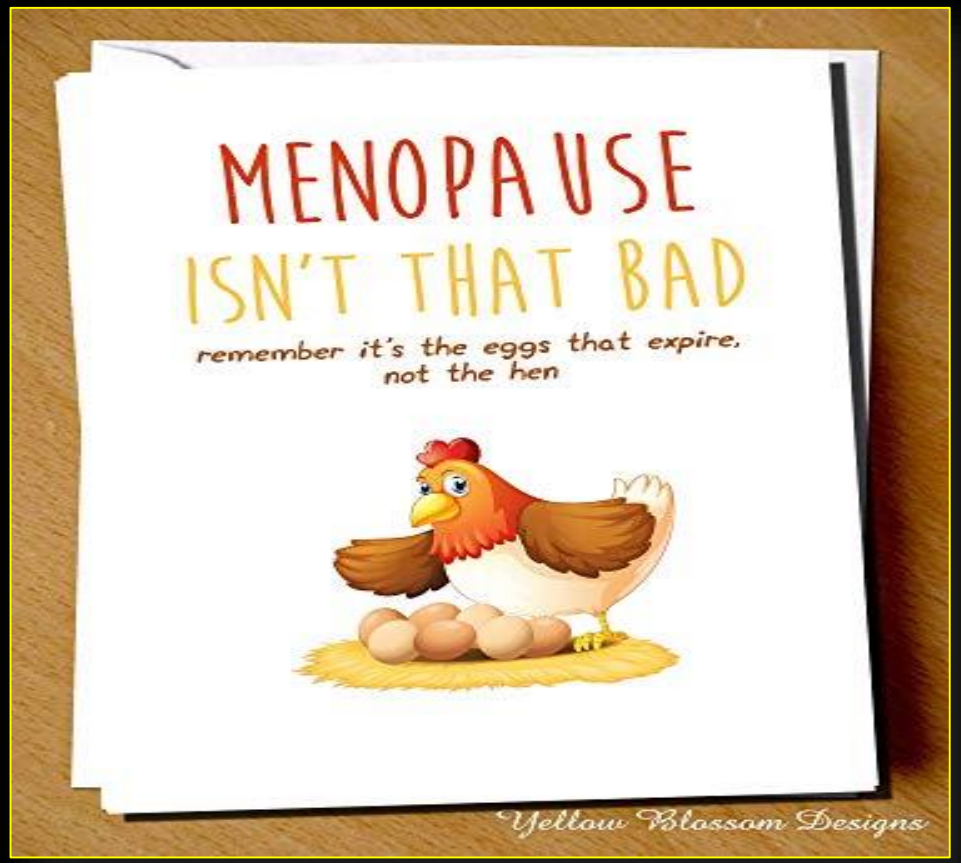


Menopause and HRT

Dr Fida Al-Asali

Terminology

- **Menopausal transition**
- ovaries start to fail - last menstrual period
- lasts for 4 years (shorter in smokers)
- age 47.5 years
- 10% of women will cease menstruation abruptly

Terminology

- **'Climacteric' = perimenopause:** period from when the ovaries start to fail - 12 months after last menstrual period
- **Menopause**: the last menstrual period
- **Postmenopause:** time after complete cessation of menstruation
- **Primary ovarian insufficiency:** menopause that occurs before the age of 40 years.

Age of Menopause

- **Average age: 51 years**
- **Earlier menopause : < 45yrs**
  - **Family hx of early menopause (heritability 30–70%)**
  - **Type 1 diabetes mellitus**
  - **Smoking**
- At 54 years, 80% of women will be at least one year postmenopause

Premature menopause
POI

- Menopause < 40 yrs
- 1% < 40
- 0.1% < 30
- The cause of spontaneous ovarian failure is usually unknown

Causes of Premature ovarian failure

- Idiopathic
- Genetic: Turner's, Galactosemia, 17α-hydroxylase deficiency, Aromatase deficiency,…
- Auto-immune-hypothyroidism, Addison's,..
- Infections-T.B, mumps, malaria, CMV,…
- Induced: Bilateral oophorectomy, Chemotherapy & Radiation

Pathophysiology

The number of primordial follicles that a female has declines throughout life without replacement:

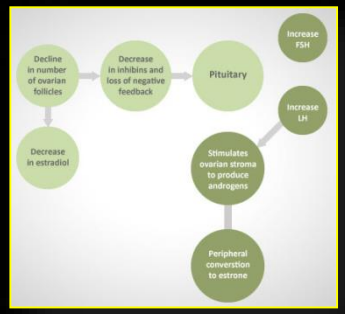
- Newborn: 2 million
- Puberty: 300000–400000
- 40yrs+: few thousands
- Postmenopause: few or no ova

2 critical landmarks in the ovarian failure process:

First: marked decline in **fertility** (no cycle dysfunction)

Second: **Menstrual cycle** changes with a shortened follicular phase and luteal dysfunction

↓ follicles → ↓ E2 & inhibin B



'compensated failure' ↑ FSH

FSH → remaining follicles –E2 more rapidly leading to shorter cycles

Then FSH fails to stimulate E2 production

'Decompensated failure' when follicle pool is very low

10-20 X FSH / 3 X LH / E2 levels drop

Other hormonal changes

Adrenal & ovarian androgens ↓ (testosterone & androstenedione)

