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MENOPAUSE-A REVIEW

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1. INTRODUCTION

Menopause, also known as the climacteric, is the time in most women's lives when menstrual periods stop permanently, and they are no longer able to bear children.[1,2] Menopause typically occurs between 49 and 52 years of age.[3] Medical professionals often define menopause as having occurred when a woman has not had any vaginal bleeding for a year.[4] It may also be defined by a decrease in hormone production by the ovaries.[5] In those who have had surgery to remove their uterus but still have ovaries, menopause may be considered to have occurred at the time of the surgery or when their hormone levels fell.[5] Following the removal of the uterus, symptoms typically occur earlier, at an average of 45 years of age.[10] In the years before menopause, a woman's periods typically become irregular,[11,12] which means that periods may be longer or shorter in duration or be lighter or heavier in the amount of flow.[6] During this time, women often experience hot flashes; these typically last from 30 seconds to ten minutes and may be associated with shivering, sweating, and reddening of the skin.[7] Hot flashes often stop occurring after a year or two.[8] Other symptoms may include vaginal dryness, trouble sleeping, and mood changes.[11] The severity of symptoms varies between women.[8] While menopause is often thought to be linked to an increase in heart disease, this primarily occurs due to increasing age and does not have a direct relationship with menopause.[8] In some women, problems that were present like endometriosis or painful periods will improve after menopause.[8]

Menopause is usually a natural change.[10] It can occur earlier in those who smoke tobacco.[9,13] Other causes include surgery that removes both ovaries or some types of chemotherapy.[9] At the physiological level, menopause happens because of a decrease in the ovaries' production of the hormones estrogen andprogesterone.[8] While typically not needed, a diagnosis of menopause can be confirmed by measuring hormone levels in the blood or urine.[14] Menopause is the opposite of menarche, the time when a girl's periods start.[15]

Specific treatment is not usually needed.[9] Some symptoms, however, may be improved with treatment.[9] With respect to hot flashes, avoiding smoking, caffeine, and alcohol is often recommended.[6] Sleeping in a cool room and using a fan may help.[9] The following medications may help: menopausal hormone therapy(MHT), clonidine, gabapentin, or selective serotonin reuptake inhibitors.[9,10] Exercise may help with sleeping problems.[11] While MHT was once routinely prescribed, it is now only recommended in those with significant symptoms, as there are concerns about side effects.[6] High-quality evidence for the effectiveness of alternative medicine has not been found.[8] There is tentative evidence for phytoestrogens.[12]

1.1 Definition

Menopause is the end of the menstruation. The word menopause come from the Greece word ―men‖ meaning ―monthly‖and pausis meaning ―cessation‖. Menopause is a part of womens natural ageing process when her overies produce lower level of the estrogen & progesterone and when she no longer able to become pregnant.[3]

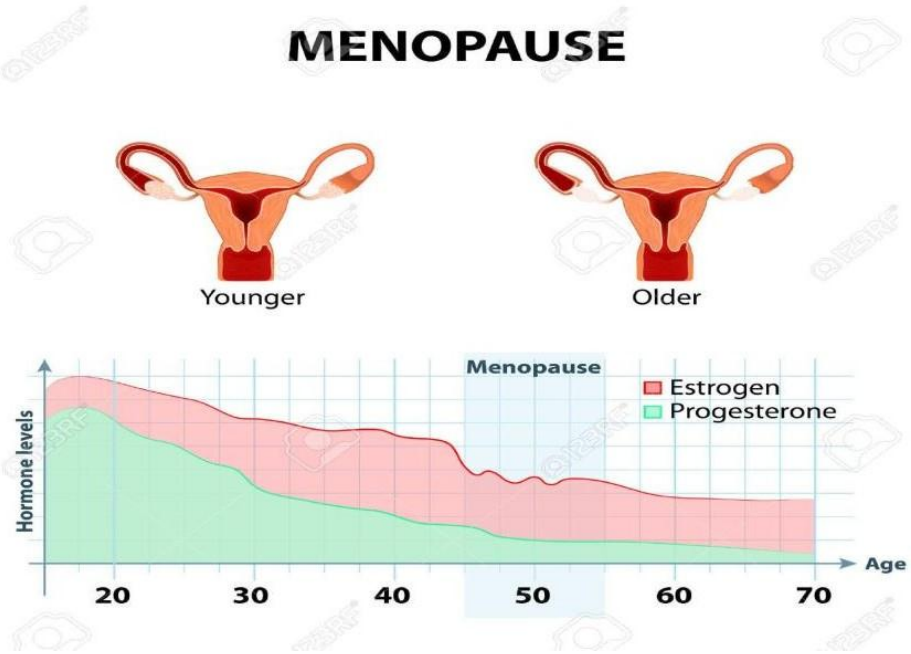

Fig. 1: fluctuation of hormones that occurs during menopause. Menopause as a stage in women's lives when their bodies lose the ability to produce enough hormones that keep the body balanced and healthy. Younger and older women uterus.

1.2 Epidermiology

Physiological Menopause: The normal decline in ovarian function due to ageing begins in most women between ages 45 & 55 on average 51 and results in frequent ovulation, decrease

of menustrual function and eventually cessation of menustruation.

Pathological menopause: The gradual or abrupt cessation of menustration before 40 years occur idiopathically in about 5% of women in USA.

1.3 Etilogy

Menopause can be induced or occur naturally. Induced menopause occurs as a result of medical treatment such as chemotherapy, radiotherapy,oophorectomy, or complications of tubal ligation, hysterectomy, unilateral or bilateral salpingo-oophorectomy or leuprorelin usage.[13]

1. Age

Menopause typically occurs between 49 and 52 years of age.[14] The majority of women have their last period between the ages of 48 and 55.

For example The average age of the last period in the United States is 51 years, in the United Kingdom is 52 years, in Ireland is 50 years and in Australia is 51 years. In India and thePhilippines, the median age of natural menopause is considerably earlier, at 44 years.[15] The menopausal transition or perimenopause leading up to menopause usually lasts 7 years (sometimes as long as 14 years).[8,16]

In rare cases, a woman's ovaries stop working at a very early age, ranging anywhere from the age of puberty to age 40. This is known as premature ovarian failure and affects 1 to 2% of women by age 40.[17]

Undiagnosed and untreated coeliac disease is a risk factor for early menopause. Coeliac disease can present with several non-gastrointestinal symptoms, in the absence of gastrointestinal symptoms, and most cases escape timely recognition and go undiagnosed, leading to a risk of long-term complications. A strictgluten-free diet reduces the risk. Women with early diagnosis and treatment of coeliac disease present a normal duration of fertile life span.[18,19]

Women who have undergone hysterectomy with ovary conservation go through menopause on average 3.7 years earlier than the expected age. Other factors that can promote an earlier onset of menopause (usually 1 to 3 years early) are smoking cigarettes or being extremely thin.[20]

2. Premature ovarian failure

Premature ovarian failure (POF) is when the ovaries stop functioning before the age of 40 years.[41,42] It is diagnosed or confirmed by high blood levels offollicle stimulating hormone (FSH) and luteinizing hormone (LH) on at least three occasions at least four weeks apart.[21]

Known causes of premature ovarian failure include autoimmune disorders, thyroid disease, diabetes mellitus, chemotherapy, being a carrier of the fragile X syndrome gene, and radiotherapy.[42] However, in about 50–80% of spontaneous cases of premature ovarian failure, the cause is unknown, i.e., it is generally idiopathic.[19,21]

Women who have a functional disorder affecting the reproductive system (e.g., endometriosis, polycystic ovary syndrome, cancer of the reproductive organs) can go into menopause at a younger age than the normal timeframe. The functional disorders often significantly speed up the menopausal process.

