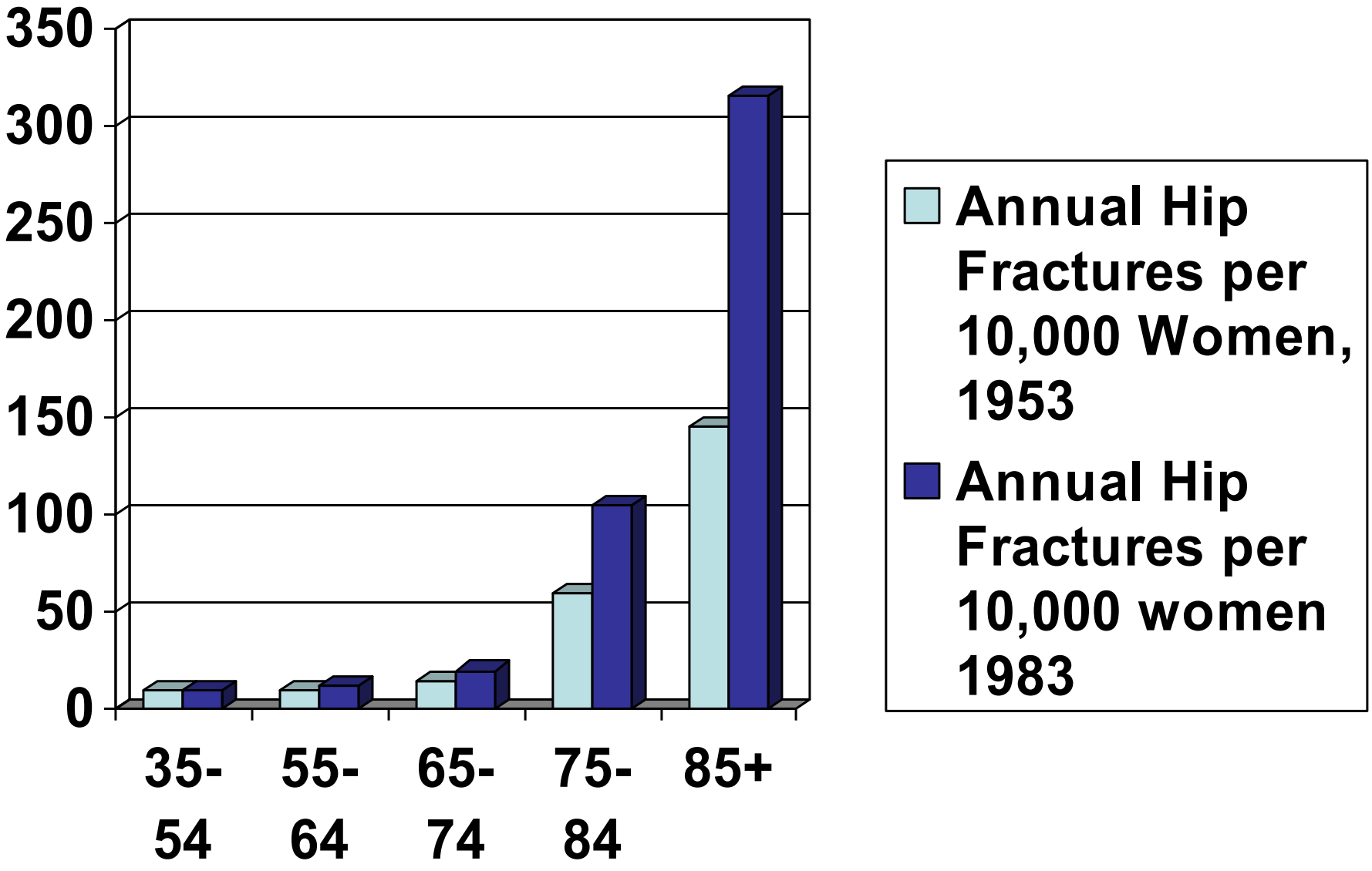
Clinical Risks of Menopause

- Fractures
- Cardiovascular disease
- Incontinence & prolapse

Fractures

Common Fractures

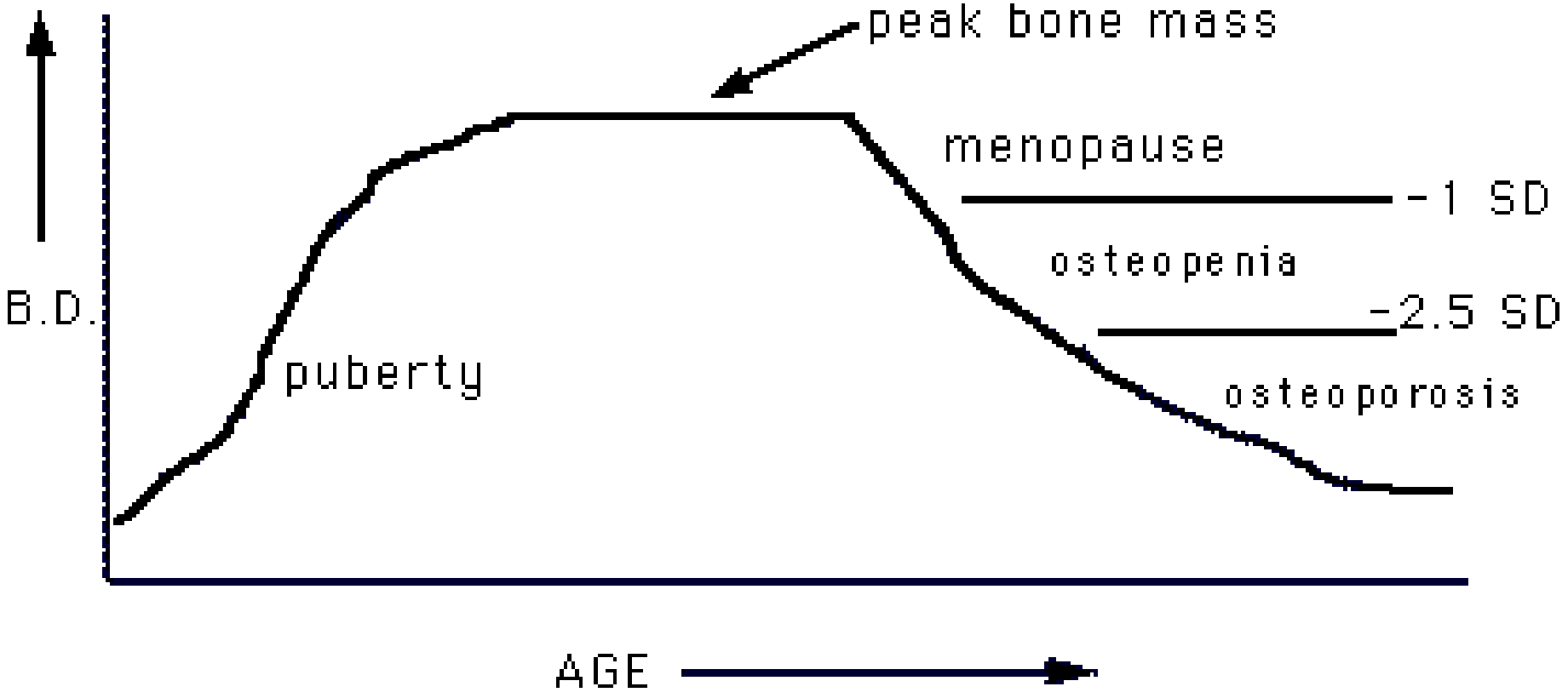
- Vertebral compression fractures
- Wrist fractures
- Hip fractures
  -most serious
  -20% mortality within 1st year
  -Only 20% of survivors return to previous levels of activity


