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THE MENOPAUSE

Learning objectives

- Know the definition of menopause.
- Understand physiological and non-physiological menopause.
- Understand the effect of menopause on women.
- Understand the modifiable and non-modifiable aspects of menopausal health.
- Explain the main forms of treatment of the menopause.
- Know the side-effects and the relative and absolute contraindications of hormonal replacement therapy (HRT).

Definition

Climacteric: Period of life in which female is changed from reproductive to non reproductive states.

Menopause: Permanent cessation of menstruation for > 12 months due to complete depletion of all primordial follicles from ovaries (ovaries become insensitive to pituitary gonadotropins).

Premenopause: 40-45 years.

Perimenopause: 45-55 years (5 years before & 5 years after the average age of menopause).

Postmenopause: Period which begins one year after last period.

PHASES OF MENOPAUSE

Menopause

Premenopause

Postmenopause

Perimenopause



Type of Menopause

A) Natural menopause: Its range of age is 45-55 years è average of 51 years (age of menopause isn't affected by SES, racial factors or body weight & height).

B) Premature menopause : Premature ovarian insufficiency (POI); Before 40 years.

C) Delayed menopause: After 55 years.

D) Artificial (induced) menopause:

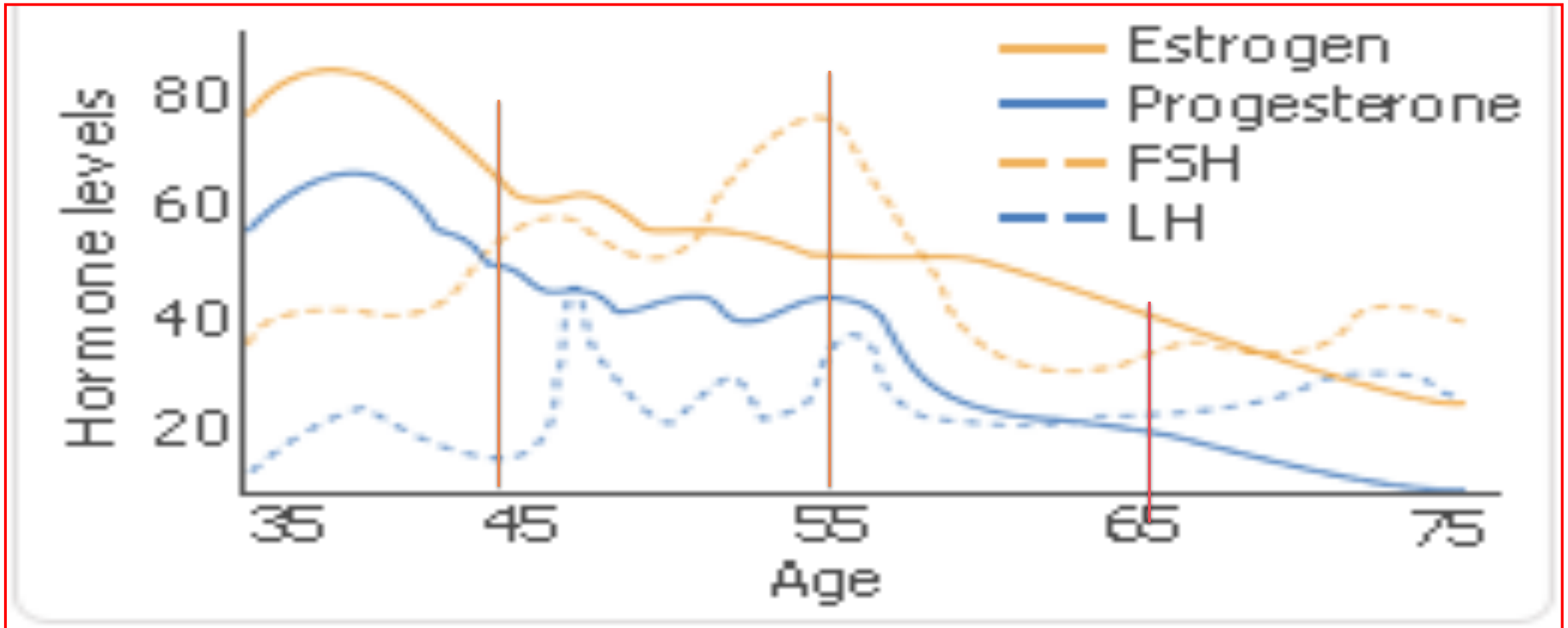
- 1) Bilateral oophorectomy (surgical menopause).
- 2) Postirradiation (radiological menopause).
- 3) Administration of chemotherapy.
- 4) Continuous administration of GnRH agonists (medical oophorectomy).

