

Menopause

Learning Objectives:

By the end of this lecture, you need to:

- Define menopause.
- Describe physiological and non-physiological menopause.
- Understand the menopause consequences on women.
- Determine the modifiable and non-modifiable aspects of menopausal health.
- Analyze the treatment options for menopause.

Definitions:

A- **Menopause:** It is defined as the woman's final menstrual period and the accepted confirmation of this is made retrospectively after 1 year of amenorrhoea. The cause of the menopause is cessation of regular ovarian function.

B- **Perimenopause:** Time of life from the onset of ovarian dysfunction until one year after the last period and the diagnosis of menopause is made. This time is also known as the climacteric.

C- **Postmenopause:** All women who have been one year since their last period.

Physiology:

Timing of the menopause:

The average age of the menopause remaining at a median age of between 51 and 52 years, with 95% of women attaining menopause between the age of 45 and 55 years. Apart from premature ovarian failure that may occur early. Since life expectancy is increase, so a woman with menopause now expect to live 30 or 40 years of her age with a state of relatively profound estrogen deficiency.

Endocrine changes:

Ovarian follicles:

- Current understanding is that menopause occurs at the time of the depletion of oocytes from the ovary and is irreversible.
- Though current researches findings of oogonial stem cells from primordial follicles in the ovary. This might radically affect our understanding of the menopause and offer the remote possibility of being able to influence the timing of menopause.

Hormonal status:

- Reproductive function is maintained at younger age by hormonal interaction of the hypothalamic production of gonadotrophin-releasing hormone (GnRH), the pituitary hormones luteinizing hormone (LH) and follicle-stimulating hormone (FSH), the ovarian peptide hormone inhibin B and the steroid hormones oestrogen, progesterone and testosterone.
- These hormones not only change during the menstrual cycle but also throughout a woman's reproductive life, with their production changing at differing times and rates according to the age of the woman (Table 1).

Table 1: Female hormone production and changes around the menopausal years

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.

- **Inhibin B** is produced by follicles within the ovary, so as the number of follicles decline the production of inhibin decreases. In the perimenopausal years small declines in inhibin drive an overall increase in the pulsatility of GnRH secretion and overall serum FSH and LH levels, which results in an increased drive to the remaining follicles in an attempt to maintain follicle production and oestrogen levels.
- Androgenic hormone production comes from ovaries, peripheral adipose tissue and the adrenal glands, with the ovaries producing approximately 30–50% of total circulating levels.
- **Menstruation:**
 - May stop abruptly.
 - Or may cease after a prolonged stage of infrequent cycle.

Types of menopause:

- **Physiological menopause:** That discussed above.
- **Non physiological menopause:**
- **Premature ovarian insufficiency (POI), or called premature ovarian failure (POF), or premature menopause:**
It occurs in approximately 1% of women under 40 years and 0.1% under 30 years. It is a distressing diagnosis for a woman, especially if it occurs prior to the completion of her family. For young women who wish to conceive, gamete donation is the only option. POI is usually diagnosed following either primary or secondary amenorrhoea. While no cause is found in most cases of primary POI, otherwise the important causes are shown in table 2:

Table 2: Principal causes of premature ovarian insufficiency

Primary	Chromosome anomalies (e.g. Turner's, fragile X) Autoimmune disease (e.g. hypothyroidism, Addison's, myasthenia gravis) Enzyme deficiencies (e.g. galactosaemia, 17 α -hydroxylase deficiency)
Secondary	Chemotherapy or radiotherapy Infections (e.g. tuberculosis, mumps, malaria, varicella)

- **Iatrogenic menopause – medical treatments and menopause after cancer treatment:**

Non-surgical treatments could result in an iatrogenic temporary or permanent menopause:

- 1- Using **GnRH** is given in a constant high dose, it desensitizes the GnRH receptor and reduces LH and FSH release. Drugs that are GnRH agonists (e.g. buserelin and goserelin) can be used as treatments for endometriosis and other gynaecological problems. Although they mimic the GnRH hormone, when administered continuously they will down-regulate the pituitary and consequently decrease LH and FSH secretion. This will induce a temporary menopause with a relatively rapid onset, which can be managed with the introduction of hormone therapies and other drugs to relieve some of the unwanted menopausal symptoms – known as add-back therapy.

Such women, especially those under the age of 40 years, must be carefully counselled as and then managed as someone with POI.

- **Iatrogenic menopause – surgical menopause:**

Some time bilateral salpingo-oophorectomy (BSO) may be used to treat:

- 1- Benign gynaecological conditions such as menstrual disorders, fibroids and endometriosis.
- 2- Prophylactic for women at high risk of inherited malignancies such as breast and ovarian cancer, with BRCA 1 and 2 gene mutation screening.
- 2- Treatment for genital tract malignancy at early age. Modern screening programmes, technologies to achieve early diagnoses in suspected malignancy and early radical treatment of female reproductive tract malignancy have contributed to this.