350
300
250
200
150
100
50
0
35-54
55-64
65-74
75-84
85+
Annual Hip Fractures per 10,000 Women, 1953
Annual Hip Fractures per 10,000 women 1983

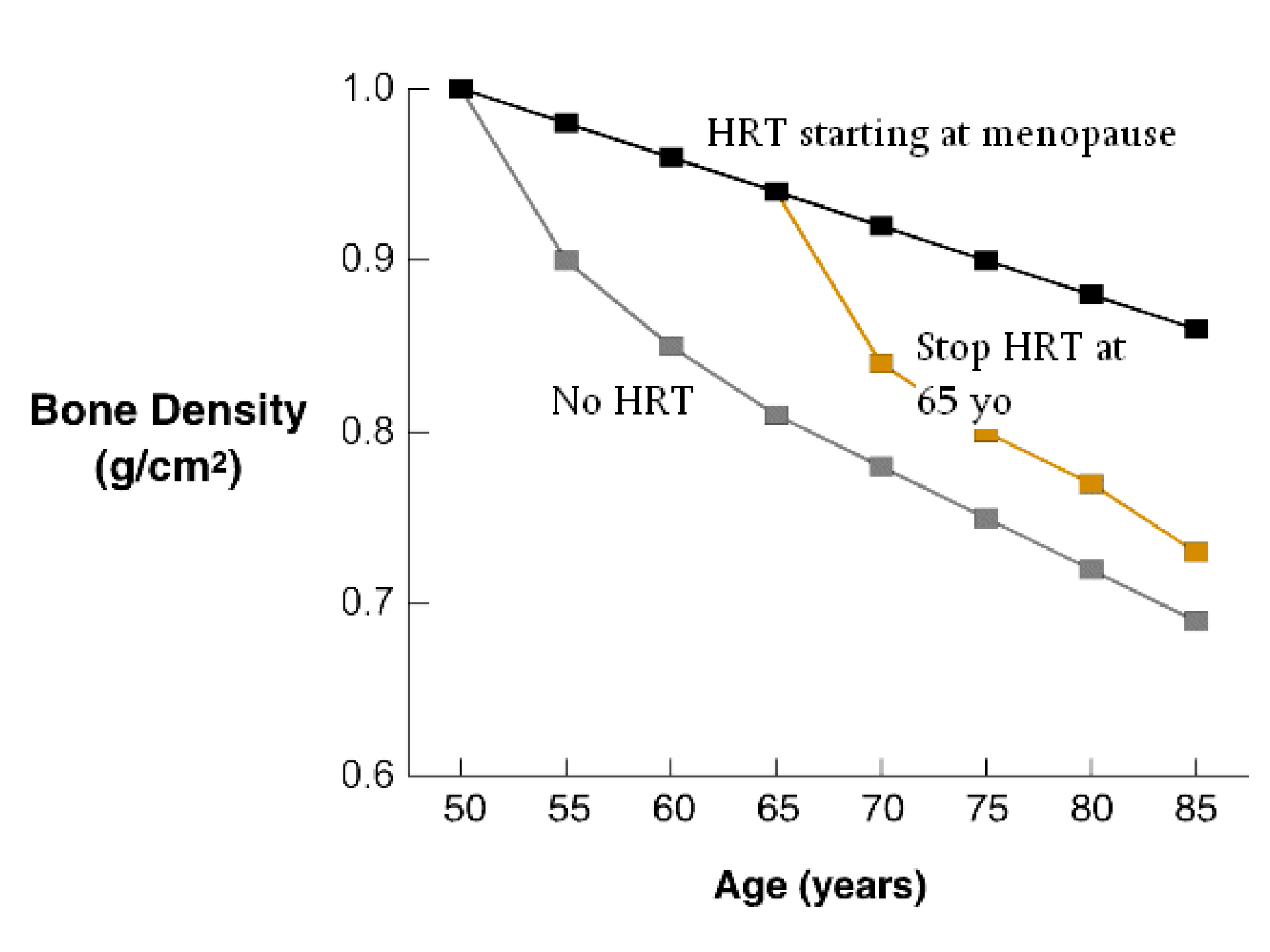
Prevalence is Increasing

- Population is now less active
- Less sun exposure
  -Vitamin D deficiency now common
- Less dairy consumption