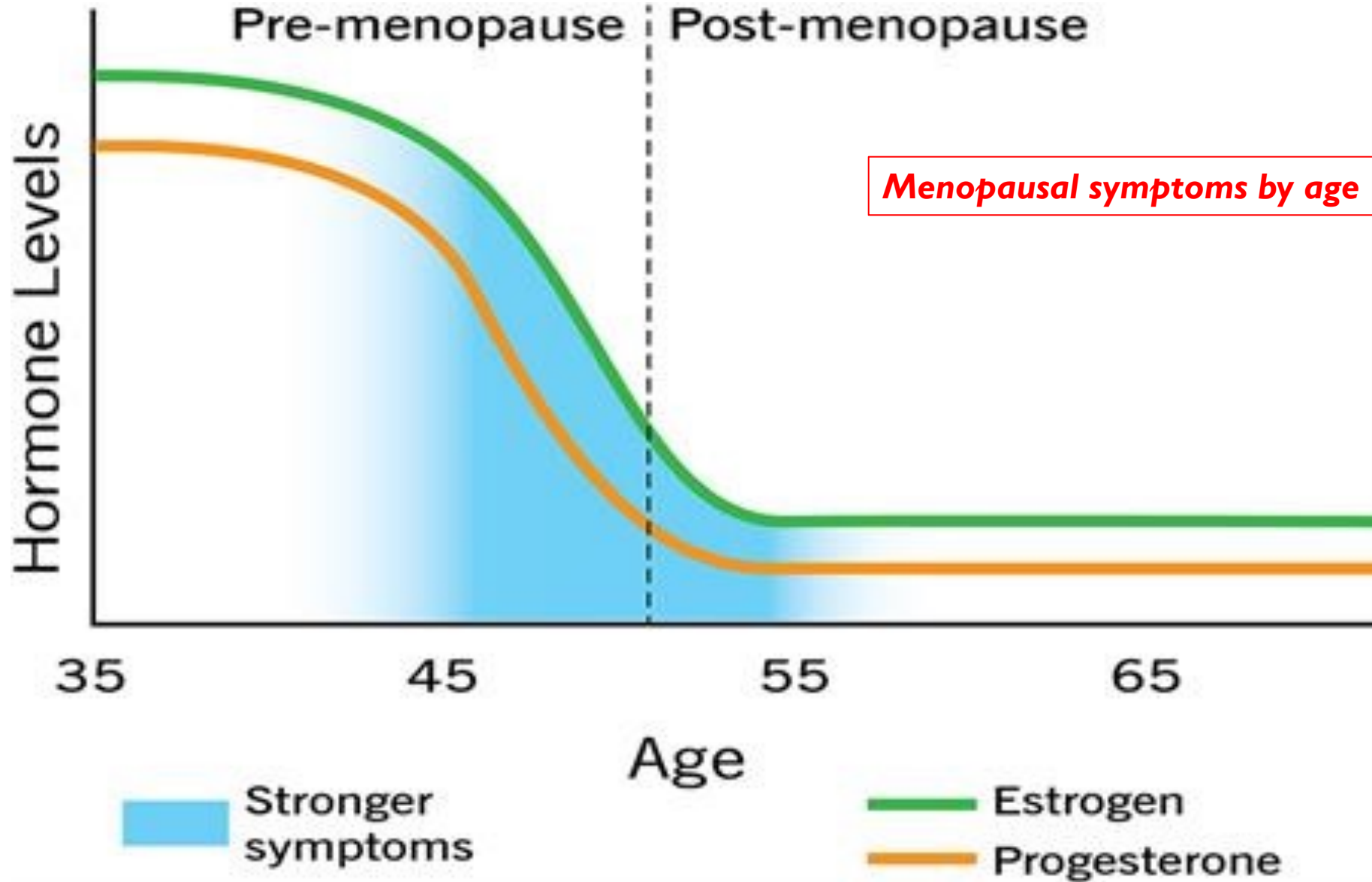
Principal causes of premature ovarian insufficiency