Some T is still produced by theca cells

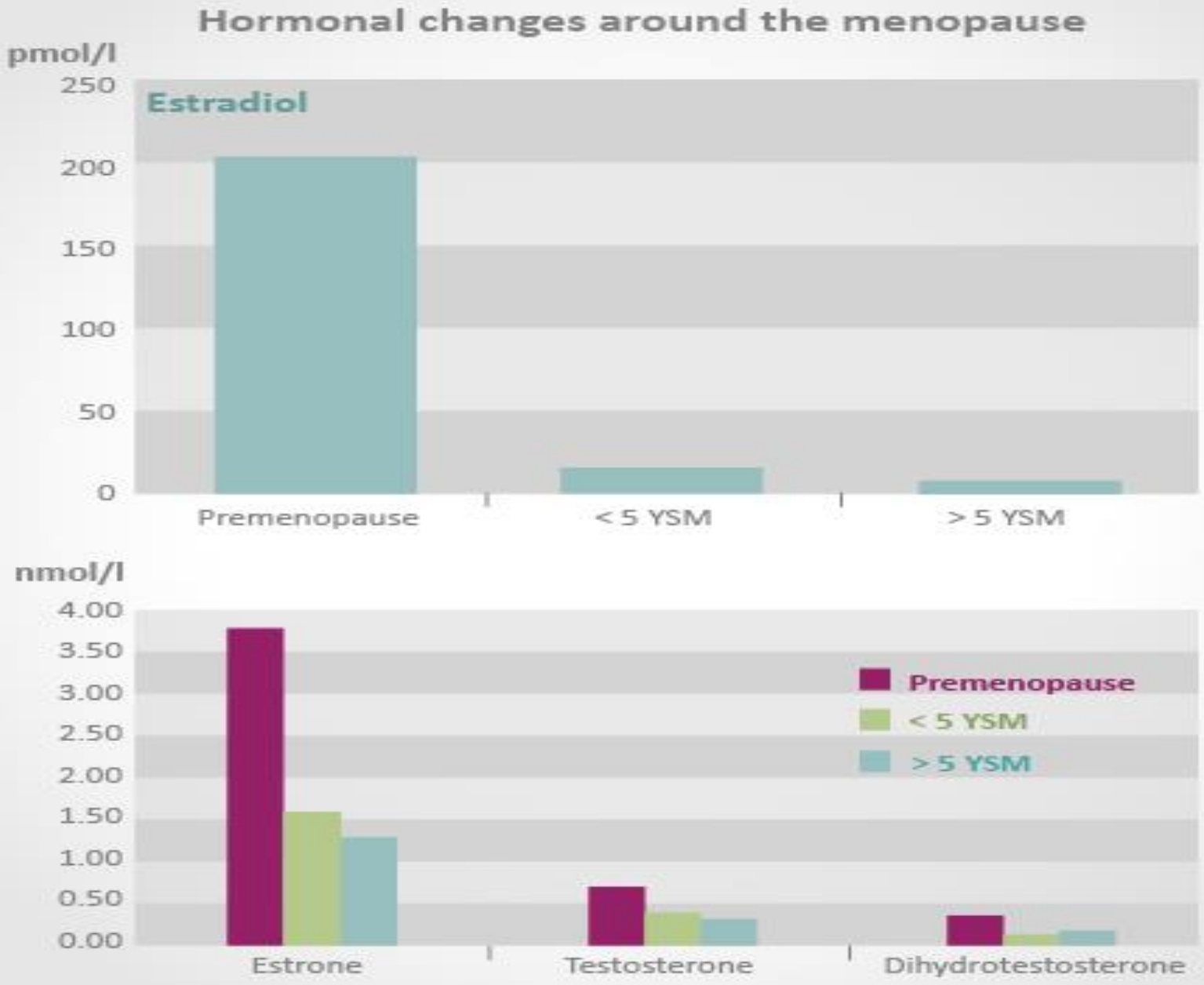
Androstenedione production mainly adrenals (1:4 ratio)

SHBG ↓ due to ↓ ovarian oestradiol

Postmenopausal estrogen is derived from ovarian stromal and adrenal secretion of androstenedione, which is aromatised to **estrone (E1)** in the peripheral tissues

E1 produced is related to body weight and age

Insulin resistance ↑ after the menopause ⟶ increase in central adiposity (android rather than gynaecoid shape) and a decreased lean body mass


Hormonal changes around the menopause
pmol/l
250
200
150
100
50
0
Estradiol
Premenopause
< 5 YSM
> 5 YSM
nmol/l
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
Premenopause
< 5 YSM
> 5 YSM
Estrone
Testosterone
Dihydrotestosterone

Organ changes

Ovaries shrink in size, wrinkled and white.

There is thinning of the cortex with increase in medullary components.

Fallopian tubes –atrophy/muscle coat becomes thinner, the cilia disappear

Uterus - smaller / body : cx reverts to the 1:1.