The sequences of menopause on woman health:

The hormonal changes during and after the menopause have radical changes on the woman. The timing of when each system is affected not only varies dramatically between women, but also the degree of how the changes influence each woman is remarkably unpredictable. The reasons for these variations are not clearly understood but there is some evidence that genetic influences play a part. These changes categorized as early, medium or long term.

Obesity increases the risk of CVD and type 2 diabetes, but it is less well known if obesity in the postmenopausal woman increases the risk of hot flushes, breast cancer and endometrial cancer. In addition, as the woman gets older obesity increases the risk of falls, fractures and stroke, all of which attract a high mortality rate.

Table 3: Effects of the menopause by time of onset

Immediate (0–5 years)	Vasomotor symptoms, (e.g. hot flushes, night sweats) Psychological symptoms (e.g. labile mood, anxiety, tearfulness) Loss of concentration, poor memory Joint aches and pains Dry and itchy skin Hair changes Decreased sexual desire
Intermediate (3–10 years)	Vaginal dryness, soreness Dyspareunia Urgency of urine Recurrent urinary tract infections Urogenital prolapse
Long term (>10 years)	Osteoporosis Cardiovascular disease Dementia

➤ **Central nervous system:**

• **Vasomotor symptoms**

- Vasomotor symptoms are some of the earlier changes that often appear during the perimenopausal years.
- It include ‘hot flush’, and when a hot flush occurs at night it is termed ‘night sweat’.
- The exact aetiology of a vasomotor symptom is unknown but is thought to be loss of the modulating effect of oestrogen on serotonergic receptors within the thermoregulatory centre in the brain, resulting in exaggerated peripheral vasodilatory responses to minor atmospheric changes in temperature.
- It could affect the woman sleep and lead to tiredness, exhaustion, poor performance during the day and impaired quality of life.

• **Psychological symptoms**

Menopause is associated with low mood, irritability, lack of energy, tiredness and impaired quality of life from the early perimenopausal period.

• **Cognitive function**

No clear evidence that menopause is associated with an acceleration of the onset or incidence of dementia. Most women, however, complain of some change in memory.

➤ **The genital tract:**

• **Endometrial effects**

The initial irregular or scanty vaginal bleeding is due to the reduction in oestrogenic endometrial stimulation with failing ovarian function, then the periods completely stopping when the endometrium is no longer stimulated.

- **The urogenital tract and vulvovaginal atrophy:**

- Oestrogen levels decrement in the perimenopausal years, especially in those who are sexually active may cause vaginal dryness, irritation, burning, soreness and dyspareunia.
- Loss of the oestrogenic support to the vaginal epithelium leads to reduced cellular turnover and reduced glandular activity, leading to a vaginal epithelium that is less elastic and more easily traumatized.
- Other conditions that frequently worsen during the menopause, including incontinence and prolapse.
- The inherent resistance of the urogenital system to infection is also impaired, due to an increase in pH of the normally mildly acidic environment within the vagina.
- The incidence of urinary tract infections is also increased.
- Examination of women with postmenopausal urogenital atrophy normally demonstrates dryness affecting most of the surfaces of the vagina along with pallor and, in extreme cases, small petechial haemorrhages. Older women may also have shrinkage and fusion of the labia along with narrowing of the vaginal introitus.

- **Bone health:**

- One of the most important areas is the long-term postreproductive health which include the changes in bone that occur on loss of the oestrogenic support of skeletal metabolism. To fully understand this area, it is important to be aware of the fact that the skeleton is maintained by a constant process of remodelling, with bone being laid down by osteoblasts and resorbed by osteoclasts. The balance of the rates of resorption vs. deposition is affected by many different factors, one of which is oestrogen. Bone density naturally increases during childhood, reaching a peak between 20 and 30 years of age.
- Osteoporosis is defined as ‘a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture’. It is more frequent in women than men with an approximate ratio of 4:1.
- Risks factors includes: Family history of osteoporosis or hip fracture, Smoking, Alcoholism, Long-term steroid use, POI and hypogonadism, Disorders of thyroid and parathyroid metabolism, Immobility, Disorders of gut absorption, malnutrition and liver disease.