PRIMARY	<ul style="list-style-type: none">- <u>Chromosome anomalies</u> (Turner's synd., Fragile X synd)- <u>Autoimmune disease</u> (hypothyroidism, Adisson's , myasthenia gravis)- <u>Enzyme deficiencies</u> (galactosemia, 17 α hydroxylase deficiency)
SECONDARY	<ul style="list-style-type: none">- Chemotherapy, radiotherapy- Infections (tuberculosis, mumps, malaria, varicella)

OWarda

Hormonal changes by age





Normal changes at menopause

A) Hormonal changes:

- 1) **FSH:** ↑↑ 13 folds (> 40 mIU/ml).
- 2) **LH:** ↑↑ 3 folds **with** ↓↓ LH/FSH ratio.
- 3) **Estrogen:** ↓↓ & the main type is E₁ **with** ↓↓ E₂/E₁ ratio.
- 4) **Progesterone:** ↓↓ markedly (no ovarian progesterone).
- 5) **Androgens:** Relatively ↑↑.

Different reproductive hormones in menopause

Hormones	Perimenopause	Early postmenopause	Late postmenopause and elderly
GnRH	Increased pulsatility	Progressive decrease in pulsatility	Reduction in overall levels
LH & FSH	Increased	Increased	Progressive decline
Oestrogen	Slight declines	Rapid decline in levels	Sustained very low levels
Progesterone	Moderate falls	Unpredictable	Undetectable
Inhibin	Slight decline	Significant decline	Undetectable
Testosterone	Progressive decline	Progressive decline	Sustained low levels

FSH, follicle-stimulating hormone; GnRH, gonadotrophin-releasing hormone; LH, luteinizing hormone.

Normal changes at menopause

B) Genitourinary (local) changes:

- 1) **Vulva:** Becomes atrophic with gaping of introitus.
- 2) **Vagina:** Becomes atrophic & narrow (no glycogen deposition) è thin mucosa & loss of rugae & ↓↓ vaginal acidity.
- 3) **Cervix:** Becomes small, atrophic & flushed with vagina.
- 4) **Uterus:** Becomes small & atrophic with atrophic endometrium.
- 5) **Ovaries:** Shrink & become small & atrophic.
- 6) **Urinary tract:** Epithelial atrophy with ↑↑ susceptibility to UTI.
- 7) **Pelvic floor & ligaments:** Become weak with tendency to prolapse & stress incontinence.

Normal changes at menopause

C) General changes:

- 1) **Psychological:** Anxiety & depression.
- 2) **Vasomotor instability:** VD after VC leading to hot flushes.
- 3) **Breast:** Shrinks & becomes atrophic & flat.
- 4) **Bones:** Osteoporosis due to ↓↓ osteoblastic activity (leading to ↓↓ bone formation) & ↑↑ osteoclastic activity (leading to ↑↑ bone resorption).
- 5) **Hair:** Weakness & grayness.
- 6) **Skin:** Wrinkling.
- 7) **Lipoprotein metabolism:** ↓↓ HDL & ↑↑ LDL → ↑↑ incidence of atherosclerosis & cardiovascular diseases.

Menopausal syndrome:

Definition: Exaggerated normal physiological changes at menopause to become symptomatizing.

Incidence: About 50% of women don't develop these symptoms.

Onset: May occur before, during or after cessation of menstruation.