- endometrium -thin and atrophic

- cervical secretion - scanty

Vagina - narrower due to gradual loss of elasticity

-epithelium –thin, rugae progressively flatten

-No glycogen

-pH - alkaline

Vulva –atrophy

-flat labia / pubic hair becomes scantier

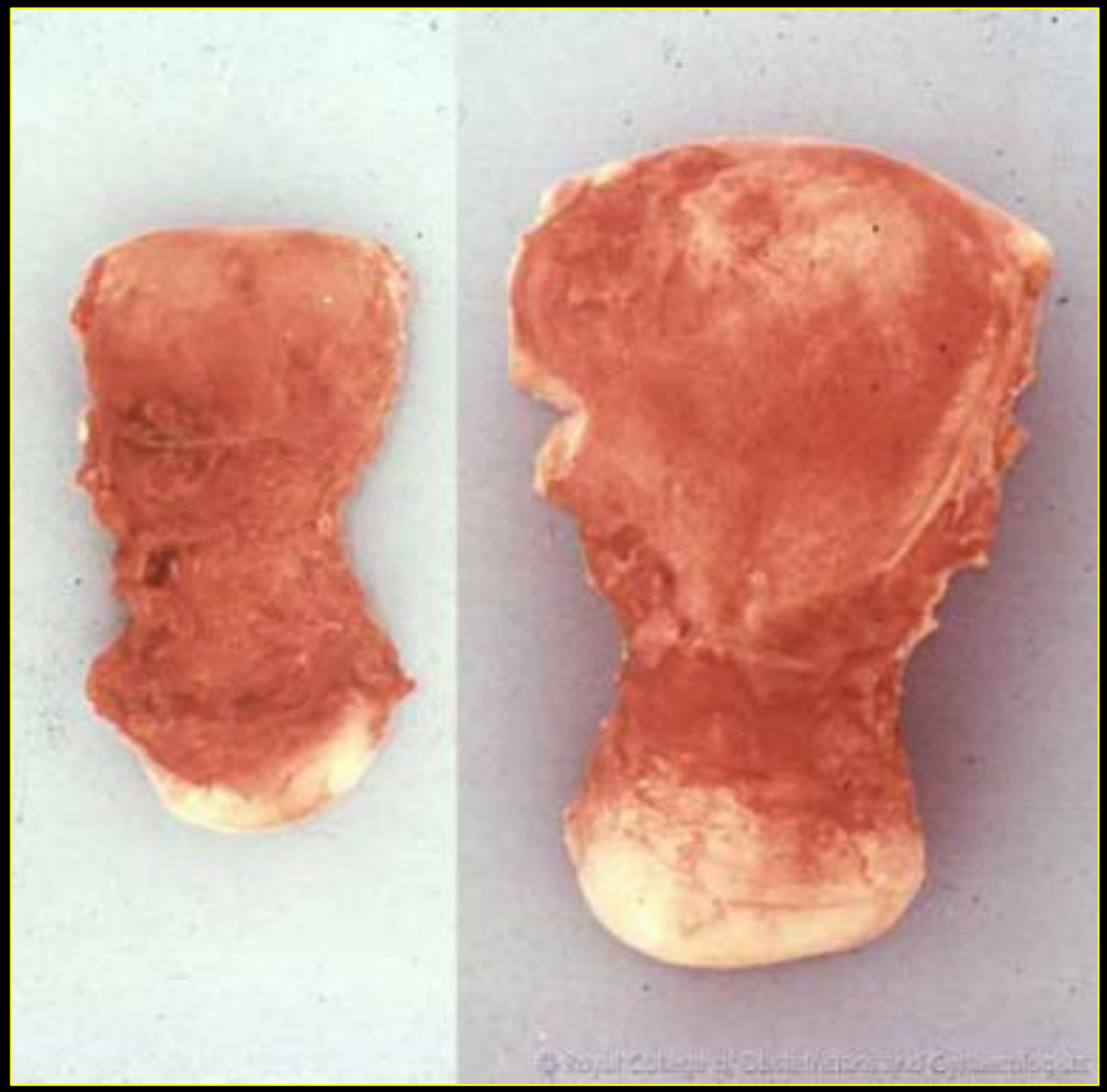
Breast fat is reabsorbed and the glands atrophy