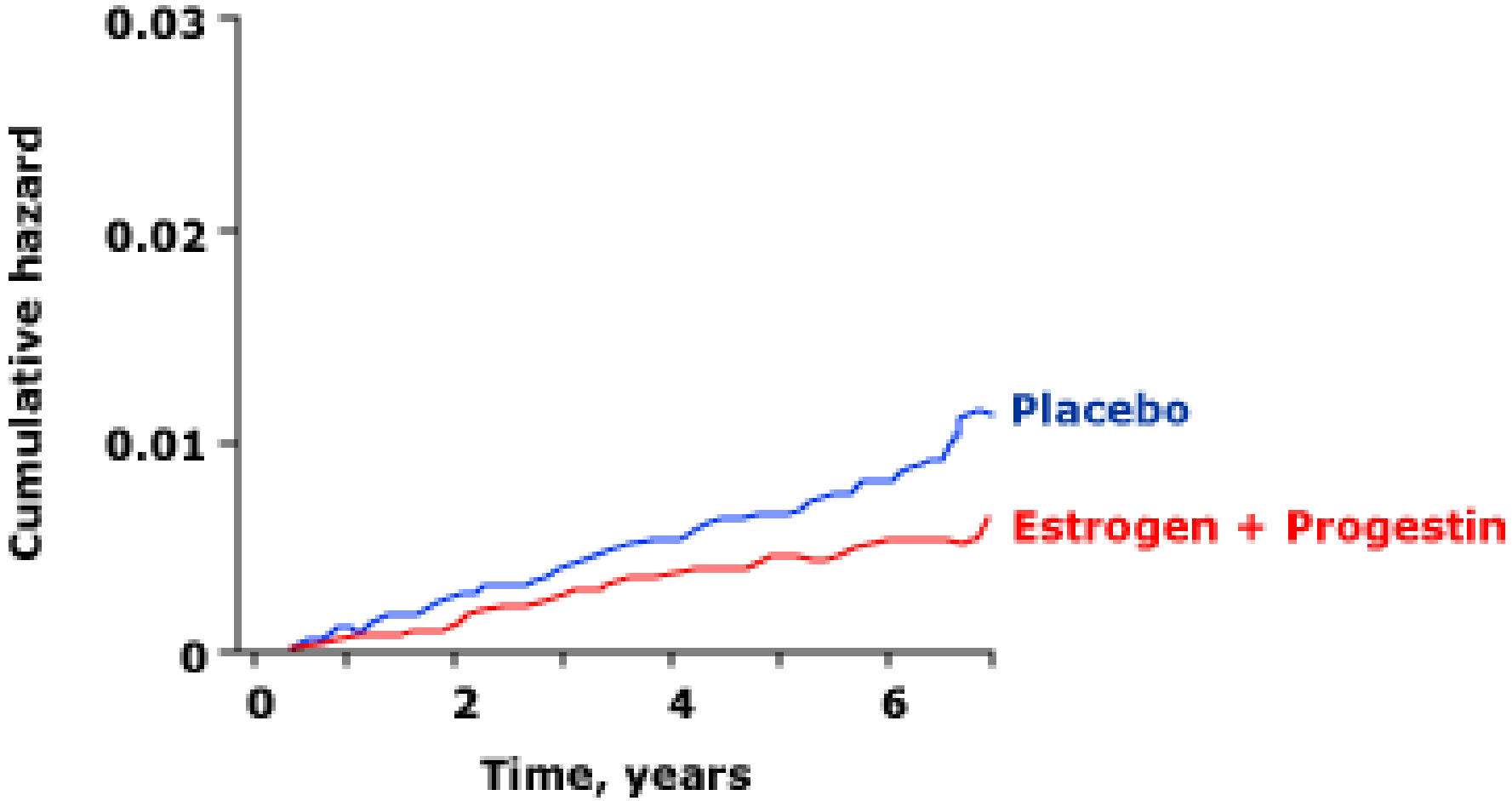
Critical to build as much bone density as possible before menopause with exercise, calcium & vitamin D


peak bone mass
menopause
-1 SD
osteopenia
-2.5 SD
B.D.
puberty
osteoporosis
AGE

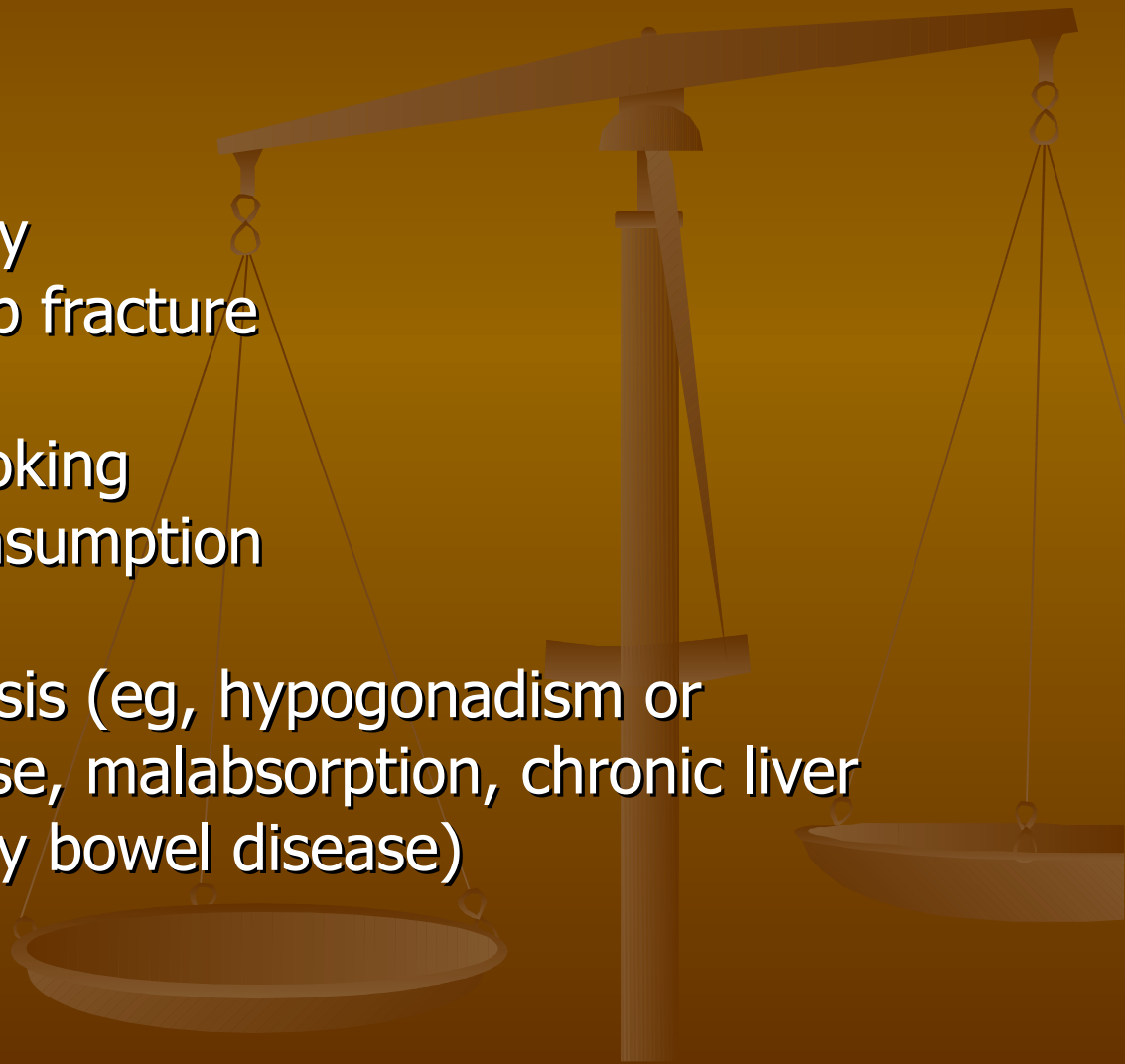
Hormone replacement will slow loss of bone density after menopause and will reduce fracture risk