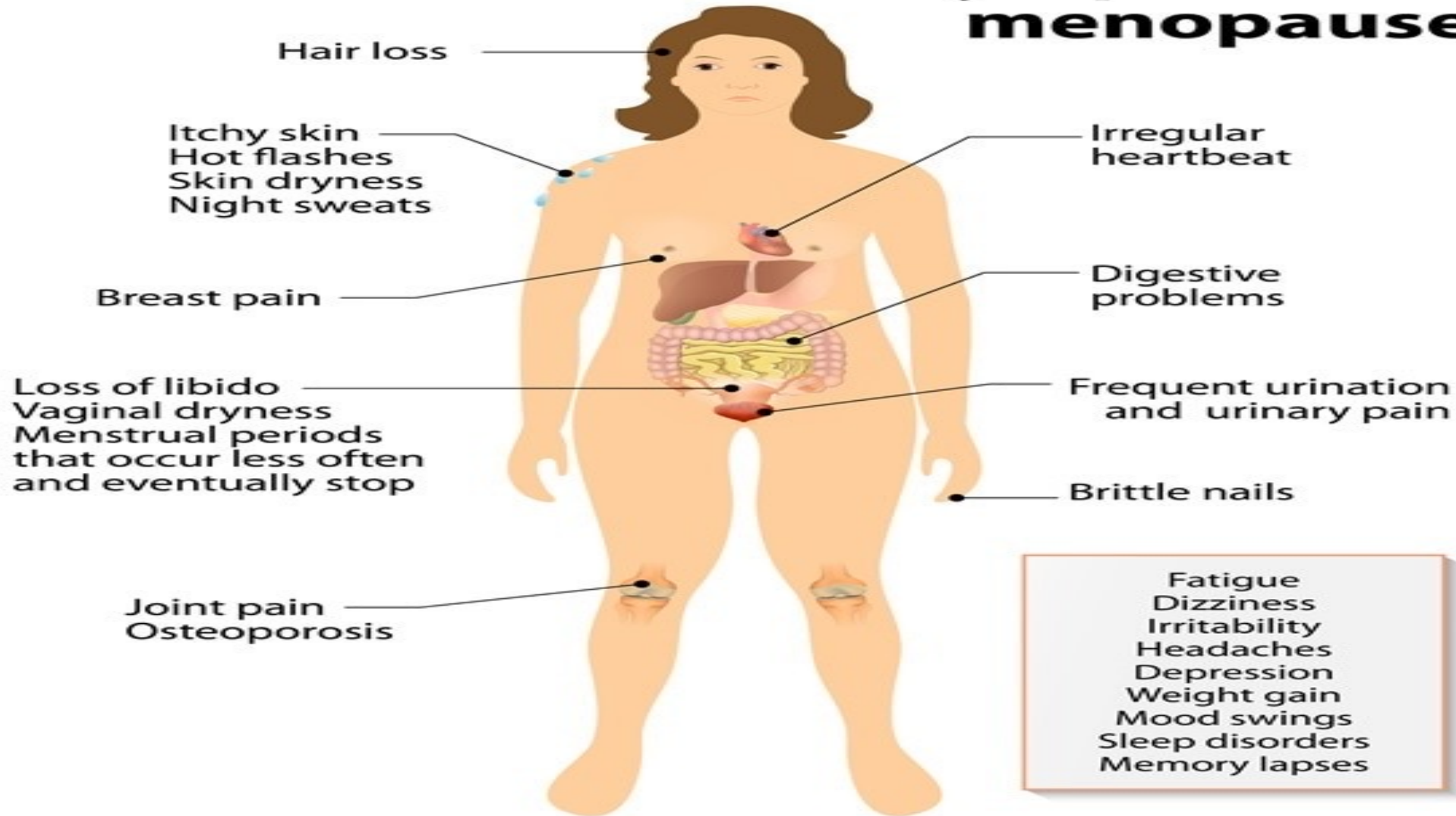
Duration & severity: Vary in different women.

Pathogenesis: Related to estrogen deficiency.