nipples decrease in size

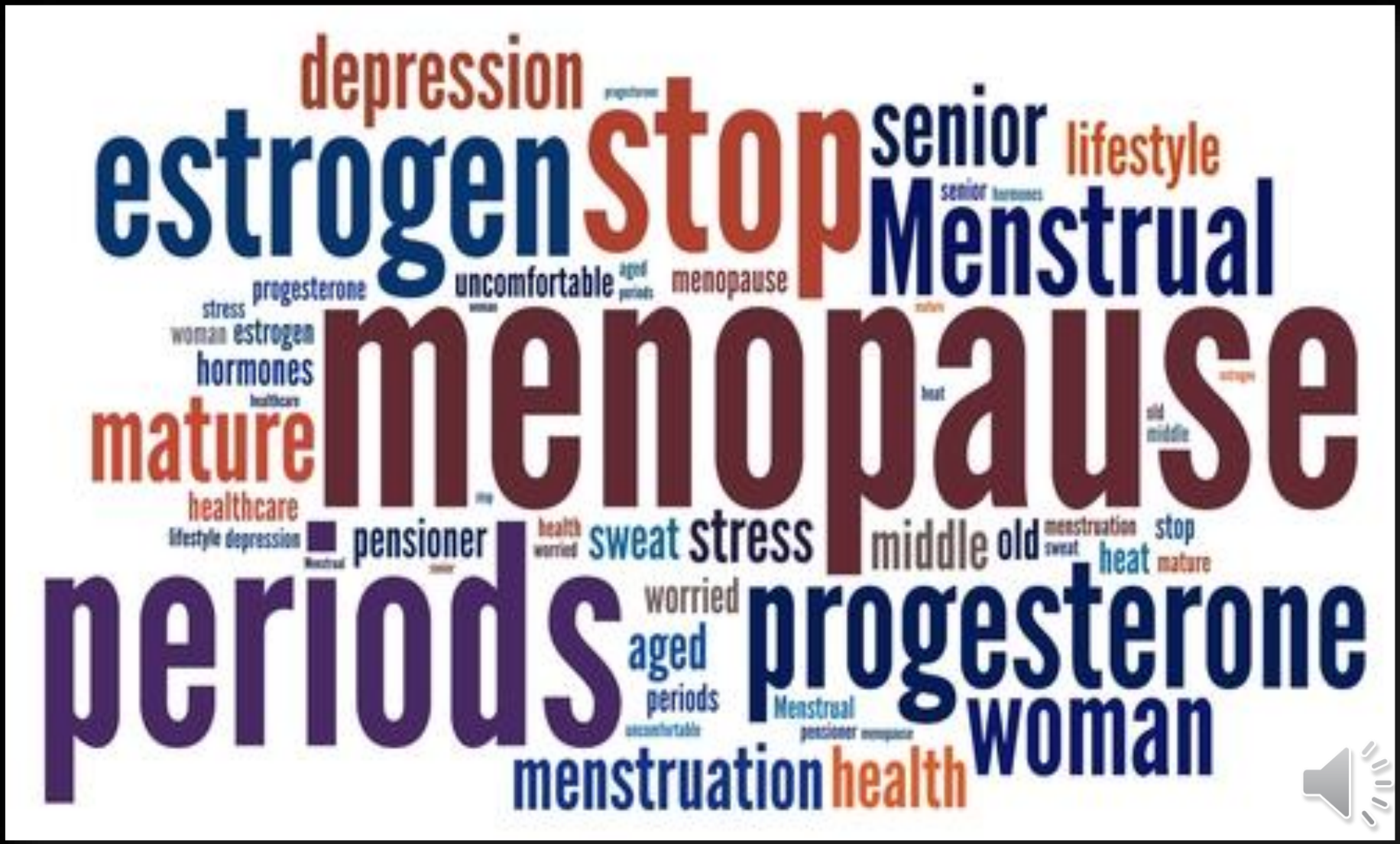
breasts become flat and pendulous

Bladder and urethra similar changes to those of the vagina

Loss of muscle tone leads to pelvic relaxation, prolapse



Signs and symptoms



Acute clinical manifestations

- Changes in menstrual pattern – cycle length longer or shorter by 2-3wks , amount of blood loss may alter and, most commonly, increases slightly
- Hot flushes & night sweats 70-80%

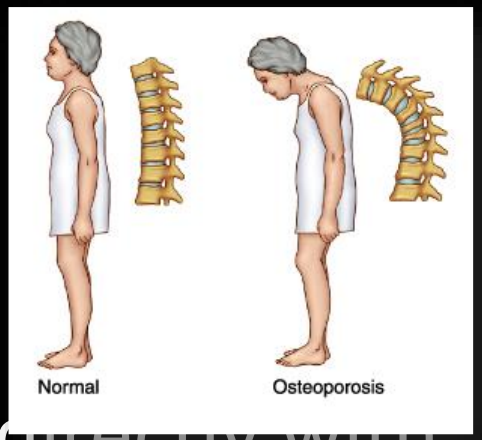
  self-limited 7 years

- Mood swings, panic attacks, depression, forgetfulness, and difficulty concentrating
- headaches

Medium term symptoms

- Vaginal dryness and dyspareunia
- Reduced libido- dyspareunia/ androgen deficiency
- Raised vaginal pH (above 4.5) enhances enterobacterial growth & contributes to recurrent UTI
- Atrophic urethritis, diminished urethral mucosal seal, loss of compliance & irritation; these changes predispose to both stress and urge urinary incontinence.
  - Thinning of skin/hair loss, brittle nails
  - Generalised aches and pains are associated with reduced estrogen levels.

Long term health implications



- **Osteoporosis**
- **Cardiovascular disease**
- **Stroke**
- **Dementia** –unclear if associated directly with a fall in estrogen levels.
- **Increase in bodyweight** with age
- **Body fat redistribution**

to the abdomen

independent risk factor for:

CVD, type II DM & breast cancer

As a direct consequence of loss of estrogen

- less able to conserve her collagen: bone, skin, nails, vagina, pelvic ligaments
- less able to maintain healthy endothelium: development of hypertension& atherosclerosis
- less able to synthesise neurotransmitters, particularly acetyl choline (cognition), serotonin & dopamine (low moods, irritability, insomnia), & sustains changes to adrenergic and noradrenergic transmission with development of panic attacks and palpitations.