Bone Density
(g/cm²)
1.0
0.9
0.8
0.7
0.6
HRT starting at menopause
Stop HRT at
65 yo
No HRT
50
55
60
65
70
75
80
85
Age (years)

HRT Reduces Hip Fractures



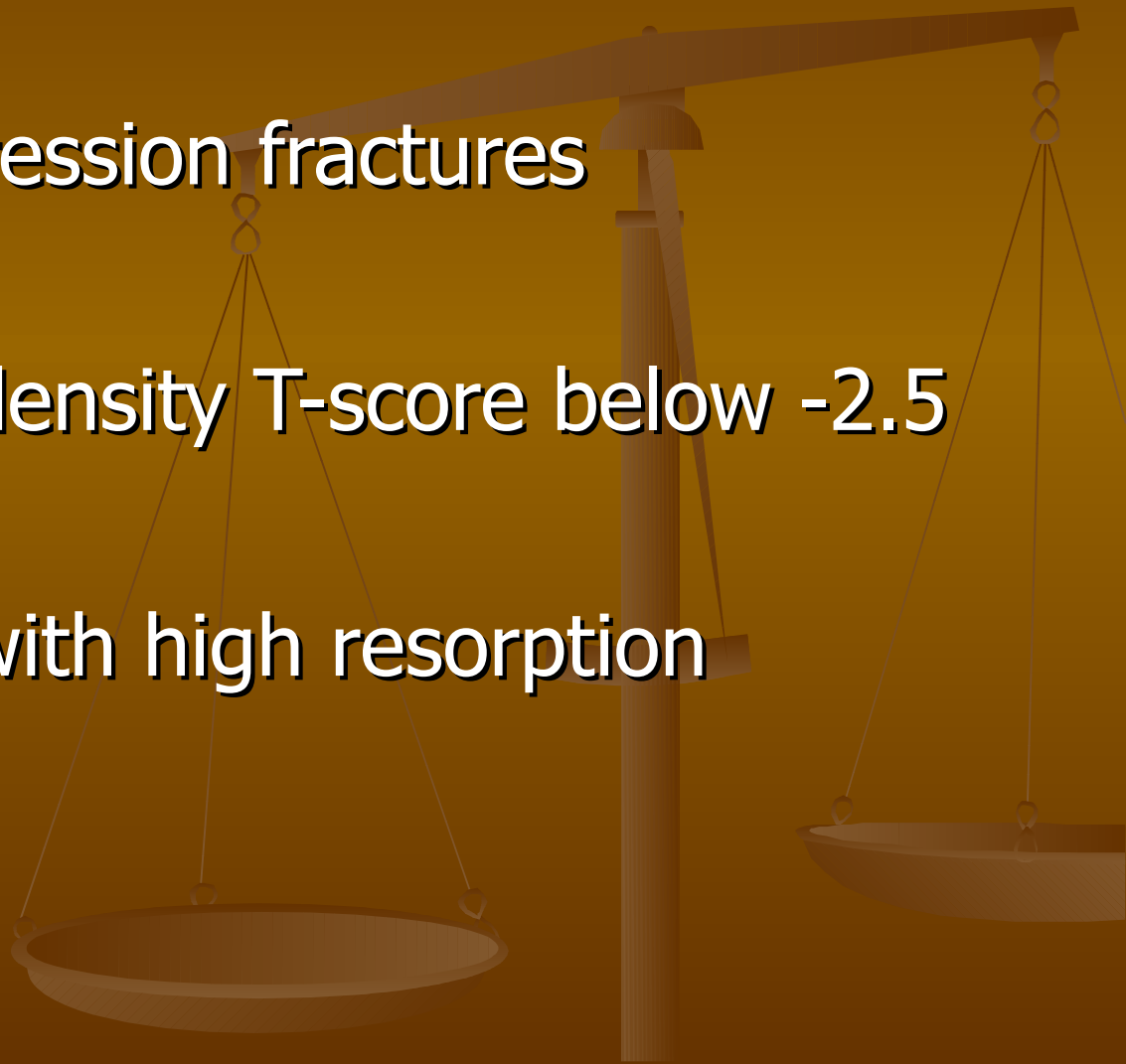
Clinical Risk Factors for Fracture



- Advancing age
- Previous fracture
- Glucocorticoid therapy
- Parental history of hip fracture
- Low body weight
- Current cigarette smoking
- Excessive alcohol consumption
- Rheumatoid arthritis
- Secondary osteoporosis (eg, hypogonadism or premature menopause, malabsorption, chronic liver disease, inflammatory bowel disease)

Drug Therapy Recommended for

- Vertebral compression fractures
- Total hip bone density T-score below -2.5
- Bone diseases with high resorption



Non-HRT Fracture Prevention

- Exercise- very, very important

  -no copay

  -reduces hip fracture risk by 40%
- Calcium- 1500 mg/day
- Sunlight- vitamin D (free!)