An early menopause can be related to cigarette smoking, higher body mass index, racial and ethnic factors, illnesses, and the surgical removal of the ovaries, with or without the removal of the uterus.[22]

Rates of premature menopause have been found to be significantly higher in fraternal and identical twins; approximately 5% of twins reach menopause before the age of 40. The reasons for this are not completely understood. Transplants of ovarian tissue between identical twins have been successful in restoring fertility.

3. Surgical menopause

Menopause can be surgically induced by bilateral oophorectomy (removal of ovaries), which is often, but not always, done in conjunction with removal of the Fallopian tubes (salpingo-oophorectomy) and uterus (hysterectomy).[23] Cessation of menses as a result of removal of the ovaries is called "surgical menopause". Surgical treatments, such as the removal of ovaries, might cause periods to stop altogether.[18] The sudden and complete drop in hormone levels usually produces extreme withdrawal symptoms such as hot flashes, etc. The symptoms of early menopause may be more severe.[18]

Removal of the uterus *without* removal of the ovaries does *not* directly cause menopause, although pelvic surgery of this type can often precipitate a somewhat earlier menopause, perhaps because of a compromised blood supply to the ovaries. The time between surgery and possible early menopause is due to the fact that ovaries are still producing hormones.[18]

1.4 Staging

During the Stages of Reproductive Aging Workshop (STRAW) in 2011, the STRAW+10 staging system was established. Since then, this system has become the gold standard in the staging of menopause. Its principal criteria rely on the menstrual cycle (with supportive criteria being lab work), and divides the female reproductive cycle into 3 categories: reproductive, menopause transition, and post-menopause.[23]

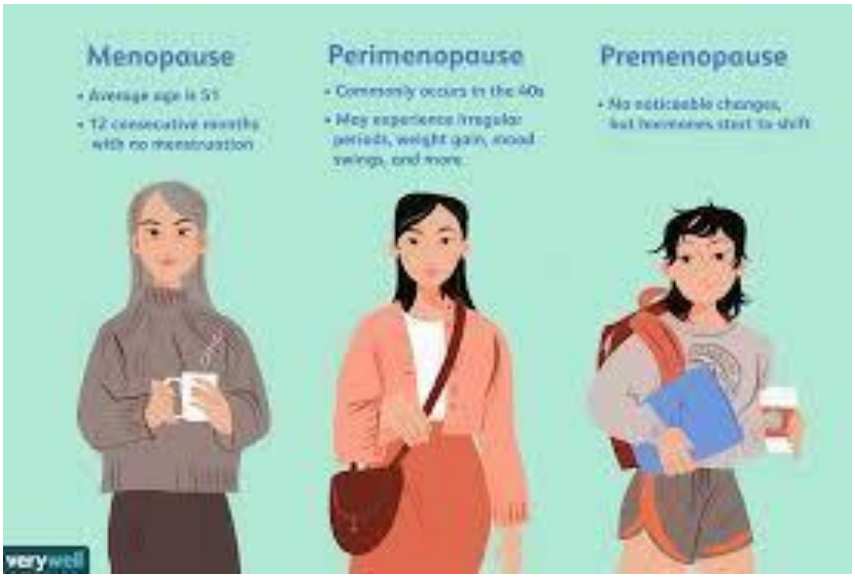

Fig.2 Stages of reproductive aging.

1. Premenopause

Premenopause is a term used to mean the years leading up to the last period, when the levels of reproductive hormones are becoming more variable and lower, and the effects of hormone withdrawal are present.[23] Premenopause starts some time before the monthly cycles become noticeably irregular in timing.[24]

2. Reproductive

During the reproductive stage, the menstrual cycle is regular. There may be variability earlier on following menarche, as well as slight changes to flow (lighter or heavier) and duration (shorter or longer) before entering the next stage. Supportive lab work may be done during the late reproductive stage, and typically conveys low to variable levels of FSH when blood is

drawn between day 2 and 5 of the cycle.[24]

3. Menopausal Transition/ Perimenopause

The term "perimenopause", which literally means "around the menopause", refers to the menopause transition The menopausal transition stage is where perimenopause primarily occurs. Earlier on in this stage, the menstrual cycle undergoes variability of its duration, such that the length of time between menstruations differs by 7 or more days each cycle. As this stage progresses, women typically experience amenorrhea for a period of 60 or more days. Once this occurs, women are in late menopausal transition, which takes place for 1 to 3 years. Supportive lab work may show a variable elevated FSH level earlier on in the menopausal transition stage, and an elevated FSH greater than 25 IU/L later on. The FSH greater than 25 IU/L is due to the decline of estrogen. At this stage, women may likely experience vasomotor symptoms.[24]

Causes

As you go through the menopausal transition, your body's production of estrogen and progesterone rises and falls. Many of the changes you experience during perimenopause are a result of decreasing estrogen.[25]

Risk factor

Menopause is a normal phase in life. But it may occur earlier in some women than in others. Although not always conclusive, some evidence suggests that certain factors may make it more likely that you start perimenopause at an earlier age, including:

- **Smoking:** The onset of menopause occurs one to two years earlier in women who smoke than in women who don't smoke.
- **Family history:** Women with a family history of early menopause may experience early menopause themselves.
- **Cancer treatment:** Treatment for cancer with chemotherapy or pelvic radiation therapy has been linked to early menopause.
- **Hysterectomy:** A hysterectomy that removes your uterus, but not your ovaries, usually doesn't cause menopause. Although you no longer have periods, your ovaries still produce estrogen. But such surgery may cause menopause to occur earlier than average. Also, if you have one ovary removed, the remaining ovary might stop working sooner than expected.[26]

Complications

Irregular periods are a hallmark of perimenopause. Most of the time this is normal and nothing to be concerned about. However, see your doctor if:

- Bleeding is extremely heavy — you're changing tampons or pads every hour or two for two or more hours
- Bleeding lasts longer than seven days
- Bleeding occurs between periods
- Periods regularly occur less than 21 days apart

Signs such as these may mean there's a problem with your reproductive system that requires diagnosis and treatment.[26]

4. Post-Menopause

During the post-menopause state, menstruation has ceased. Perimenopause continues until there has been no menstruation for 1 year. Then early post-menopause continues for another year. Supportive lab work conveys that this interval of time is characterized by an elevated FSH level greater than 40 IU/L, in which women are more likely to experience vasomotor symptoms. As the post-menopause stage progresses, lab work indicates that FSH levels stabilize and antral follicle count is very low. After 3 to 6 years, women enter into late post-menopause, in which they may experience more symptoms of urogenital atrophy.[24]

Stages of reproductive aging workshop

Stage terminology	STRAW stage	Menstrual cycle	FSH level	LH level	Menopause symptom prevalence
Early reproductive	-5	variable → regular	normal	normal	none
Peak reproductive	-4	regular	normal	normal	none
Late reproductive	-3	regular	↑	normal to ↑	sporadic
Early menopausal transition	-2	variable ength (>7days from normal)	↑↑	↑↑	vasomotor 15-20% vaginal —
Late menopausal transition	-1	≥ 2 skipped cycles + interval of amenorrhea of ≥ 60 days	↑↑	↑↑	vasomotor 20-30% vaginal —
Final menstrual period (FMP)	0				
Early postmenopause	+1a menopause	+1a = 12 mos amenorrhea	↑↑↑	↑↑↑	vasomotor 35-55%

	+1b = years 2-5 after FMP	+1b = none			vaginal 10-30%
Late postmenopause	+2	none	↑↑↑	↑↑↑	vasomotor 30%& declining vaginal 35-47%

Straw: Stages of reproductive aging workshop

1.5 Signs & Symptoms

Menopause is a natural change in the body. It causes symptoms such as hot flashes.