Management of menopause

- Advise on a healthy lifestyle
- Psychological support

- Hormone replacement therapy HRT
- Alternatives to HRT

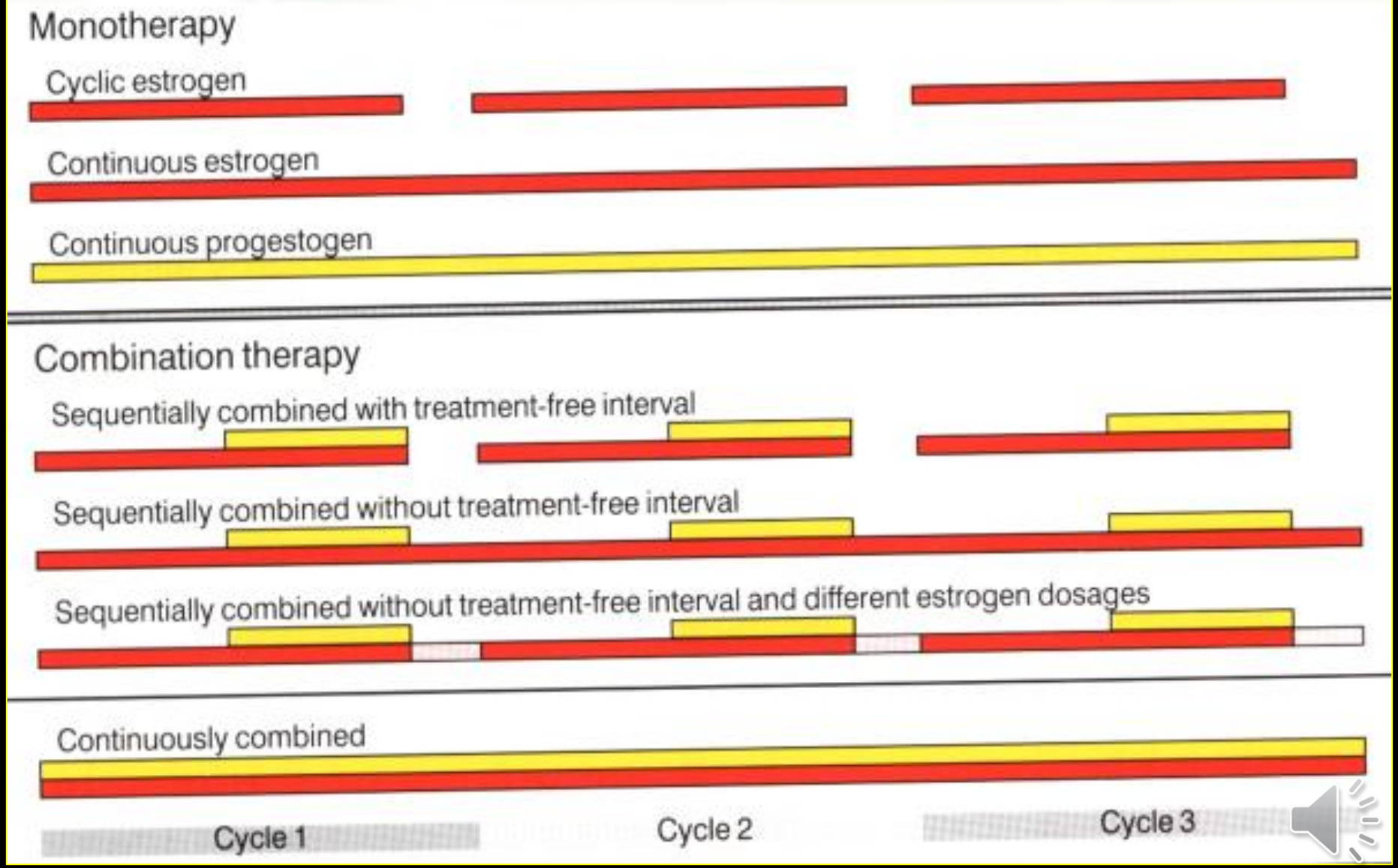
Special group of women to whom HRT should be prescribed:

- Premature ovarian failure
- Gonadal dysgenesis
- Surgical or radiation menopause