  -deficiency is very common
- Stop smoking!!!!
- Bisphosphonates
- SERMS

Bisphosphonates

- Didronel
- Aredia
- Fosamax
- Actonel
- Boniva
- Zometa, Reclast

Bisphosphonates

To be effective must have normal blood levels of

- Calcium
- Vitamin D

Bisphosphonates

- Clinically significant reduction in hip fractures only in those women with vertebral fractures
- No additional benefit beyond 5 years of use
- No fracture data supports use for preventing fracture in those without osteoporosis

Bisphosphonate Fracture Reduction

A group of postmenopausal women were treated with a bisphosphonate for 3 years. Hip fracture rates were then compared to similar group that was not treated

- In those with no prior vertebral fracture

  2.9% per year vs 3.2% per year
- Prior vertebral fracture

  4.5% per year vs 6.1% per year

Bisphosphonate Fracture Reduction

That is

- Using these very expensive drugs with known side effects provided only a very small benefit

SERMS

- Selective Estrogen Receptor Modulators
  -ex.- Raloxifen
- Improves bone density
  -but, provides no hip fracture risk reduction
- Increases blood clot risk but not CHD risk
- Decreases breast cancer risk
- Worsens hot flashes and vaginal atrophy
- Expensive

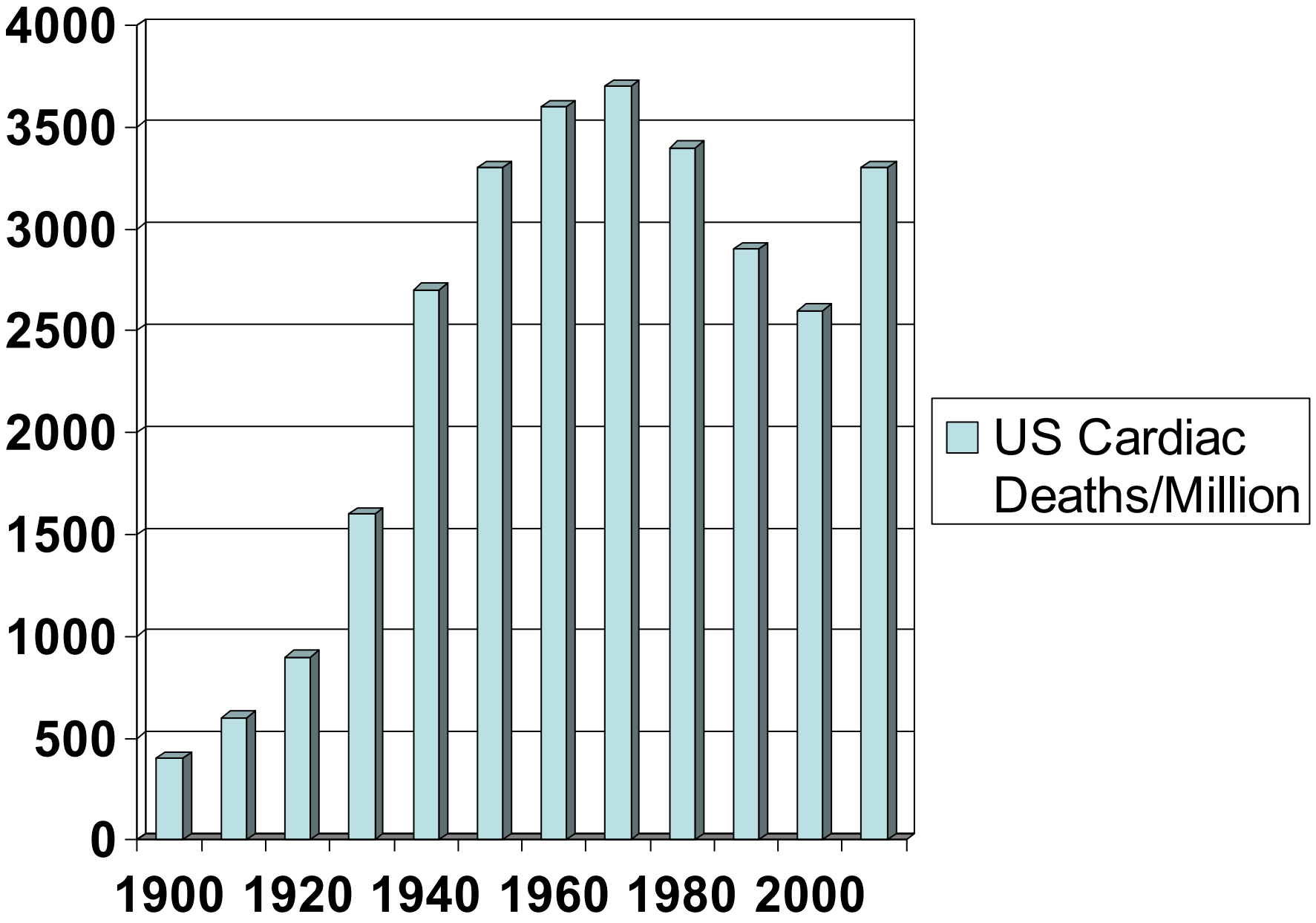
Risks of HRT

Heart Attack

Or, How to rearrange the Deck Chairs

There was an epidemic increase in US cardiac deaths in the past century that began long before HRT was introduced

This increase is thought to have been due to a dramatic decrease in physical labor and a radical decline in quality of diet


4000
3500
3000
2500
2000
1500
1000
500
0
1900
1920
1940
1960
1980
2000
US Cardiac Deaths/Million

How much cardiac risk does HRT add?

Lets look at the data

- HERS

  -Heart and Estrogen/progestin Replacement Study

- WHI

  -Women's Health Initiative

To understand the results of HRT trials we must understand the concept of Hazard Ratio

Hazard Ratio (HR)

- HR= 1.5= 50% increase in relative risk
- Must not confuse with absolute risk

For Example

- Suppose: in 1000 people not taking HRT
  2 have a heart attack

- Compare to: in 1000 people taking HRT
  3 have a heart attack
  HR=3/2= 1.5 or
  In those taking hormones the

  Relative risk of a heart attack= 50%

However

Absolute risk of hormones causing a heart attack is only

1/1000= 0.1%, **yet**

Relative Risk makes for a better headline

HERS

- Large, well designed clinical trial
- 7 years
- 2763 postmenopausal with heart disease
- Avg age- 67 years
- Premarin + provera

HERS Result

Premarin + Provera had no impact on heart attack risk in

- Older postmenopausal women with
- Documented heart disease

Women's Health Initiative (WHI)