- **Cardiovascular system**

- Approximately 30% of all deaths occur as a result of ischaemic heart disease and stroke.
- Oestrogen has a supportive effect on the vessel wall that favours vasodilatation and prevents atherogenesis; effects that are reduced after the menopause.
- In addition to lifestyle issues such as nutrition and exercise, changes in the distribution in fat from a more gynaecoid (fat on breasts and hips) to android (abdominal fat deposition) and changes in serum lipid levels that include increases in triglycerides, total cholesterol and low-density lipoprotein (LDL) cholesterol with reduction in high-density lipoprotein (HDL) cholesterol.

Management:

Diagnosis:

- The diagnosis of menopause is a **largely clinical diagnosis** that is made according to symptoms experienced, such as menstrual irregularities, amenorrhoea, and oestrogen deficiency symptoms, such as vasomotor symptoms, joint aches and minor cognitive changes.
- There is rarely a need for investigations to confirm menopause.
- The use of serum endocrine tests such as hormone levels are of little value in the perimenopausal years as they are unpredictable due to the hormonal variations.
- Serum FSH levels more than 30 IU/l is highly suspicious of menopause. An elevated serum FSH in association with a low serum oestradiol may be suggestive of menopause, (but as this combination of levels can occur during a normal menstrual cycle this test can therefore be misleading).
- Pregnancy should also be excluded.

Assessment of menopausal woman:

Consultation of a woman around the menopause would be a good opportunity not only to assess the impact of the menopause on the woman health, but also to take the opportunity to look to the presence of other risk factors, both modifiable and non-modifiable, that may affect health and longevity.

Table 4: Modifiable and non-modifiable risk factors affecting health and longevity.

Family history	Personal medical/gynaecological history	Lifestyle	Signs	Relevant symptoms
CVD	Obstetric history	Exercise levels	Blood pressure.	Vasomotor
Osteoporosis	Administration of drugs that influence oestrogen levels	Nutrition	BMI.	Urogenital tract, including sexual concerns
Thromboembolic disease	Age of menopause	Smoking & alcohol intake	Vaginal assessment including cervical smear	Cognition
	History of cancer and cancer treatment	Relationship & sexual history	Breast examination if indicated	Joint pains
	Chronic disease and treatment	Contraceptive needs		Vaginal bleeding (if relevant)
	Corticosteroid administration			
	Fracture history			

Treatment and lifestyle modification:

➤ Diet and lifestyle

That could improve quality of life, as regular exercise, stopping smoking and reducing alcohol consumption. That will reduce heart disease and prevent lung cancer and liver disease.

There is on average body weight increases by approximately 1 kg per year and this, along with a more android fat distribution, contributes to a greater sensation of being overweight.

➤ **Non-hormonal approaches**

Most women on experiencing the early symptoms of the menopause will seek out a solution from the wide range of alternative and ‘natural’ solutions available in pharmacies, supermarkets, health food shops, on-line suppliers.

- **Alternative and complementary treatments**

These groups of treatments are widely available (Table 5) but very poorly researched in the scientific manner. Efficacy is usually limited and of a short duration, with the potential for interactions with other pharmaceutical agents.

Table 5: Alternative and complementary treatments:

Complementary drug-free therapies (delivered by a practitioner)	Acupuncture Magnetism
Herbal/natural preparations (designed to be ingested)	Evening primrose oil (<i>Oenothera biennis</i>)
‘Natural’ hormones (designed to be ingested or applied to the skin)	Phytoestrogens such as isoflavones Natural progesterone gel Dehydroepiandrosterone (DHEA)

- **Non-hormonal prescription treatments**

This group of therapies (Table 6) is important to consider in the management of women to reduce symptoms of hot flushes when **hormones are not wanted or contraindicated**, for example previous diagnoses of hormone-sensitive cancers such as breast cancer.

Other non hormonal treatment:

- Vaginal moisturizers and lubricants for vaginal dryness.
- Therapies for osteoporosis, which include bisphosphonates and raloxifene.

Table 6: Non-hormonal treatments for vasomotor symptoms

Alpha-adrenergic agonists	Clonidine
Beta-blockers	Propranolol
Modulators of central neurotransmission	Fluoxetine Gabapentin

➤ **Hormones replacement therapy (HRT):**

There was much controversies about the risk and benefit of HRT.

- **Types of hormones contained in HRT**

➤ **Oestrogens**

There is a group of hormones with oestrogenic activity. If oestrogen is given without progestogenic opposition, there is a risk that in time endometrial hyperplasia and cancer may develop. Systemic oestrogen-only HRT is suitable for women who no longer have a uterus following a hysterectomy.