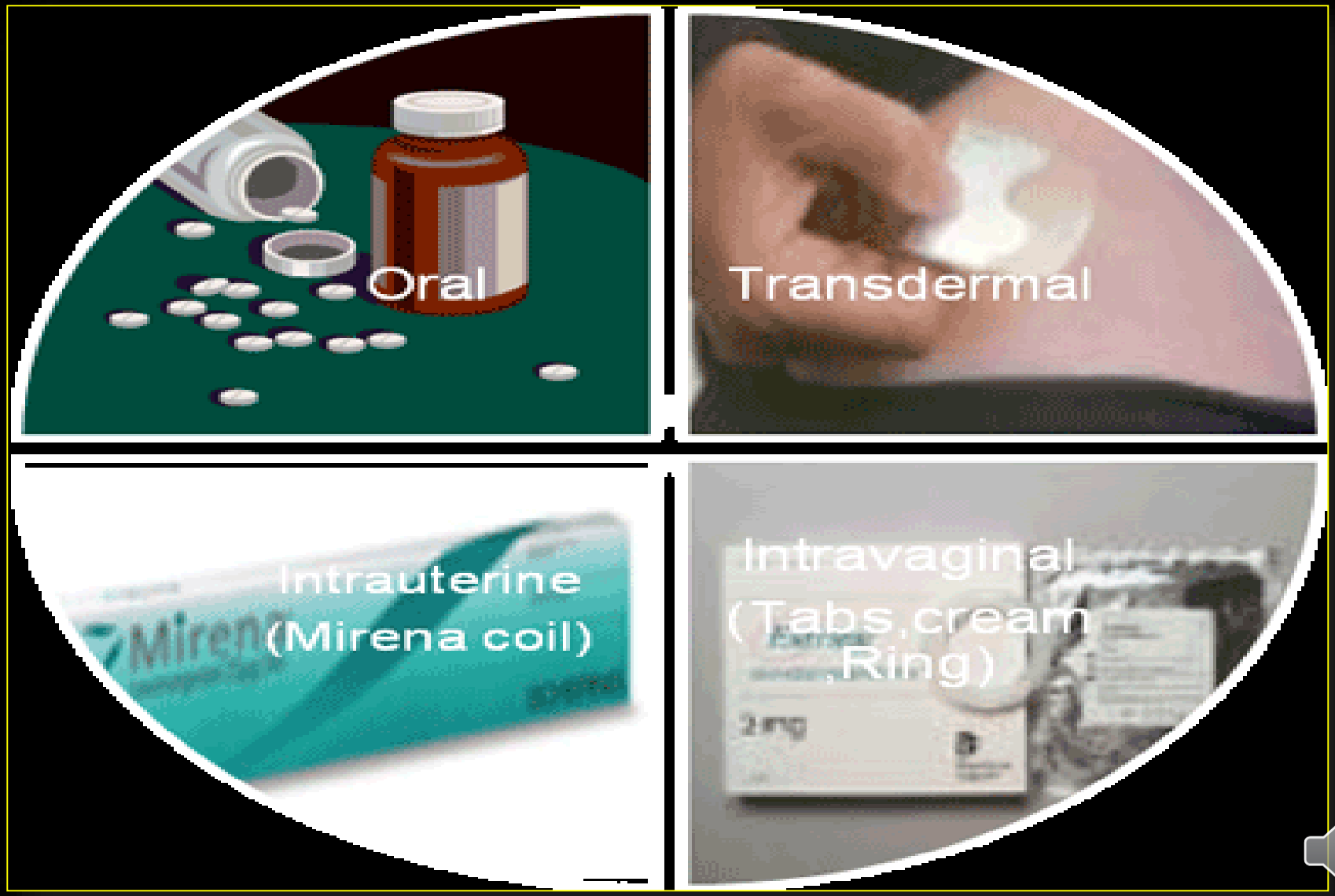
HRT-Types

- Oestrogen only
- Sequential combined regimens
- Continuous combined regimens
- Synthetic steroidal alternatives, e.g. Tibolone.
  - estrogenic, progestogenic & weak androgenic activity
  - converted in endometrium to a metabolite w/o estrogenic activity
  - bleed-free HRT
- Testosterone

HRT …


Monotherapy
Cyclic estrogen
Continuous estrogen
Continuous progestogen
Combination therapy
Sequentially combined with treatment-free interval
Sequentially combined without treatment-free interval
Sequentially combined without treatment-free interval and different estrogen dosages
Continuously combined
Cycle 1
Cycle 2
Cycle 3

HRT Routes


Oral
Transdermal
Intrauterine
(Mirena coil)
Intravaginal
(Tabs,cream
,Ring)

HRT-Routes

❖ Oral:

first choice/cost-effective/acceptable

beneficial effect on HDL-C, LDL-C, and total cholesterol

high doses required/variation in absorption

all tablets contain lactose

affects liver protein synthesis (increase in triglycerides).

❖ Transdermal (patch, gel) :

avoids gut and liver breakdown; so lower dose is required

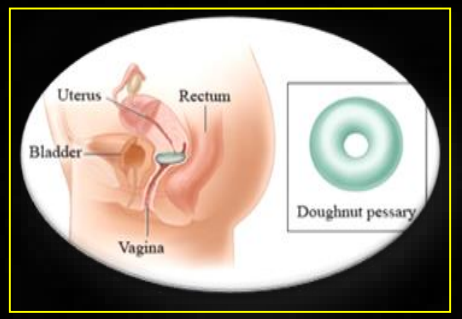
generally more expensive

avoids bolus first-pass effect on the liver (less adverse effect on gallbladder disease and coagulation factors)

produces more physiological hormone levels than oral therapy

patch adhesive sensitivity/residue.

HRT-Routes..



❖ **Intrauterine system (Mirena coil)**

2X risk of breast cancer when used with estrogens

It should not be used with history of breast cancer

❖ **Subcutaneous estradiol pellets**

❖ **Vaginal estrogen preparations**

- 2 types: vaginal tablets and vaginal cream
- Indicated for GUS: vaginal dryness, dyspareunia, urgency, recurrent cystitis.
- Endometrial protection is not required

Indications for non-oral route

- Patient preference
- Poor symptom control with oral treatment
- Side effects, e.g. nausea, with oral treatment
- History of migraine
- Risk of stroke, VTE (HRT only considered after full discussion and appropriate investigation)
- Hypertriglyceridaemia
- Current hepatic enzyme inducing agent
- History of gallstones
- Bowel disorder that may affect absorption of oral therapy
- Lactose sensitivity

Benefits of HRT

- ↓ Vasomotor symptoms
- Mood or sleep disturbances
- ↓ Urogenital symptoms and improved sexuality
- ↓ Risk of osteoporosis(↑ BMD 2–5% & ↓ vertebral & hip fracture (25–50%)
- ↓ Risk of colorectal cancer

Risks of HRT

The absolute increase in risks is small; the extra number of cases of each of the conditions associated with HRT is typically smaller than the health risks associated with smoking or being obese.

Breast cancer

- Combined HRT increases mammographic density
- Estrogen-only does not increase mammographic density.
- Tibolone seems to have a limited effect on breast density on mammography.

HRT is not a single class of hormones, Risk differs in these 3 different classes of regimens

Progestogen addition increases breast cancer risk compared with estrogen alone, but this has to be balanced against the reduction in risk of endometrial cancer associated with combined therapy.

Tibolone also increases the risk of breast cancer but to a lesser extent than with continuous combined HRT.

- Risk of breast cancer increases with duration of use.
- No increased risk of breast cancer in women who start HRT early for POI

Risks of HRT

- ↑ Risk of endometrial cancer with unopposed oestrogen
- ↑ Risk of VTE

  1st year/ E+P> E only

  No increase risk of VTE with non-oral estrogens
- ↑ Risk of gallbladder disease

  lower with transdermal

Uncertainties concerning HRT

- CHD
- Stroke
- Dementia and cognition
- Ovarian cancer
- Quality of life

Summary of the risks associated with HRT

The risks associated with HRT are summarised in the tables published by the NICE Guidelines NG23.

https://www.nice.org.uk/guidance/ng23

HRT Consultation

The decision to use HRT should be discussed with each woman on an individual basis, taking into consideration her history, risk factors and personal preferences.