While menopause is not a disease or disorder, it does trigger some profound changes in a woman's body.

A diagnosis of menopause is confirmed when a woman has not had a menstrual period for one year. However, the symptoms of menopause generally appear before the end of that one-year period. Clover, and black cohosh have also been safely used to treat menopause symptoms. Though studies on black cohosh have shown mixed results when treating hot flashes, soy and red clover have been.

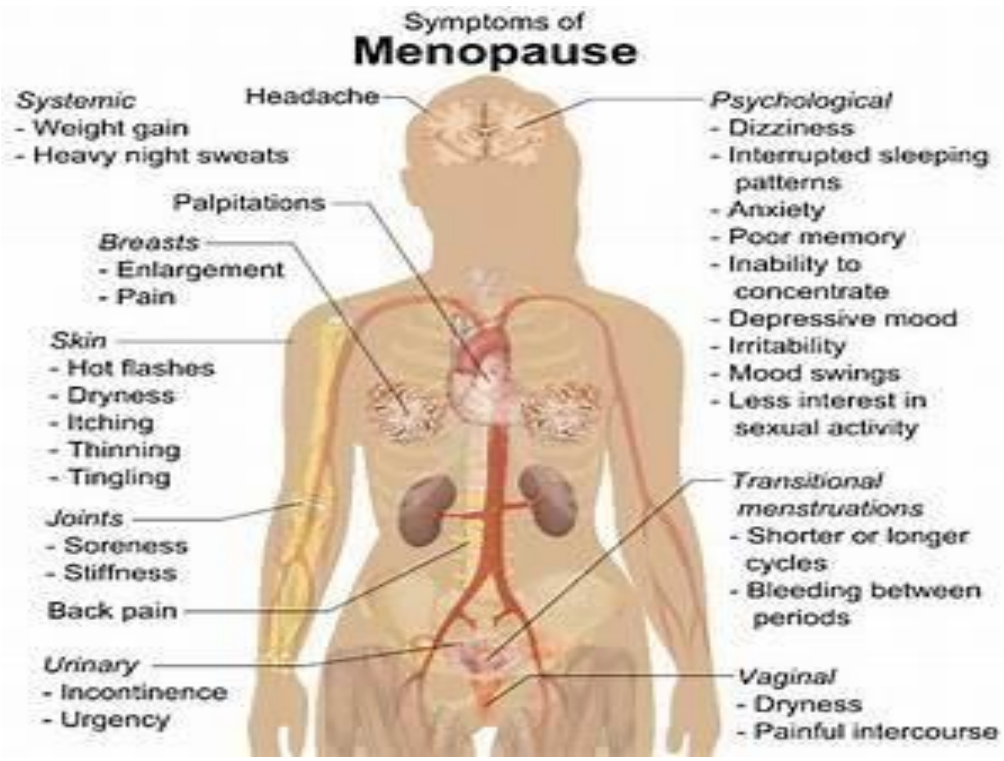

Fig. 3: Signs & Symptoms of menopause.

Irregular periods

Changes to the menstrual pattern are the first noticeable symptoms of menopause. Some women may experience a period every 2 to 3 weeks. Others will menstruate for months at a time.[27]

Vasomotor symptoms

Vasomotor symptoms affect up to 75% of peri-menopausal women. Symptoms last for 1–2 years after menopause in most women, but may continue for up to 10 years or longer in others.

❖ **Hot flashes**

A hot flash is a sudden sensation of heat in the upper body. It may start in the face, neck, or chest, and progress upward or downward. The skin may become red and patchy, and a woman will typically start to sweat. Her heart rate may suddenly increase, strengthen, or become irregular. Hot flashes generally occur during the first year after a woman's final period.[28] Hot flushes are the primary reason women seek care at menopause. Hot flushes not only disturb women at work and interrupt daily activities, but also disrupt sleep. Many women report difficulty concentrating and emotional lability during the menopausal transition. Treatment of vasomotor symptoms should improve these cognitive and mood symptoms if they are secondary to sleep disruption and resulting daytime fatigue.[29] The incidence of thyroid disease increases as women age; therefore, thyroid function tests should be performed if vasomotor symptoms are atypical or resistant to therapy.

The physiological mechanisms underlying hot flushes are incompletely understood. A central event, probably initiated in the hypothalamus, drives an increased core body temperature, metabolic rate, and skin temperature; this reaction results in peripheral vasodilation and sweating in some women. The central event may be triggered by noradrenergic, serotoninergic, or dopaminergic activation. Although an LH surge often occurs at the time of a hot flush, it is not causative because vasomotor symptoms also occur in women who have had their pituitary glands removed.[30] Exactly what role estrogen plays in modulating these events is unknown. Vasomotor symptoms are a consequence of estrogen withdrawal, not simply estrogen deficiency.

❖ **Night sweats**

Hot flashes that occur during the sleep cycle are called night sweats. Most women say their

hot flashes do not last more than a few minutes.

However, studies have confirmed that moderate-to-severe night sweats and hot flashes may pose a problem for around 10.2 years.[28]

Urogenital atrophy

❖ **Vaginal dryness**

Dryness, itching, and discomfort of the vagina tend to occur during perimenopause.

As a result, some women may experience dyspareunia, or pain during sex. Women experience this pain due to lowering estrogen levels. These lower levels cause vaginal atrophy.[31]

Vaginal atrophy is an inflammation of the vagina that happens as a result of the thinning and shrinking of the tissues, as well as decreased lubrication.

Systemic estrogen therapy is effective for the relief of vaginal dryness, dyspareunia, and urinary symptoms. Another option is a topical application.

Women using vaginal estrogen therapy should be asked to report any vaginal bleeding, and this bleeding should be evaluated thoroughly. Typically, systemic progestin therapy is not prescribed to women using low-dose vaginal estrogen.

Lubricants are a non-hormonal alternative for reducing discomfort with intercourse in the presence of urogenital atrophy.[32]

❖ **Urinary problems**

Menopause can disrupt a woman's urinary cycle.

Women tend to be more susceptible to urinary tract infections (UTIs) during menopause, such ascystitis. They may also find that they also need to visit the toilet more often.

Vaginal estrogen therapy appears to reduce urinary symptoms, such as frequency and urgency and has been shown to reduce the likelihood of recurrent urinary tract infections in postmenopausal women.[33] The effect of estrogen therapy on urinary incontinence is unclear. Whereas the results of some studies suggest improvement in incontinence with estrogen therapy, others show a worsening of symptoms.[34]

Depression

❖ **Emotional changes**

Women can experience depression and low mood during menopause.