- Series of well designed clinical trials
- "Healthy" postmenopausal women
- 50-79 yo (Avg- 63 yo)

- Two of these trials were HRT studies

  1) Premarin + Provera (uterus present)

  2) Premarin only (hysterectomy)

WHI: Premarin + Provera

- 16,608 women
  -8,506 on premarin + provera
  -8,102 on a placebo pill
- Planned to run 8 years
- Stopped at 5 years
  -increased breast cancer risk

Heart Attack Risk

- HR= 1.29= 29% increase in relative risk
- Premarin + Provera group (8506 women)
  -162 heart attacks over 5 years
- Placebo group (8102 women)
  -125 heart attacks over 5 years

Or

In 10,000 Women on Premarin + provera

- 37 will have a heart attack each year
  7 are caused by premarin + provera
  30 are caused by lifestyle & diet

- The absolute risk of premarin+provera causing a heart attack is **0.07%/yr**

WHI: Premarin only

- 10,739 healthy postmenopausal women
- Ages 50-79 yo
- Stopped after 7 years due to increased stroke risk

- No impact on heart attack risk

Suggests that

Provera (progesterone) may be the cause of increased heart attack risk

Just how healthy were the WHI participants?

- 50% were smokers
- 34% were obese
- No valid dietary or lifestyle intervention

Average age of women in WHI- 63 years

Average age of menopause- 51 years

Now

We know that the risk of heart disease in women rises rapidly after menopause

And

Most women seek hormone replacement in early menopause when they are having symptoms and before significant heart disease is established

So

How valid is applying data from an older population that is not having symptoms to a younger population that

- is having symptoms and
- has less heart disease risk

Timing Hypothesis

The age that postmenopausal hormones are started may be extremely important in determining the impact of hormones on heart disease risk

Timing Hypothesis

- Second look at WHI by age groups
- Women who start HRT earlier appear to actually have lower heart attack risk when they take hormones

	Hazard Ratio	Heart Attacks Per 10,000 per-yrs
50-59 yo	0.93	-1
60-69 yo	0.98	-2
70-79 yo	1.26	+19

KEEPS Trail

- Kronos Early Estrogen Prevention Study
- In progress
- To determine impact of early HRT

Factors not affecting heart attack risk with HRT in the WHI Study

- Obesity
- Aspirin therapy
- Diabetes
- Family history
- High blood pressure
- Smoking
- Statin use
- C reactive protein

Breast Cancer

WHI- Premarin + Provera

- HR= 1.26= 26% relative risk breast ca

In 10,000 women on Premarin + Provera

- 38 will develop breast cancer each year

  8 are due to premarin + provera

  30 are due to other factors

- Absolute Risk- 0.08%/yr

However

- Increased risk was not seen until 4 years of premarin + provera use
- Risk declined when Premarin + Provera was stopped
- Risk continued to increase if Premarin + Provera was not stopped after four years

WHI- Premarin only

- HR= 0.77= relative risk decrease= -23%

In 10,000 women on premarin only

- **28** will develop breast cancer each year

  vs

  32 per year in placebo group

Again, suggesting

Provera (progesterone) and not premarin (estrogen) may be the problem

Best to avoid HRT in breast cancer survivors

Risk in Breast Cancer Survivors

- HABITS Trial
- 442 women randomized- HRT vs placebo
- Stopped at four years due to increased risk of recurrent breast cancer
- Total cancer incidence over four years
  39 out of 221 subjects in hormone group
  17 out of 221 subjects in placebo group

Stroke

WHI Stroke Risk

Relative Risks

- Premarin + Provera= 41%
- Premarin= 39%

In 10,000 women, each year, strokes for HRT vs placebo

- Premarin + Provera- 31 vs 24 strokes
- Premarin only- 38 vs 25 strokes

WHI Stroke Risk

- Absolute risk in 50-59 yo group- 0

Do not use HRT if history of ischemic stroke

-stroke caused by a blood clot

-does not apply to stroke due to a ruptured blood vessel

WHI HRT Stroke Risk was not affected by

- Hypertension
- Documented cardiovascular disease
- Smoking
- Diabetes
- Biomarkers of inflammation
- Statin or aspirin use

Thromboembolism

(DVT & Pulmonary embolism)

WHI Thromboembolism Risk (DVT, Pulmonary Embolus)

In 10,000 women, yearly events for

	HRT	vs	Placebo
Premarin + Provera	34	vs	16

For Premarin only group- risk was smaller and was significant only for DVT's

WHI Thromboembolism Risk (DVT, Pulmonary Embolus)

Risk increased by

- Increased age
- Obesity
- Leiden V mutation

  HR- 6.7

Risk not affected by

- Smoking
- Aspirin
- Statins
- Other genetic clotting disorders

HAZARD RATIOS (HR) IN MAJOR TRIALS

Clinical event	HERS (E+P)	WHI (E+P)	WHI (E only)
CHD events	0.99	1.29	0.91
Stroke	1.23	1.41	1.39
Pulmonary embolism	2.79	2.13	1.34
Breast cancer	1.30	1.26	0.77
Colon cancer	0.69	0.63	1.08
Hip fracture	1.10	0.66	0.61
Death	1.08	0.98	1.04

WHI Bottom Line

Overall the risk for any adverse event being caused by hormone replacement is extremely low.

WHI Participant Website

- http://www.whi.org/
- Extended discussions and information posted by WHI Study

WHI Premarin + Provera
Extra Events/10,000 women/year

- 8 more breast cancers
- 6 more heart attacks
- 8 more strokes
- 8 more pulmonary emboli
- 6 fewer colon cancers
- 5 fewer hip fractures

WHI Premarin only
Extra Events/10,000 women/year

- 12 more strokes
- No impact on colon cancer risk
  -does provera protect the colon?
- No impact on heart attack risk
  -decreased risk in 50-59 yo?
- Decreased breast cancer risk?

Summing It All Up

- In the final analysis, HRT most likely does not either increase or decrease longevity
  -any increased risk is very, very small
- HRT does improve quality of life for symptomatic women around the time of menopause
- There is no firm data yet for the most pertinent issue- what is the impact of HRT on women just entering menopause?
  -currently being investigated by the KEEPS trial

Summing It All Up

- When discussing risk the most important questions are
  -Has there been a hysterectomy- i.e.- is progesterone needed?
  -What is the patient's age?
  -Is there a history of either breast cancer or stroke?
  -Is there a genetic risk of breast cancer?
  -Is there a Leiden Factor V mutation?
  -What symptoms are being treated and will alternative treatments be effective?