Ideally, all perimenopausal women should be given the opportunity to discuss the menopause and the potential role of HRT, alternatives to HRT, and lifestyle changes.

RCOG Statement on HRT November 2004

- Continue to prescribe HRT for women with significant menopausal symptoms
- For women who are not symptomatic, the risks outweigh the benefits
- Women should have the final decision to take HRT provided they understand the risks
- For women with a premature menopause, HRT can be used until the normal age of menopause and then reviewed

International Menopause Society (IMS) recommendations (2011)

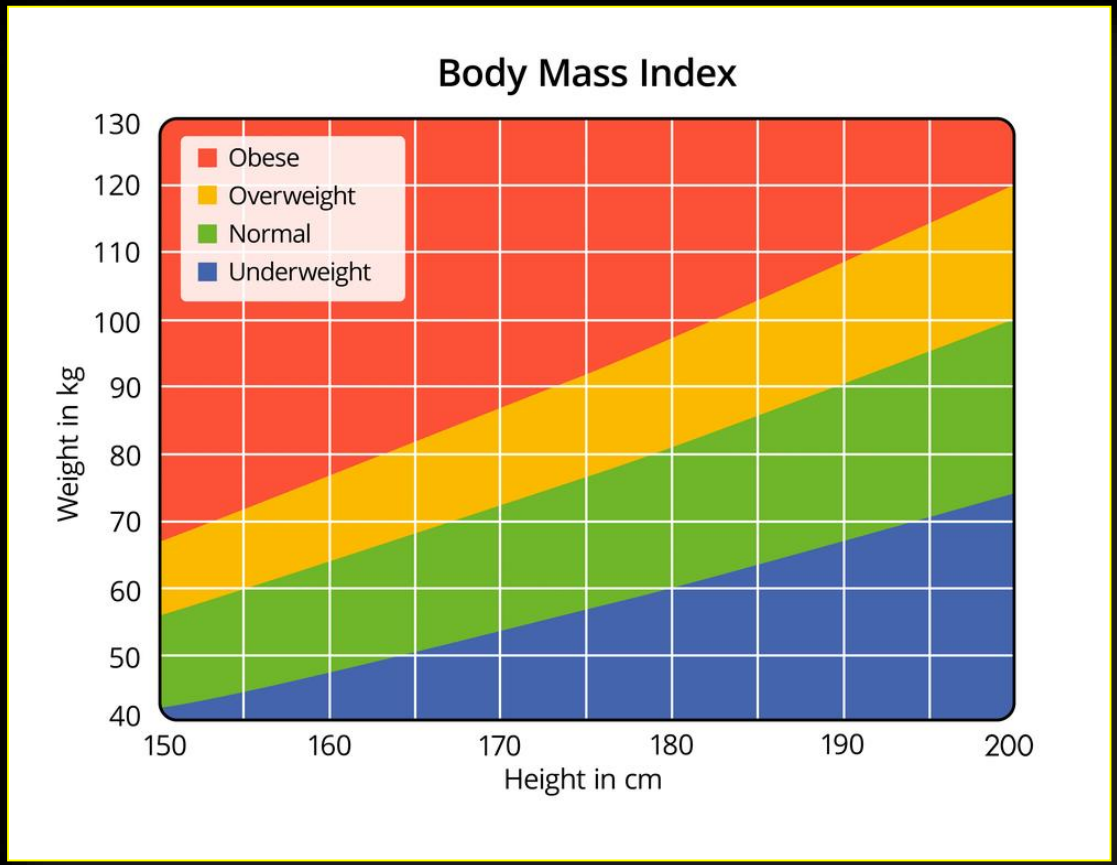
- HRT should be prescribed with a clear indication
- Women can have the option of HRT as long as they have a symptomatic benefit and are aware of the risks.
- The risks and benefits have to be clearly explained
- The lowest effective dose should be used.
- Healthy women <60yrs should be informed that HRT given for a clear indication has many benefits and few risks
- Women taking HRT should be assessed at least annually

Assessment prior to starting HRT

Assess menopausal state and symptoms	
Check for contraindications 	**Active liver disease & renal** **Breast cancer** **CVD, angina, MI, stroke, uncontrolled HTN** **Deep venous thrombosis (VTE)** **Endometrial cancer** **& Abnormal uterine bleeding**
Ask about family history of...	CVD,OP, VTE Breast, bowel & ovarian cancer
Check risk factors for CHD	DM, HTN, smoking, obesity, sedentary life style F. Hx of premature MI & stroke
Check risk factors for Osteoporosis	
What does the patient want?	
Discuss healthy lifestyle options	

Examination prior to starting HRT

- BMI
- BP



- Breast and pelvic examination if indicated by personal or family history

Investigation prior to starting HRT

No investigations are routinely indicated before starting HRT.