Hormonal changes can often trigger depressed feelings and mood swings. In many cases, these emotional symptoms also go hand-in-hand with sleep disturbance.

Women may also experience low libido, or sex drive, as a result of these emotional changes. Although most women transition to menopause without experiencing psychiatric problems, an estimated 20% have depression at some point during menopause.[33]

Studies of mood during menopause have generally revealed an increased risk of depression during perimenopause with a decrease in risk during postmenopausal years.

Pathophysiology

Depression during perimenopause is likely due to fluctuating and declining estrogen levels in part. Steroid hormones, such as estrogen, act in the central nervous system (CNS) by means of various mechanisms. For instance, they stimulate the synthesis of neurotransmitters, the expression of receptors, and influence membrane permeability.[37]

Although the precise mechanisms are yet unknown, regulation of serotonin and norepinephrine may change as estrogen levels fluctuate and thus contribute to depression. Because estrogen facilitates the actions of serotonin and norepinephrine, a decline in estrogen concentrations may, in turn, decrease levels of these hormones.[35,37,38] Changes in estrogen levels, perhaps due to mechanisms involving these neurotransmitters, may be related to depressive symptoms in the menopausal transition of some women.[36]

Cognitive functions

❖ **Problems focusing and learning**

Menopause can affect cognitive functions, such as concentration.

Some women may also experience short-term memory problems and difficulty focusing for long periods.

Memory problems are common complaints in perimenopausal and recent postmenopausal women. The increased frequency of cognitive complaints in menopausal women suggests that

memory problems in this population are related to the menopause transition rather than to the aging process.[34] Clinical trials describing the enhancement of cognition with HRT support the etiologic role of estrogen in cognitive difficulties expressed by perimenopausal and recent postmenopausal women.[33,34,35,36] Specific cognitive domains (e.g., attention, verbal memory, and learning capacity) that may be influenced by the menopause transition have not been well characterized. The apparent relationship between the menopause transition and cognitive difficulties in some women suggests that such cognitive disturbance may be related to the hormonal changes of the menopause.[37]

Sexual dysfunction

Many women experience sexual dysfunction during menopause, although the exact incidence and etiology are unknown. Sexual dysfunction may involve decreased interest or desire to initiate activity, as well as decreased arousal or ability to achieve an orgasm during sexual relations. The etiology of sexual dysfunction often is multifactorial, including psychological problems such as depression or anxiety disorders, conflict within the relationship, issues relating to prior physical or sexual abuse, medication use, or physical problems that make sexual activity uncomfortable, such as endometriosis or atrophic vaginitis.[40]

❖ **Lower fertility**

Perimenopause is the 3-to-5-year period before menopause.

During the perimenopausal stage, a woman's estrogen levels will drop significantly. This reduces her chances of becoming pregnant.

Female sexual dysfunction after menopause is a complex problem with many etiologies. Careful evaluation of physiological, psychological, lifestyle, and relationship variables is required to optimize therapy. Treatment of anxiety and depression, adjustment of antidepressant medication, and relationship counseling may improve sexual function. Specific exercises and activities, often performed under the guidance of a sex therapist, help many women and couples with sexual dysfunction. Specific treatment of genitourinary atrophy with systemic or local vaginal estrogen therapy or vaginal lubricants effectively reduces dyspareunia and may improve sexual arousal and response. Sildenafil citrate was ineffective in a large randomized, double-blind, placebo- controlled study of women with sexual dysfunction.[41]

Androgen therapy may have a role in the treatment of sexual dysfunction in menopausal women who have low androgen levels and no other identifiable cause for their sexual problem.[42]

Problems with sleep

Insomnia occurs in 40–50% of women during the menopausal transition, and problems with sleep may or may not be connected to mood disorders.[43] Women with insomnia are more likely than others to report problems such as anxiety, stress, tension, and depressive symptoms.

Sleep disturbances during menopause have been associated with estrogen deficiency, as exogenous estrogen has been shown to improve both subjective and objective sleep, attributed to a decrease in hot flushes. A recent study proposed elevated LH levels during late menopause produce poor sleep quality through a thermoregulatory mechanism, resulting in high core body temperatures.[44] Whether the sleep problems are associated with age-related changes in sleep architecture, hormonal status or other symptoms of menopause (e.g., vasomotor symptoms) is unclear.

Rates of a sleep apnea increase with age, rising from 6.5% in women aged 30–39 years to 16% in women aged 50–60 years. The pathophysiology is not known, but theories include a relationship to postmenopausal weight gain or to decreased progesterone levels because progesterone stimulates respiration.[45,46] In addition to undergoing changes in estrogen and progesterone levels, postmenopausal women experience a decline in melatonin and growth hormone levels, both of which have effects on sleep.[47]

Estrogen may be helpful in relieving vasomotor symptoms that disrupt sleep, or that may have a direct effect on sleep itself.[48] In a study of postmenopausal women with hot flushes, night sweats, insomnia, anxiety, and/or mood swings, low-dose estrogen and low-dose micronized progesterone improved sleep to a greater extent than could be explained by a reduction in vasomotor symptoms.[47]

Course of some important psychiatric disorders during menopause

❖ **Schizophrenia**

In most cases, schizophrenia first manifests in young adulthood, with the rate of new cases declining in both male and female individuals after early adulthood. A second peak in the

incidence of schizophrenia is noted among women aged 45–50 years; this second peak is not observed in men.[49]

Some researchers have observed a worsening of the course of schizophrenia in women during the menopausal transition. These observations may suggest that estrogen plays a modulatory role in the pathophysiology of schizophrenia.[50]

❖ **Bipolar disorder**

Exacerbation of mood symptoms during menopause has been noted in women with the pre-existing bipolar disorder. Research has suggested that women with bipolar disorder have higher rates of depressive episodes during the menopausal transition. The frequency of depressive episodes in this population appears to be higher than during premenopausal years.[51] Earlier studies suggested an increase in rapid cycling during the menopausal transition; however, this finding has not been reproduced.[52]

❖ **Panic disorder**

Panic disorder is common during perimenopause. New-onset panic disorder may occur during menopause, or pre-existing panic disorder may worsen. Panic disorder may be most common in women with many physical symptoms of menopause.[53]

In a cross-sectional survey of 3369 postmenopausal women aged 50–79 years, panic attacks were most prevalent among women in the menopausal transition. Panic attacks were associated with negative life events, functional impairment, and medical comorbidity.[54]

❖ **Obsessive-compulsive disorder**

New-onset obsessive-compulsive disorder (OCD), a relapse of OCD, or a change in OCD symptoms may occur during menopause. Fluctuations in OCD have been correlated with the menstrual cycle and with pregnancy, suggesting that hormone levels may contribute to the disorder.[55]

Long term effects

Menopause confers

- A possible but contentious increased risk of atherosclerosis.[27] The risk of acute myocardial infarction and other cardiovascular diseases rises sharply after menopause, but the risk can be reduced by managing risk factors, such as tobacco smoking, hypertension, increased blood lipids and body weight.[28,29]

- Increased risk of osteopenia, osteoporosis,[30] and accelerated lung function decline.[31,32]

Women who experience menopause before 45 years of age have an increased risk of heart disease,[33] death,[34] and impaired lung function.[31]

Other effects

Other symptoms of menopause include:

- a buildup of fat in the abdomen, sometimes leading to overweight and obesity
- hair loss and thinning hair
- breast shrinkage

Without treatment, symptoms usually taper off over a period of 2 to 5 years. However, symptoms can persist for longer. In some cases, vaginal dryness, itching, and discomfort can become chronic and eventually get worse without treatment.