Summing It All Up

- In those needing estrogen + progesterone (have uterus)
  -yearly absolute risks of heart attack, breast cancer and stroke are each less than 1/1000
  -yearly absolute risk of thromboembolism is 1.8/1000
  -breast cancer risk is not increased until after 4 years of HRT- the risk then recedes if HRT is stopped
  -In women with known heart disease HRT does not increase the risk of another heart attack
  -Colon cancer and hip fracture risks are slightly lower

Summing It All Up

- In those needing only estrogen (prior hysterectomy)
  -Yearly absolute risks of stroke or thromboembolism are less than 1/1000
  -Heart disease risk is not increased and may actually be decreased especially in women starting HRT early
  -There is no increased pulmonary embolus risk
  -Breast cancer risk is not increased
  (may actually be decreased)
  -Fracture risk is slightly decreased
  -No impact on colon cancer risk

Summing It All Up

- For women beyond the symptomatic years of menopause, the only real benefits of adding HRT is for a very small decrease in fracture risk and for treatment or prevention of vaginal atrophy
  -vaginal estrogen is adequate for both and for vaginal health is superior to systemic HRT

Summing It All Up

- Topical estrogen may be safer and may decrease total body fat and increase total body lean tissue
  -mostly theory with no firm data
- If taking drugs that may interact with liver metabolism of estrogen, better to use a topical estrogen
- Prometrium, a progesterone that is the same as that produced by your body, may be safer than synthetic
  -again, mostly theory with no firm data

A Reasonable Strategy

- If symptomatic with menopause begin systemic HRT as soon as possible provided there is no history of
  -stroke due to blood clot
  -breast cancer or breast cancer gene (BRCA)
  -pulmonary embolus or deep vein thrombosis
- If uterus is still present taper off systemic HRT and start vaginal estrogen before four years
  -if prior hysterectomy may continue systemic estrogen
- Consider Effexor XR if cannot take HRT

So if I do need or choose to use something

What are my options?

Types of Systemic Hormone Replacement

Estrogen, progesterone, testosterone

- Pills
- Patch
- Other topical- creams, emulsions, sprays
- Vaginal Rings
- Herbal & phytoestrogens
- Bioidenticals

Types of Estrogen

- Conjugated equine estrogen
- Conjugated synthetic estrogen
- 17-B estradiol
- Esterified estradiol
- Ethinyl estradiol (birth control pills)

Type of Estrogen may have an impact on CHD Risk

- WHI & HERS trials- conjugated estrogen
- Estrogen in Prevention of Atherosclerosis Trial (EPAT)- Estradiol (not premarin)
  -surrogate CHD marker improved
- Adding a progesterone may negate benefit

Transdermal Estrogen may be safer for secondary CHD prevention

- Improved markers of heart disease
- Less impact on clotting than oral
- However, no firm evidence far so

Effects of Progestins

- Synthetic progestins negate improved lipid effects of estrogen

  -However, prometrium does not. Prometrium is a natural progesterone

- Increase serum markers of inflammation

Oral Estrogen

- Quickly metabolized by the liver
- Has an effect on the liver
  -Increases proteins made by the liver
  -Increases HDL cholesterol & triglycerides
- Increases clearance of certain drugs
  -seizure medicines, thyroid replacement
- Increases gallstone risk

Oral Estrogens

- All preparations have similar efficacy
- All are either absorbed as or converted to estrone sulfate. The body then slowly converts to estradiol which is the from acting on estrogen receptors.
- Unproven but suspected that risk may vary with the type of estrogen preparation

Cardiovascular effects of Oral Estrogen

- Improved lipid profile

  -except for increased triglycerides
- Improved endothelial function

  -however, seen only in healthy younger women
- Possible improved insulin sensitivity
- Decreased clotting factors- fibrinogen, Factor VII, and antithrombin III (important anti-clot factor)
- Increased vascular inflammatory markers

Oral Estrogens- Equivalents

- Sulfocongugated estrogens- 0.625 mg
- Esterified estrogens- 0.625 mg
- Micronized estradiol- 1.0 mg
- Ethinyl estradiol- 0.005 mg

Transdermal17B-estradiol 0.05 mg

Low Dose Estrogen

- 0.3 mg congugated estrogen
- 0.5 mg micronized estradiol

Ultralow dose

- 0.25 mg micronized estradiol
- 0.014 mg transdermal

Ultra Low Dose Estrogen

- Reduces bone loss
- May not control vasomotor symptoms
- May not prevent vaginal atrophy

Topical Estrogens

- Less impact on liver related items
  - -Liver proteins
  - -cholesterol
  - -gallstone risk
- Possible
  - -reduction in body fat
  - -increase in lean body tissue

Topical Estrogens

- Patches, gels, emulsions, sprays
- All provide 17B-Estradiol
- Allow variable dosing
- Femring (vaginal ring) is also form of topical estrogen for systemic dosing
- All are more expensive than pills
- Beware of “bioidenticals”
  -Premarin gel is not absorbed through the skin
  -most forms of progesterone gel are not well absorbed through the skin

Topical Estrogens

- Gels, emulsions and sprays
  -daily application
- Patches
  -either once or twice weekly application
- Vaginal ring
  -placed by patient every three months
  -excellent option if vaginal atrophy is also an issue

Progesterones

- Provera (medroxyprogesterone acetate)
  -most commonly prescribed progestin
  -used in most of studies

- Testosterone derivatives
  -used in birth control pills & Mirena IUD
  -may have mild testosterone effect

Progesterones

- Prometrium

  -micronized natural progesterone

  -less well studied

  -less negative impact on serum lipids

  -reasonable alternative

  -vaginal application may be coming

Progesterones

- Drospirenone

  -newer

  -used in birth control pills

  -derived from sprironolactone

  -anti-testosterone effect

  -debatable effect on electrolytes

  -favorable impact on lipids

Progesterones

- Mirena IUD

  -excellent birth control

  -endometrial protection: off label use

  -not a safe alternative with breast cancer

Testosterone

- Efficacy and safety data are very limited
- No clear criteria for deficiency
- Supplements can have side effects