➤ **Oestrogen with progestogen**

- The administration of progestogen is necessary to protect the endometrium in women who have not had a hysterectomy.
- It is normally given cyclically in preparations over a 28-day cycle, of which 16–18 days will provide oestrogen alone and 10–12 days will provide oestrogen and progesterone combined (**cyclical HRT**). This results in regular monthly menstruation and is suitable for women during the perimenopause or early postmenopausal years.
- Oestrogen and progesterone may be given continuously (**continuous combined HRT**) to women who are known to be postmenopausal or over the age of 54 years. These are usually preparations with the same dose of daily oestrogen combined with a smaller dose of progestogen taken every day. These regimes normally result in about 90% of women not experiencing vaginal bleeding.

➤ **Types of hormones used:**

- Oestrogens: oestradiol (the main physiological oestrogen), oestrone sulphate, oestriol & conjugated equine oestrogen.
- Progestogens: • norethisterone, levonorgestrel, dydrogesterone, medroxyprogesterone acetate, drospirenone and micronized progesterone.
- Testosterone: given to women with disorders of sexual desire and energy levels who have failed to respond to normal HRT.

➤ **Routes of hormone therapy administration:**

- The two main routes of HRT delivery are oral and transdermal.
- The oral route is convenient and cheap but does influence lipid metabolism and the coagulation system through its effects on the liver during first-pass metabolism.
- The transdermal route, either given as patches applied to the skin on the trunk or as measure gel, is also effective, with the advantage of delivery of oestradiol directly into the circulation, avoiding the above potentially adverse effects on the liver and the coagulation system.
- Oestradiol is also available as small vaginal tablets and a vaginal ring, and oestriol as measured dose vaginal creams that are important in the management of lower genital tract symptoms.
- Progestogen in the form of levonorgestrel may be administered as an intrauterine releasing system (IUS), Mirena[®]. It provides contraception and control of bleeding, but also provides endometrial protection for up to 5 years.

➤ **Beneficial effects of hormone therapy:**

Symptoms improved	Prevention of osteoporosis	Lower genital tract improve:	CVD
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<ul style="list-style-type: none"> • vasomotor symptoms • sleep patterns • performance during the day 	<ul style="list-style-type: none"> • increased bone mineral density • reduced incidence of fragility fractures (hip & spine) 	<ul style="list-style-type: none"> • dryness • soreness • dyspareunia • cystitis • dysuria 	<ul style="list-style-type: none"> • preventative effect if started early in menopause
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➤ **Contraindications and potential side effects:**

In general, side-effects with HRT are few and minor. It is therefore important before starting HRT to ensure that the woman has no contraindications to HRT.

Absolute contraindications	Relative contraindications:	Side-effects associated with oestrogen:	Side-effects associated with progestogen
<ul style="list-style-type: none"> • suspected pregnancy • breast cancer • endometrial cancer • active liver disease • uncontrolled hypertension • known current venous thromboembolism (VTE) • known thrombophilia (e.g. Factor V leiden) • otosclerosis 	<ul style="list-style-type: none"> • uninvestigated abnormal bleeding • large uterine fibroids • past history of benign breast disease • unconfirmed personal history or a strong family history of VTE • chronic stable liver disease • migraine with aura 	<ul style="list-style-type: none"> • breast tenderness or swelling • nausea • leg cramps • headaches 	<ul style="list-style-type: none"> • fluid retention • breast tenderness • Headaches • mood swings • depression • acne

Side effects of HRT, most can be managed with:

- Change in dose of oestrogen.
- Or change in type of progestogen.
- Or changing the rout. Many women find the Mirena a useful device as it delivers much less progestogen into the circulation, thus reducing progestogenic side-effects.

Duration of HRT:

- There is little clear evidence to support how long the woman can use HRT.
- No exact maximum age at which a woman should stop HRT.
- The woman need regular assessment for her needs along with review of the type and dose of HRT she is taking.

➤ **Risks of hormone therapy**

New studies had been done regarding HRT which make a better understanding of risk, make many more women considering HRT in the management of their menopause.

- **Cancer:**

The new studies have shown that:

- Breast cancer: recent data with oestradiol HRT suggest that mortality from breast cancer is not increased and that certain types of HRT may promote the growth of pre-existing malignant cells rather than initiate tumours.
- Endometrial cancer and ovarian cancer are not considered significant risks with HRT use. Endometrial malignancy risk is largely eliminated if women are given progestogens. Incidence of ovarian cancer has **not** been shown to significantly increase with HRT use.

- **Cardiovascular disease and stroke:**

- Most of the effects of HRT on the cardiovascular system when given to younger women are beneficial. However, when given to older women the effects may become deleterious and is likely to be higher in women taking combined HRT.

- **Venous thromboembolism:**

- The influence of HRT on the clotting system is similar to that of the oral contraceptive.
 - The background incidence of all VTE in women over 50 is low (approximately 15–20 per 10,000) and HRT doubles this risk.
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