1.6 Pathophysiology

Menopause is a normal physiologic process in aging women, in which the number of ovarian, primary follicles quickly diminish, such that there are inadequate amounts to respond to the effects of FSH. In turn, there is no LH surge, and ovulation does not take place, resulting in the decline of estrogen production and the cessation of menstruation. Moreover, LH and FSH go uninhibited and remain at high levels years after the onset of menopause. Small amounts of estrogen may still be produced via conversion from testosterone released by the adrenal glands, such that symptoms other than the discontinuation of periods may be negligible in some individuals.[61]

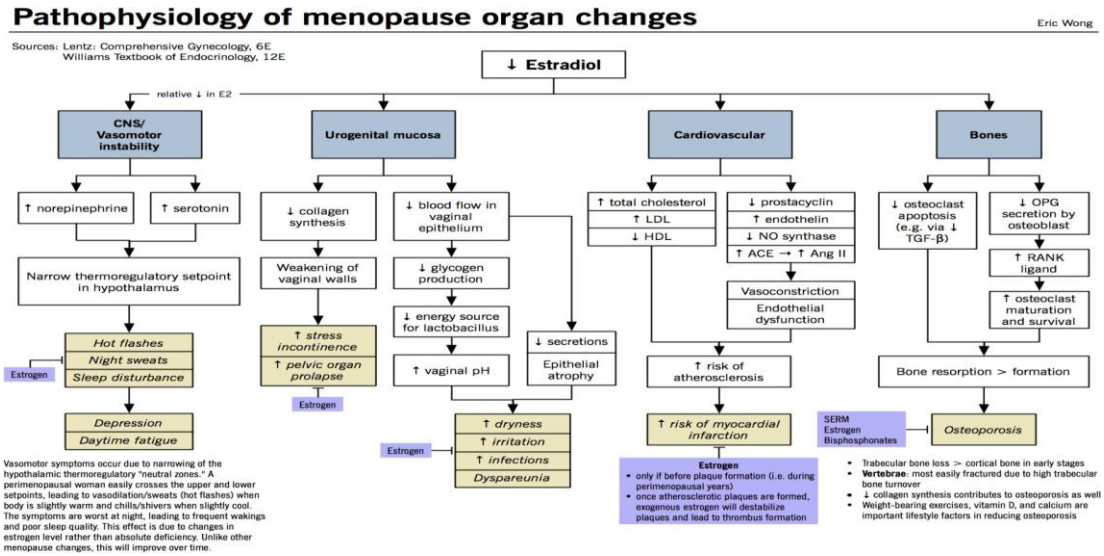

Fig. 4: Pathophysiology of menopause.

1.7 Mechanism

The menopausal transition, and postmenopause itself, is a natural change, not usually a disease state or a disorder. The main cause of this transition is the natural depletion and aging of the finite amount of oocytes (ovarian reserve). This process is sometimes accelerated by other conditions and is known to occur earlier after a wide range of gynecologic procedures such as hysterectomy (with and withoutovariectomy), endometrial ablation and uterine artery embolisation. The depletion of the ovarian reserve causes an increase in circulating follicle- stimulating hormone (FSH) and luteinizing hormone (LH) levels because there are fewer oocytes and follicles responding to these hormones and producing estrogen. The transition has a variable degree of effects.[46]

The stages of the menopause transition have been classified according to a woman's reported bleeding pattern, supported by changes in the pituitary follicle-stimulating hormone (FSH) levels.[47]

In younger women, during a normal menstrual cycle the ovaries produce estradiol, testosterone andprogesterone in a cyclical pattern under the control of FSH and luteinizing hormone (LH), which are both produced by the pituitary gland. During perimenopause (approaching menopause), estradiol levels and patterns of production remain relatively unchanged or may increase compared to young women, but the cycles become frequently shorter or irregular.[48] The often observed increase in estrogen is presumed to be in response to elevated FSH levels that, in turn, is hypothesized to be caused by decreased feedback by inhibin.[49] Similarly, decreased inhibin feedback after hysterectomy is hypothesized to contribute to increased ovarian stimulation and earlier menopause.[50,51]

The menopausal transition is characterized by marked, and often dramatic, variations in FSH and estradiol levels. Because of this, measurements of these hormones are *not* considered to be reliable guides to a woman's exact menopausal status.[49]

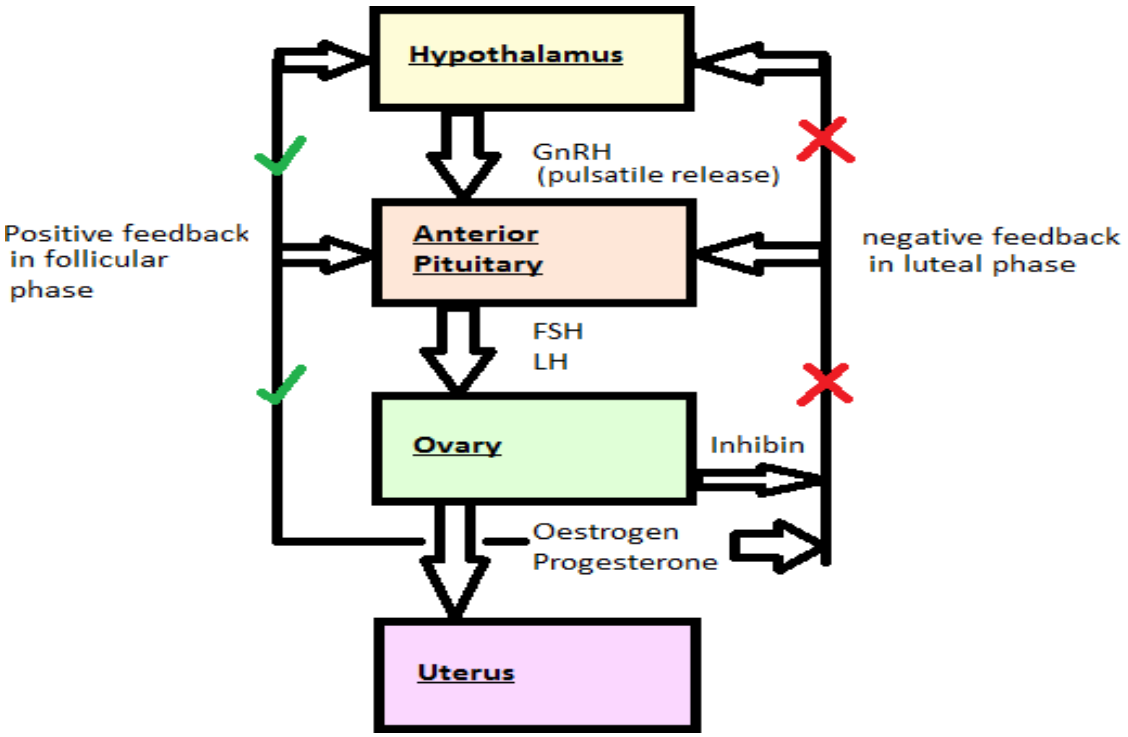

Fig.5: Mechanism of menopause.