Symptoms of menopause

- 1) **Nervous & psychological:** Headache, lack of concentration, memory changes, anxiety, irritability, insomnia, dizziness, depression & sense of end of life.
- 2) **Hot flushes:** Most characteristic symptom:. Occurs in form of waves of heat over chest, neck & face followed by profuse sweating. Usually lasts for few seconds but can last up to 30 minutes. May occur at night disturbing sleeping.
- 3) **Cardiovascular:** Palpitation.
- 4) **Gastrointestinal:** ↓↓ appetite, dyspepsia, distension & constipation.
- 5) **Urinary:** Frequency of micturition, dysuria or stress incontinence.
- 6) **Genital:** Dyspareunia & genital displacement.
- 7) **Hirsutism.**

Symptoms of menopause



Effects of the menopause by time of onset

Immediate (0–5 years)	<ul style="list-style-type: none">Vasomotor symptoms, (e.g. hot flushes, night sweats)Psychological symptoms (e.g. labile mood, anxiety, tearfulness)Loss of concentration, poor memoryJoint aches and painsDry and itchy skinHair changesDecreased sexual desire
Intermediate (3–10 years)	<ul style="list-style-type: none">Vaginal dryness, sorenessDyspareuniaUrgency of urineRecurrent urinary tract infectionsUrogenital prolapse
Long term (>10 years)	<ul style="list-style-type: none">OsteoporosisCardiovascular diseaseDementia

Health hazards related to menopause

A) Osteoporosis:

Definition: Low bone mass & microarchitectural deterioration of skeleton leading to ↑↑ bone fragility & ↑↑ risk of fractures.

Incidence: By 60 years, 25% of women develop spinal compression & fractures.

Risk factors:

- 1) Early menopause.
- 2) Sedentary life.
- 3) ↓↓ weight for height.
- 4) White race.
- 5) ↑↑ proteins & ↓↓ Ca⁺⁺ intake.
- 6) ↑↑ coffee intake.
- 7) Smoking & alcohol intake.
- 8) Drugs: Heparin & corticosteroids.

Health hazards related to menopause

A) Osteoporosis: / Diagnosis:

1) Clinical presentation: Osteoporosis is clinically **silent** until fractures occur (commonest fracture sites are **vertebrae, femoral neck, distal radius & calcanium**). Patients may present with complaints of loss of height, bony pain or kyphosis.

2) Investigations:

- a) Bone densitometry: $\downarrow\downarrow$ bone mineral density (BMD) by ≥ 2.5 standard deviations (SDs) below young adult mean value.
- b) Biochemical markers of bone turnover.