  -hair growth and acne

  -Decreases HDL (the “good” cholesterol)

Testosterone

- Pills, patches, creams, implants
- One small study shows sexual benefit
- Controls of hot flashes in difficult cases
- Improved sense of well being
- Improved mental function- data very weak
- Improved bone density- increased estrogen?
- Use with caution- risk vs benefit unclear

Clearest Indications for Testosterone Supplementation

- Adrenal failure
- Premature ovarian failure
- Surgical removal of ovaries
- Pituitary failure

Medical Conditions to consider when prescribing HRT

- Anticonvulsants- increase hormone clearance
- Thyroid and glucocorticoid replacement
  -increased dosing may be needed
- Alcohol- increases estrogen levels 3x
- End stage renal disease requires lower dosing

Phytoestrogens

- Naturally occurring compounds in fruits and vegetables
- Act by varying degrees on estrogen receptors
- Three main types

-isoflavons- greatest effect

-coumestans

-lignans- weakest

Phytoestrogens

- Isoflavons

  -soy, chickpeas & lentils

- Coumestans

  -sprouts- legume, clover, alfalfa

- Lignans

  -flaxseed, grains, fruit, lentils, vegetables

Little to no evidence of benefit for

- Hot flashes
- General health
- Bone mineral density- conflicting data
- Breast cancer- ?antiestrogen at high dose

Herbal Medicines

- Evidence of any benefit debated
- Safety concerns legitimate
  -manufacturers are not required to report adverse events
- Unregulated
  - huge potential variation in quality
- Play strongly into placebo effect

Dr Tierraona Low Dog

- DrLowDog.com
- Respected bridge between traditional and alternative medicine
- Herbalist and Family Physician
- Evidenced based medicine
- University of New Mexico
- Menopause strongly open to placebo

Bioidentical Hormones

- No evidence of safety or efficacy
- Require frequent testing
- Very expensive
- Unregulated (but not for long)
- Quality varies
- Variable absorption

Bioidentical Hormones

The appeal of paying more for less
-quality
-benefit

A clever way to make money on novelty and public distrust

Plays strongly into placebo effect

HRT Drug List

ORAL ESTRADIOL*	
-Estrace (Warner Chilcot)	0.5, 1, 2 mg
-Gynodiol (Fielding)	0.5, 1, 1.5, 2 mg
ORAL ESTERIFIED ESTROGEN*	
-Menest (Monarch)	0.3, 0.625, 1.25, 2.5 mg
-Ogen (Pharmacia)	0.75, 1.5, 3 mg estropipate (equivalent to 0.625, 1.25, 2.5 mg conjugated equine estrogen)
-Ortho-Est (Women First Healthcare)	0.75, 1.5 mg estropipate (equivalent to 0.625, 1.25 mg conjugated equine estrogen)
ORAL CONJUGATED EQUINE ESTROGEN*	
-Premarin (Wyeth-Ayerst)	0.3, 0.45, 0.625, 0.9, 1.25 mg
ORAL CONJUGATED SYNTHETIC ESTROGENS*	
-Cenestin (Elan)	0.3, 0.45, 0.625, 0.9, 1.25 mg
-Enjuvia (Elan)	0.625, 1.25 mg

ORAL ESTROGEN-PROGESTIN COMBINATIONS

Prempro (Wyeth-Ayerst)	0.3 mg CEE/1.5 mg medroxyprogesterone, 0.45/1.5 mg, 0.625/2.5 mg, 0.625/5 mg
Prefest (Duramed)	1 mg estradiol/0.9 mg norgestimate
Activella (Novo Nordisk)	1 mg estradiol/0.5 mg norethindrone acetate
FemHRT (Warner Chilcot)	5 mcg ethinyl estradiol/1 mg norethindrone acetate
Angeliq (Berlex)	1 mg estradiol/0.5 mg drosperinone

ORAL ESTROGEN-TESTOSTERONE COMBINATIONS*

Estratest (Solvay)	1.25 esterified estrogen/2.5 mg methyltestosterone
Estratest HS (Solvay)	0.625 mg esterified estrogen/1.25 mg methyltestosterone
Syntest DS (Breckenridge)	1.25 mg esterified estrogen/2.5 mg methyltestosterone
Syntest HS (Breckenridge)	0.25 mg esterified estrogen/1.25 mg methyltestosterone

ESTRADIOL PATCHES*

Alora (Watson)	0.025, 0.05, 0.075, 0.1 mg/d
Climara (Berlax)	0.025, 0.05, 0.06, 0.075, 0.1 mg/d
Esclim (Women First)	0.025, 0.0375, 0.05, 0.075, 0.1 mg/d
Estraderm (Novartis)	0.05, 0.1 mg/d
Vivelle (Novartis)	0.025, 0.0375, 0.05, 0.075, 0.1 mg/d
Menostar (Bayer)	0.014 mg/d

ESTROGEN-PROGESTIN PATCH

Combi-Patch (Novartis)	0.05 mg estradiol/0.14 mg norethindrone, 0.05 mg/0.25 mg
Climara Pro (Berlex)	0.045 mg estradiol/0.015 mg levonorgestrel

GEL*	
EstroGel (Solvay)	0.75 mg estradiol per pump
EMULSION*	
Estrasorb (Novavox)	0.025 mg estradiol/pouch
Divigel (Upsher-Smith)	0.25, 0.5, 1 mg estradiol/pouch
Elestrin (Kenwood)	0.52 mg estradiol/pump
TOPICAL SPRAY*	
EvaMist (KV Pharmaceutical)	1.5 mg estradiol/spray

INTRAVAGINAL RINGS*	
Femring (Warner-Chilcott)	0.05 & 0.10 mg estradiol/day over 3 months

VAGINAL ESTROGEN PREPERATIONS FOR GENITOURINARY ATROPHY
(inadequate dose to relieve vasomotor symptoms)

VAGINAL RING

Estring (Pharmacia)	0.0075 mg estradiol/day, released over 3 months

VAGINAL TABLET

Vagifem (Novo Nordisk)	0.025 mg estradiol/tablet

VAGINAL CREAM

Estrace (Warner-Chilcot)	0.1 mg estradiol/gram
Premarin (Wyeth-Ayerst)	0.625 mg equine conjugated estrogen/gram

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