Menopause occurs because of the sharp decrease of estradiol and progesterone production by the ovaries. After menopause, estrogen continues to be produced mostly by aromatase in fat tissues and is produced in small amounts in many other tissues such as ovaries, bone, blood vessels, and the brain where it acts locally.[52] The substantial fall in circulating estradiol levels at menopause impacts many tissues, from brain to skin.

In contrast to the sudden fall in estradiol during menopause, the levels of total and free testosterone, as well as dehydroepiandrosterone sulfate (DHEAS) andandrostenedione appear to decline more or less steadily with age. An effect of natural menopause on circulating androgen levels has not been observed.[53] Thus specific tissue effects of natural menopause cannot be attributed to loss of androgenic hormone production.[54]

Hot flashes and other vasomotor symptoms accompany the menopausal transition. While many sources continue to claim that hot flashes during the menopausal transition are caused by low estrogen levels, this assertion was shown incorrect in 1935 and, in most cases, hot flashes are observed despite elevated estrogen levels. The exact cause of these symptoms is not yet understood, possible factors considered are higher and erratic variation of estradiol level during the cycle, elevated FSH levels which may indicate hypothalamic dysregulation perhaps caused by missing feedback by inhibin. It has been also observed that the vasomotor

symptoms differ during early perimenopause and late menopausal transition and it is possible that they are caused by a different mechanism.[48]

Long-term effects of menopause may include osteoporosis, vaginal atrophy as well as changed metabolic profile resulting in cardiac risks.

Ovarian aging

Decreased inhibin feedback after hysterectomy is hypothesized to contribute to increased ovarian stimulation and earlier menopause. Hastened ovarian aging has been observed after endometrial ablation. While it is difficult to prove that these surgeries are causative, it has been hypothesized that the endometrium may be producing endocrine factors contributing to the endocrine feedback and regulation of the ovarian stimulation. Elimination of this factors contributes to faster depletion of the ovarian reserve. Reduced blood supply to the ovaries that may occur as a consequence of hysterectomy and uterine artery embolisation has been hypothesized to contribute to this effect.[63,63]

Impaired DNA repair mechanisms may contribute to earlier depletion of the ovarian reserve during aging.[65] As women age, double-strand breaks accumulate in the DNA of their primordial follicles. Primordial follicles are immature primary oocytes surrounded by a single layer of granulosa cells. An enzyme system is present in oocytes that ordinarily accurately repairs DNA double-strand breaks. This repair system is called "homologous recombinational repair", and it is especially effective during meiosis. Meiosis is the general process by which germ cells are formed in all sexual eukaryotes; it appears to be an adaptation for efficiently removing damages in germ line DNA.[66]

Human primary oocytes are present at an intermediate stage of meiosis, termed prophase I. Expression of four key DNA repair genes that are necessary for homologous recombinational repair during meiosis decline with age in oocytes.[67] This age-related decline in ability to repair DNA double-strand damages can account for the accumulation of these damages, that then likely contributes to the depletion of the ovarian reserve.[68]

1.8 Histopathology

During menopause, histopathology is focused on the ovaries, urogenital, bones, and arteries.

Ovaries

In menopause, follicles age and the 2 structures of the ovaries (cortex and medulla) change.

The cortex becomes thinner, such that the distinction between the cortex and medulla is less evident. The cortex also has fewer follicles, and there is a tendency towards the fragmentation of the corpora arenacea. Additionally, there are invaginations of the surface epithelium of the cortex, and epithelial inclusion cysts are present. The medulla develops stromal fibrosis and scars. The medulla also undergoes the hyalinization of vessel walls, with architectural changes of vessels.

Urogenital

There is also a significant change in the vagina during menopause. The vagina has several epithelial layers: mucosa (most superficial), muscularis, and the adventitia (deepest). The mucosa layer of the vagina begins to atrophy due to decreased estrogen that causes this cell layer to become drier and thinner. As a result, the vaginal mucosa loses its elasticity and becomes fragile.

Bone

Healthy normal bone is const antly remodeling via a 5-step process, which involves resorption (via osteoclasts) and production (via osteoblasts). During menopause, estrogen deficiency increases osteoclastic activity, such that there is an imbalance of osteoclastic and osteoblastic activity. This results in more bone being reabsorbed and overall bone loss. Estrogen deficiency leads the release of cytokines among them RANK ligand (RANKL), which plays a critical role on the osteoclastogenesis cascade.

Arteries

An artery consists of 3 layers, the tunica intima (surrounding the lumen), tunica media, and tunica adventitia. Estrogen is believed to have a positive effect on the tunica intima of the artery wall, helping to keep blood vessels flexible. During menopause, estrogen deficiency causes vasoconstriction of the vessel wall and an accelerated increase of low-density lipoprotein (LDL). Thus, menopause is linked to the increased risk of cardiovascular disease, which can be denoted by increased intima-media thickness.

1.11 Complications

Menopause can lead to the development of complications, including:

- **Cardiovascular disease:** A drop in estrogen levels has been associated with an increased risk of cardiovascular disease.

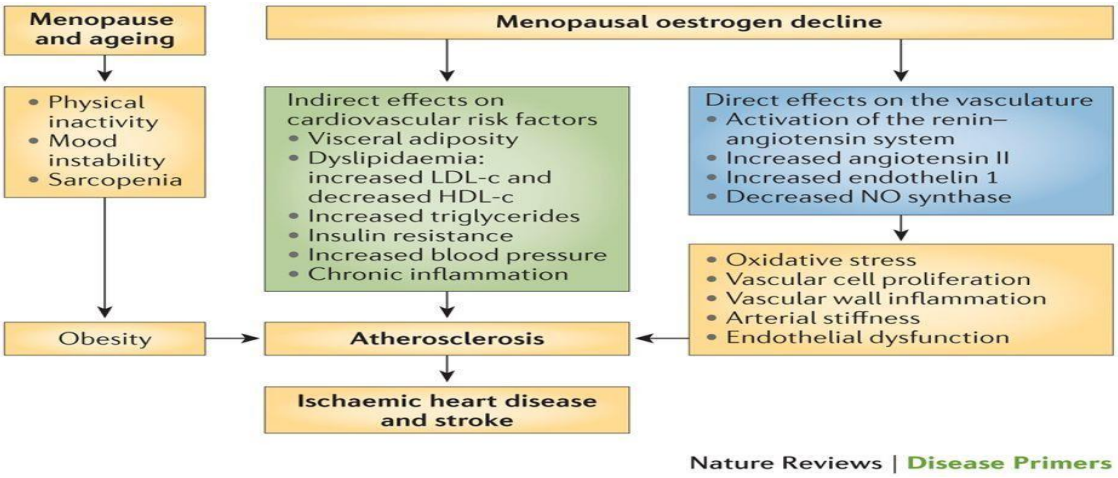

Fig. 6: Consequencies of menopause on the cardiovascular system.

- **Osteoporosis:** Musculoskeletal symptoms characterized by backache, fractures on minimal trauma, decreased height, and mobility are common due to osteoporosis. : A woman may lose bone density rapidly during the first few years after menopause. Low bone density leads to a higher risk of developing osteoporosis.