Signs & Symptoms of Osteoporosis

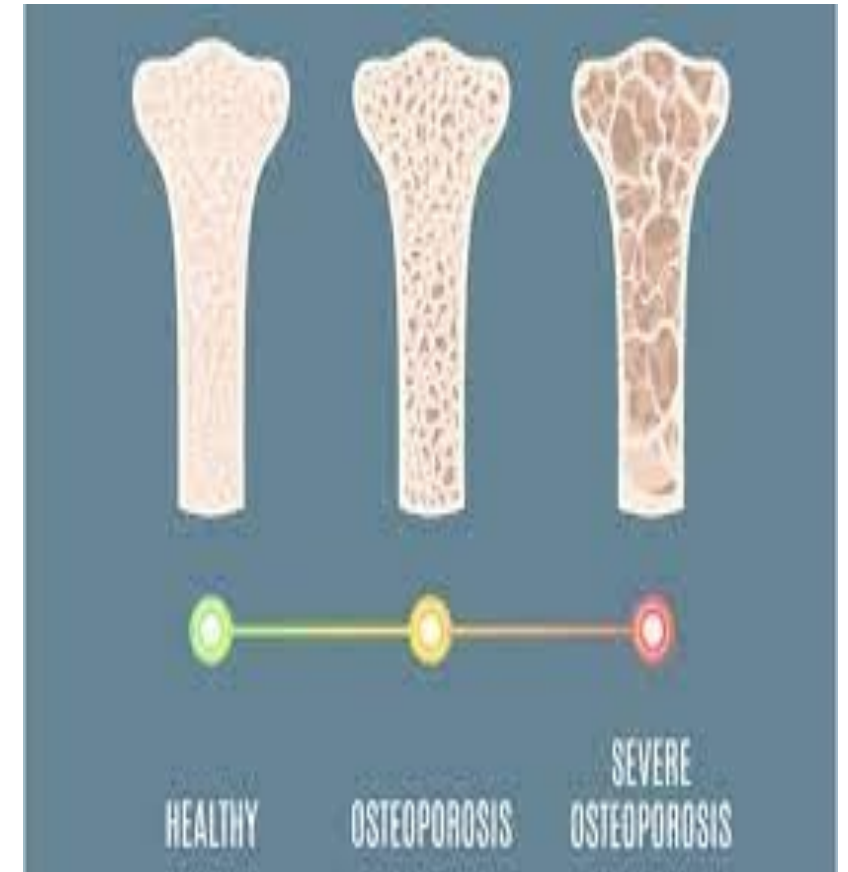
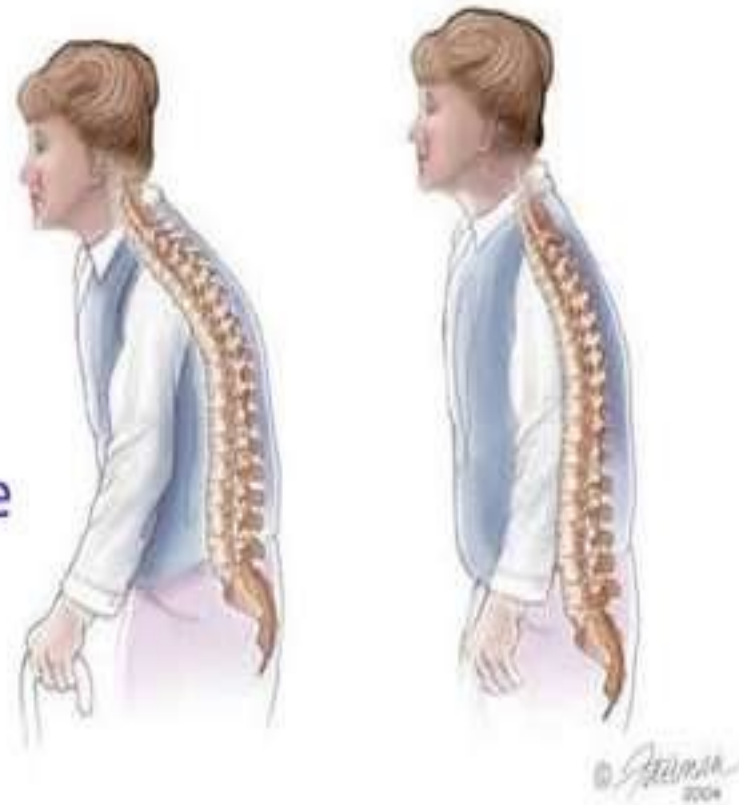
Bone pain or tenderness

Fractures with little or no trauma

Loss of height over time

Neck or lower back pain due to fractures

Stooped posture



Risk factors for osteoporosis

- Family history of osteoporosis or hip fracture.
- Smoking.
- Alcoholism.
- Long-term steroid use.
- POI and hypogonadism.
- Medical treatment of gynaecological conditions with induced menopause.
- Disorders of thyroid and parathyroid metabolism.
- Immobility.
- Disorders of gut absorption, malnutrition, liver disease.

Health hazards related to menopause

A) Osteoporosis: / Prevention & treatment :

- 1) ↓↓ coffee intake & stopping smoking & alcohol intake.
- 2) Regular exercise.
- 3) Ca⁺⁺ & vitamin D supplementation.
- 4) ERT.
- 5) Bisphosphonates (**the gold standard therapy**).

B) Cardiovascular diseases:

After menopause there is increased incidence of hypertension & coronary heart disease .

Diagnosis of menopause

A) Menopausal symptoms. (see before)

B) FSH & LH assay: Persistent high level of FSH (> 40 mIU/ml) is diagnostic of menopause.

Management of menopause

A) Assessment of woman: By history taking & routine general, abdominal & pelvic examination particularly blood pressure, breast & genitalia.

B) Non hormonal treatment:

- 1) General lines:** a) Reassurance & explanation (menopause is change of life & not the end of life).
b) Good diet & high tonics. c) Regular exercise.