- Serial FSH levels if premature menopause is suspected
- Mammogram
- Endometrial sampling if indicated
- FSH > 30 IU/l

2 measurements 2wks-3months apart

- TSH,T4

Do not use FSH test to diagnose menopause in women using combined oestrogen and progestogen contraception or high-dose progestogen

Follow up

Recommended follow up schedule for HRT is:

3/12

6/12

Yearly – BP, breast examination, V/E

(3-yearly smears & 3-yearly mammography aged 50–64*)*

Earlier visit for any specific problems

Diagnosis of perimenopause and menopause

Diagnose the following without laboratory tests in otherwise healthy women aged over 45 years with menopausal symptoms:

- Perimenopause based on vasomotor symptoms and irregular periods
- Menopause in women who have not had a period for at least 12 months and are not using hormonal contraception
- Menopause based on symptoms in women without a uterus.

Diagnosing premature ovarian insufficiency

Take into account the woman's clinical history (previous medical or surgical treatment) and FH

Diagnose POI under 40 years based on:

- Menopausal symptoms

and

- Elevated FSH on 2 blood samples taken 4–6 weeks apart

Do not diagnose premature ovarian insufficiency on the basis of a single blood test.

Factors Influencing Prescription of HRT

- **Hysterectomy**

- **Patient's preferences**

  Oral

  Non-oral preparations

Side effects with HRT

Adverse effects account for almost 35% of HRT discontinuations.

Women should be encouraged to persist with HRT for at least 3 months, as most adverse effects resolve with increased duration of use.

Side effects of systemic HRT

- ***Oestrogen-related:*** fluid retention, bloating, breast tenderness or enlargement, nausea, headaches, leg cramps, and dyspepsia.

- ***Progestogen-related:*** fluid retention, breast tenderness, headaches/migraine, mood swings, depression, acne, lower abdominal pain, and backache.

- ***Combined HRT:*** irregular, breakthrough bleeding (may need investigation).

- ***All types of HRT:*** weight gain(not proved in RCT)


ALTERNATIVE
THERAPIES

Alternatives to HRT

Lifestyle modification: Diet, exercise, clothing, avoid triggers

Non-pharmacological

Gels for vaginal symptoms, such as Replens®

Pharmacological

- Progestogens
- Alpha-2 agonists-Clonidine
- SSRIs (fluoxetine and paroxetine) and SNRIs (venlafaxine)
- Gabapentin

Complementary therapies

Phytoestrogens

Isoflavones, soya products

Herbal remedies

Chaste tree, St.Jhon's wort

Other therapies include:

Acupuncture/Hypnotherapy/reflexology

Vitamins and minerals

Vitamins E & C

Selenium

Osteoporosis-Definition

Defined on the basis of bone mineral density (BMD), which is reported as a T-score. This is the number of standard deviations (SD) by which the individual's BMD differs from the BMD of an average 25-year-old woman.

	T-score
Normal	not less than –1 SD
Osteopenia	between –1 SD and –2.5 SD
Osteoporosis	–2.5 SD or less
Established osteoporosis	below –2.5 SD, with one or more associated fragility fractures

Osteoporosis

- Systemic skeletal disease
- Low bone mass
- Increased fragility
- Susceptibility to fracture
- one in three women
- 40% of women will suffer an osteoporotic fracture during their lifetime

Risk factors

General

- Age
- Sex
- BMI ≤19 kg/m^2
- Previous fragility fracture, particularly of the hip, wrist and spine
- Parental history of hip fracture
- Current steroid treatment (any dose, by mouth for three months or more)

Lifestyle factors:

- Current smoking
- Alcohol intake of ≥3
- Sedentary life

Risk factors..

Secondary causes of osteoporosis

Estrogen deficiency:

Untreated POI

Medical conditions:

rheumatoid arthritis
type I diabetes
hyperthyroidism
malabsorption syndromes
chronic liver disease
chronic obstructive pulmonary disease
organ transplantation.

Management of osteoperosis

- There is insufficient evidence to recommend screening of the whole of the postmenopausal population
- Management is based on risk factor assessment
- BMD measurement offered selectively in high risk individuals

Osteoporosis: Rx

Lifestyle advice

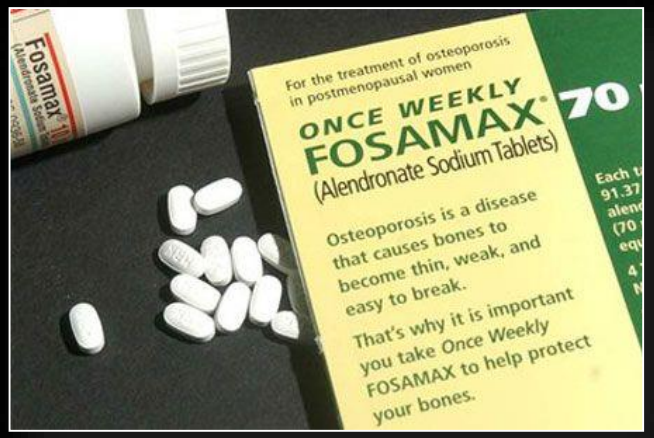
- Smoking
- Alcohol
- Preventing falls
- Hip protectors

Exercise-weight bearing

Diet

Treatment for Osteoporosis

- HRT
- Bisphosphantes
  - Etidronate (Didronel)
  - Alendronate (Fosamax)
  - Risedronate (Actonel)
- SERM's – Raloxifene (Evista)
- Calcium and vit D
- Calcitonin
- strontium (Protelos)



POI

- HRT is strongly recommended **till age of menopause**
  - control vasomotor symptoms
  - maintain sexual function
  - minimise risk of cardiovascular disease osteoporosis, and possibly Alzheimers'
- Aim is to replace hormones as close to physiological levels
- OCP can be used to control symptoms but no long term data on the protection against OP & CVD


Thank
you!