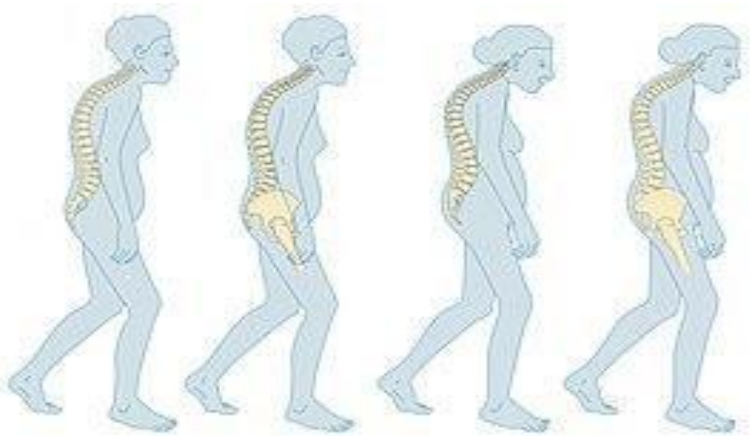

Fig.7: Bone mineral density, especially of the vertebrae, decreases with menopause.

It is important to review a woman's risk factors for osteoporosis when making treatment decisions and to consider bone mineral density screening for high-risk women. Modifiable risk factors include decreased intake of calcium and Vitamin D, smoking, and a sedentary lifestyle. Medical conditions associated with an increased risk of osteoporosis include an ovulation during the reproductive years (e.g., secondary to excess exercise or an eating disorder), hyperthyroidism, hyperparathyroidism, chronic renal disease, and diseases requiring systemic corticosteroid use

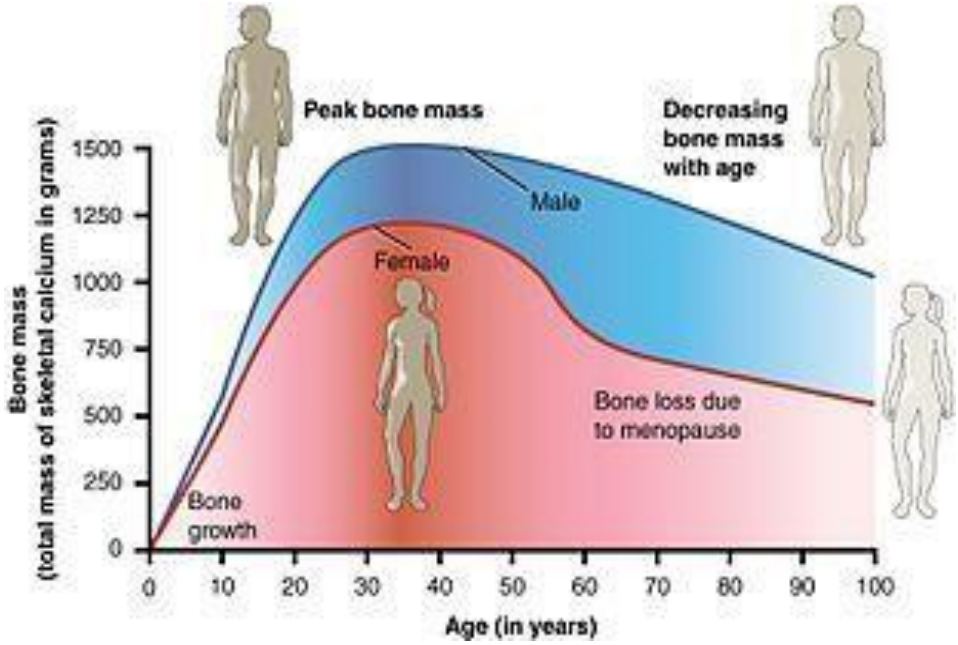

Fig. 8: Bone loss due to menopause occur due to changes in women hormone level.

Hormone therapy (HT) is effective in preventing and treating osteoporosis. In observational studies, estrogen therapy had been shown to reduce osteoporosis-related fractures by approximately 50% when started soon after menopause and continued long term. It also significantly decreases fracture rates in women with established disease.[25]

- **Urinary incontinence:** Menopause causes the tissues of the vagina and urethra to lose their elasticity. This can result in frequent, sudden, and overwhelming urges to urinate. These urges can be followed by involuntary loss of urine. Women may involuntarily urinate after coughing, sneezing, laughing, or lifting during menopause.
- **Breast cancer:** Women face a higher risk of breast cancer following menopause. Regular exercise can significantly reduce the risk.[69]
- **Excess weight:** The most common health issue that women suffer from during menopause is weight gain. There is unexplained gain in their weight which in turn leads to a lot of complications.
- **Diabetes:** The fluctuations of hormones during menopause also takes you closer to the risk of diabetes. Low estrogen can increase your insulin levels which further aggravates your sugar cravings and weight gain.[70]

1.10 Diagnosis

Women undergoing the menopause transition or menopausal changes seek medical counsel for a variety of reasons. Absent or irregular menses, insomnia, depression, cephalalgia, and

vasomotor instability are just a few of the reasons women visit their physicians. Many women access information about menopause through a variety of sources including friends, family, Internet sources, television and other forms of media, which may not be accurate sources of information.

The initial evaluation by the health care provider should include a comprehensive history and physical examination accompanied by select laboratory studies and patient education. In addition, family, social, sexual, and medication histories are imperative. A complete physical examination might provide diagnostic clues to a woman's menopausal state. For example, a loss of height might suggest osteoporosis and a pelvic examination might reveal vaginal atrophy from lack of estrogen.

40 mIU/mL is considered diagnostic of menopause. Although in this setting, a FSH evaluation is rarely needed to confirm the postmenopausal state. If a woman has taken oral contraceptives during the perimenopausal period, she must be taken off them for several months before an accurate FSH level can be determined. Serum estradiol levels fluctuate in perimenopausal women, making it a test that is seldom useful in diagnosing menopause. Testosterone and dehydroepiandrosterone levels are indicated only if a woman has symptoms of hyperandrogenism or if she is taking over-the-counter hormones that may contain these potent androgens. Baseline laboratory studies should also be performed including a screening thyroid stimulating hormone. During the menopause transition, FSH levels fluctuate, making a serum level unreliable for diagnostic purposes. In the face of prolonged amenorrhea with or without menopausal symptoms, an FSH level

1.11 Treatment/Management

Menopause treatment and management revolve around minimizing disruptive symptoms and preventing long-term complications.[5,6,7,8]

Hormonal treatment

Hormone therapy can treat vasomotor symptoms and prevent vaginal/urogenital atrophy, as well as preserve an advantageous lipoprotein profile and prevent bone loss. It can be given in various forms (i.e., tablets, creams, patches), in different modalities (i.e., continuous versus cyclic), and is available as systemic estrogen, estrogen-progestin, estrogen-bazedoxifene, progestin alone, or combined oral contraceptives. Use of unopposed estrogen may cause uterine hyperplasia and uterine cancer, therefore, should be avoided in women with a uterus.