2) Sedatives & tranquilizers.

3) Psychotherapy.

4) Vitamins & minerals supplementations (specially Ca^{++} & vitamin D supplementation for high risk groups to develop osteoporosis).

5) β -blockers (to control hot flushes). **6) Prevention** & treatment of osteoporosis & cardiovascular diseases.

Beneficial effects of various lifestyle changes in postmenopausal women

Stopping smoking

Prevention of lung cancer
Reduction of CVD
Beneficial effects on bone loss

Reducing alcohol consumption

Reduction of calorie intake
Fewer, less severe vasomotor symptoms
Beneficial effects on bone loss
Prevention of alcohol-related liver damage
Reduction in incidence of breast cancer
Reduction of CVD

Management of menopause

C) Estrogen replacement therapy (ERT):

Benefits:

- 1) Relieves menopausal symptoms.
- 2) Prevents urogenital atrophy.
- 3) Prevents osteoporosis.
- 4) ↓↓ risk of developing cancer colon.
- 5) ↓↓ risk of developing Alzheimer.

Indications:

- 1) Proved psychological factor.
- 2) Hot flushes.
- 3) Symptomizing genital atrophy.
- 4) Risky cases for IHD.
- 5) Risky cases for osteoporosis.
- 6) Premature & induced menopause.

Management of menopause

C) Estrogen replacement therapy (ERT):

CONTRAINDICATIONS FOR ERT

Absolute	Relative
<ol style="list-style-type: none">1) Unexplained AUB.2) Endometrial carcinoma (family or present history).3) Cancer breast (past, family or present history).4) Active liver disease.5) IHD.6) Thromboembolic disorders.	<ol style="list-style-type: none">1) Fibroid.2) Endometriosis.3) Migraine.

Management of menopause

C) Estrogen replacement therapy (ERT):

Regimens:

1) Estrogen alone: Used only in hysterectomized women.

2) Estrogen + cyclic progesterone:

The most **commonly** used regimen in women with intact uterus.

3) Estrogen + continuous progesterone.

Routes of administration:

1. Oral: More effective but with more side effects.

2. Injection: Combined estrogen & progesterone.

3. Percutaneous: Transdermal patches, subdermal implants & skin gel or lotion.

4. Vaginal: Cream, rings or tablets.

5. Intranasal spray.

Hormones used in HRT

- Oestrogens:
 - oestradiol (the main physiological oestrogen);
 - oestrone sulphate;
 - oestriol;
 - conjugated equine oestrogen.
- Progestogens:
 - norethisterone;
 - levonorgestrel;
 - dydrogesterone;
 - medroxyprogesterone acetate;
 - drospirenone;
 - micronized progesterone.

Management of menopause

C) Estrogen replacement therapy (ERT):

Complications (risks):

- 1) AUB.
- 2) Carcinogenicity (↑↑ incidence of endometrial carcinoma & cancer breast).
- 3) ↑↑ risk of thromboembolic diseases.
- 4) Defective liver metabolism & ↑↑ incidence of gallbladder diseases.
- 5) Altered lipid profile (↑↑ triglyceride levels).
- 6) Other effects: Nausea, vomiting, headache, dizziness, mood changes, weight gain & breast tenderness.

Management of menopause

C) Estrogen replacement therapy (ERT):

How to reduce the risk of ERT?

- 1) Give the smallest dose of estrogen that minimizes symptoms.
- 2) Add cyclic progesterone.
- 3) Avoid long term use of estrogen.
- 4) Use alternatives: Selective estrogen receptor modulators (SERMs), Tibolone or Phytoestrogen.

Follow up:

- 1) Periodic mammography.
- 2) Pap smear yearly
- 3) Bone densitometry.
- 4) Endometrial assessment (by ultrasound &/or biopsy) in AUB.

Non-hormonal treatments for vasomotor symptoms

Alpha-adrenergic agonists

Clonidine

Beta-blockers

Propranolol

Modulators of central neurotransmission

Venlafaxine

Fluoxetine

Paroxetine

Citalopram

Gabapentin

Thank you