The cyclical administration of combination estrogen-progestin therapy is recommended for women with an intact uterus. It significantly decreases the severity and frequency of hot flashes and improves urogenital atrophy and sleep disturbances. It is also useful in preventing osteoporosis and associated fractures. However, hormone therapy should only be used for the shortest duration of time and at its lowest effective dose, as it increases the relative risk of breast cancer, ovarian cancer, thromboembolism, stroke and coronary heart disease. There is an increased breast cancer risk after 3 to 5 years with estrogen-progestin and 7 years with estrogen only. It is contraindicated in those with a history of breast cancer, endometrial cancer, deep vein thrombosis, pulmonary embolism, liver disease, unexplained vaginal bleeding, and coronary heart disease. For atrophic vaginitis, in particular, systemic or vaginal estrogen can be utilized; however, localized estrogen therapy at very low doses is preferable when there are no other systemic symptoms. The use of localized estrogen therapy (via vaginal rings, creams, or tablets) has been shown to enhance blood flow and reverse vaginal atrophy. However, this also carries a small risk of venous thromboembolism.

Selective estrogen receptor modulators (SERMs)

Selective estrogen receptor modulators, such as raloxifene, bazedoxifene, and ospemifene have the ability to modulate estrogen action, without stimulating endometrial growth or increased risk of cancer. SERMs have the same outcome as hormone therapy in preventing bone loss and promoting beneficial lipoprotein levels. Raloxifene acts like an estrogen agonist (pro-estrogen) on bone and lipids, and like an estrogen antagonist (anti-estrogen) on uterus and breast. Thus, it is effective in preventing/treating mild osteoporosis and decreasing serum LDL. Having a similar profile to raloxifene, bazedoxifene when combined with estrogen, does not influence the endometrium (i.e., women with a uterus do not need to take progestin). Thus, when combined with estrogen, it is effective in treating vasomotor symptoms, like hot flashes. Ospemifene is a newer SERM, which is effective in treating urogenital symptoms, such as vaginal dryness.

Non-Hormonal treatment

Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), gabapentin, and clonidine. These treatments can be used for short durations (a few months) for menopause symptoms. SSRIs and SNRIs, like paroxetine and venlafaxine, are antidepressants that treat vasomotor symptoms, such as hot flashes and result in one fewer hot flash a day. Paroxetine, in particular, is the only FDA-approved drug for this indication,

and symptoms diminish within a week of initiating treatment. While neither is FDA-approved for the treatment of vasomotor symptoms, both gabapentin and clonidine have been shown to reduce hot flashes in menopausal women. Gabapentin reduces hot flashes by up to 2 hot flashes per day; and clonidine is most effective in mild hot flashes, as it is less effective than SSRIs/SNRIs and gabapentin.

Osteoporosis-Specific

For menopausal women experiencing osteoporosis alone, bisphosphonates, denosumab, and supplementation with calcium and vitamin D can be utilized. Bisphosphonates inhibit osteoclast action and resorption of bone. They have been shown to be safe and efficacious in treating osteoporosis. However, at high doses and over a prolonged period, there may be a risk of developing adynamic bone. For this reason, periodic discontinuation of this drug is recommended, as bone density is retained for quite a few years. Denosumab is an antibody to RANKL. It inhibits the osteoclasts and their activity, such that bone resorption is decreased and bone density is increased. In turn, it is reducing the risk of fractures in menopausal women with osteoporosis (via biannual subcutaneous treatment).

Nonprescription remedies

Complementary and alternative treatments include phytoestrogens, vitamin E, and omega-3 fatty acids. Vitamin E and omega-3 fatty acids have been used to treat the vasomotor symptoms of menopause. They are generally safe; however, studies have shown that they are no better than placebo. Phytoestrogens like soy, red shown to be effective in treating osteoporosis and high cholesterol.[55]

Therapy

One review found mindfulness and cognitive behavioural therapy decreases the amount women are affected by hot flushes.Another review found not enough evidence to make a conclusion.

Exercise

Exercise has been thought to reduce postmenopausal symptoms through the increase of endorphin levels, which decrease as estrogen production decreases. Additionally, high BMI is a risk factor for vasomotor symptoms in particular. However, there is insufficient evidence to support the benefits of weight loss for symptom management.[86] There are mixed perspectives on the benefits of physical exercise. While one review found that there was a

lack of quality evidence supporting a benefit of exercise,[85] another review recommended regular healthy exercise to reduce comorbidities, improve mood and anxiety symptoms, enhance cognition, and decrease the risk of fractures. Yoga may help with postmenopausal symptoms similar to other exercise.

Alternative medicine

There is no evidence of consistent benefit of alternative therapies for menopausal symptoms despite their popularity.

The effect of soy isoflavones on menopausal symptoms is promising for reduction of hot flashes and vaginal dryness. Evidence does not support a benefit from phytoestrogens such as coumestrol, femarelle, or the non-phytoestrogen black cohosh. As of 2011 there is no support for herbal or dietary supplements in the prevention or treatment of the mental changes that occur around menopause.

Hypnosis may reduce the severity of hot flashes. In addition, relaxation training with at-home relaxation audiotapes such as deep breathing, paced respiration, and guided imagery may have positive effects on relaxing muscles and reducing stress.

There is no evidence to support the efficacy of acupuncture as a management for menopausal symptoms. A 2016 Cochrane review found not enough evidence to show a difference between Chinese herbal medicine and placebo for the vasomotor symptoms.[57]

Fig.9: Tips to deal with menopause & Avoid complication.

CONCLUSION

Menopause, viewed as part of aging, intricately relates the biological, cultural, and social aspects of a woman's life. Women in the cultures described all experience irregular periods and cessation of menses in midlife. However, women relate to the psychological and social aspects of menopause in less universal ways.

Symptomatic relief through medical interventions remains an important aspect of treatment. However, the focus on biomedical concerns does not outweigh the social and psychological expression of internalized cultural attitudes toward aging. The culture is a source of both language and images about aging from which individuals learn to describe their experience. Their concerns extend to the interpersonal realm of relationships between husbands and wives and mothers and daughters, as well as their status in the culture and social system. One aspect is clear: Despite the tangible marker of aging and the impact on identity, many women welcome the end of reproduction as a relief to their bodies and an opportunity for new experiences. Conclusions:

As the hypotheses testing was conducted with the help of statistical analysis, it was seen that findings of study are sometimes align with previous researches and sometimes contrasting.

1. In case of relationship between positive life events score and physiological distress it is rejected and in case of relationship between negative life score and physiological distress, it is accepted. In short, it seems that married 77 women do not show physiological distress in case; positive life events take place more. They show distress only in case of negative life events. However, the unmarried women show more physiological distress in case of either of life events.
2. Women, married or unmarried, if receive social support of higher level, their physical distress is reduced.
3. Similar to relationship between social support and physiological symptoms, in case of relationship between social support and psychological symptoms also, the correlations were found negatively related in both the groups separately, resulting in no significant difference between the two groups.
4. Both Positive as well as negative life events produce the physiological distress in employed and unemployed group.
5. No significant difference was found between employed and unemployed women so far as the relationship between life events scale and physiological symptoms scale is concerned.

6. Correlations between physiological symptoms and social support symptom score were not different in employed and unemployed group. Thus the null Hypotheses was rejected. There is no difference found between the employed and unemployed groups.
7. No significant difference was found between the groups of high social support scorers and low social support scorers so far as the relationship between two menopausal symptoms scores and two life events scorers and two life event scorers are concerned.

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