

## Overview on - Menopause: A Midlife Crisis

Mugdha Nandedkar\*<sup>1</sup>, Neha Memane<sup>2</sup>, KirtiPatil<sup>3</sup>, Audumbar Mule<sup>4</sup>, Rajesh Oswal<sup>5</sup>

<sup>1</sup> Assistant Professor, Genba Sopanrao Moze College of Pharmacy, Wagholi, Pune, Maharashtra, India.

<sup>2</sup> U G Student, Genba Sopanrao Moze College of Pharmacy, Wagholi, Pune, Maharashtra, India.

<sup>3</sup> U G Student, Genba Sopanrao Moze College of Pharmacy, Wagholi, Pune, Maharashtra, India.

<sup>4</sup> U G Student, Genba Sopanrao Moze College of Pharmacy, Wagholi, Pune, Maharashtra, India.

<sup>5</sup> Principal, Genba Sopanrao Moze College of Pharmacy, Wagholi, Pune, Maharashtra, India.

Submitted: 15-11-2022

Accepted: 26-11-2022

### ABSTRACT

Menopause is a biopsychosocial phenomenon encompassing the transition in a woman's life from being fertile to infertile. Women's experiences, views, and responses to menopause which influences women's daily life and well-being, may vary between different societies and cultures. This study aimed to describe menopausal experiences, their treatments and various factors affecting menopause among women. It is important to strengthen the general well-being during the menopausal transition by relieving troublesome menopausal symptoms and detecting and preventing chronic diseases. Awareness is necessary for women seeking help in menopause-related problems and provide a basis to organize health care for menopausal women based on their needs.

**KEYWORDS** : Menarche, Menopause, Menstruation, Ovaries, Lifestyle

### I. INTRODUCTION

Scientific and technological advances have lengthened the span of life and led to an increase in world's elderly population. While in 1000 B.C., average life expectancy for women is estimated to have been 28 years of age, today this figure has reached to 8<sup>th</sup> decade of life. According to 2013 world population data, life expectancy for newborn girls is 73 years in average around the world and 78. The reports reveal that the average age of menopause is 47. Accordingly, it can be said that a woman who is expected to live 78 years spends a significant part of her life in menopause.

The word "menopause" derives from the Greek "men" (month or monthly cycle) and

"pauis" (end, stop), i.e., "the cessation of monthly cycle." The World Health Organization (WHO) describes it as the permanent cessation of menstruation as a result of the loss of ovarian follicular function. The menopause signals are a reduction of ovarian activity and a fall in fertility. With the appearance of various symptoms and irregular menstrual periods, it is a characteristic phase of the climacteric stage. The hormonal and biochemical changes that occur in this period lead to various symptoms in woman's body.

But before that we need to understand the biological process of the menstrual cycle.

### MENSTRUAL CYCLE

The reproductive system of a female, unlike men, shows regular cyclic changes that may be regarded as periodic preparation for pregnancy and fertilization.

These cyclic changes generally occur in female primates (e.g. monkeys, apes and human beings).

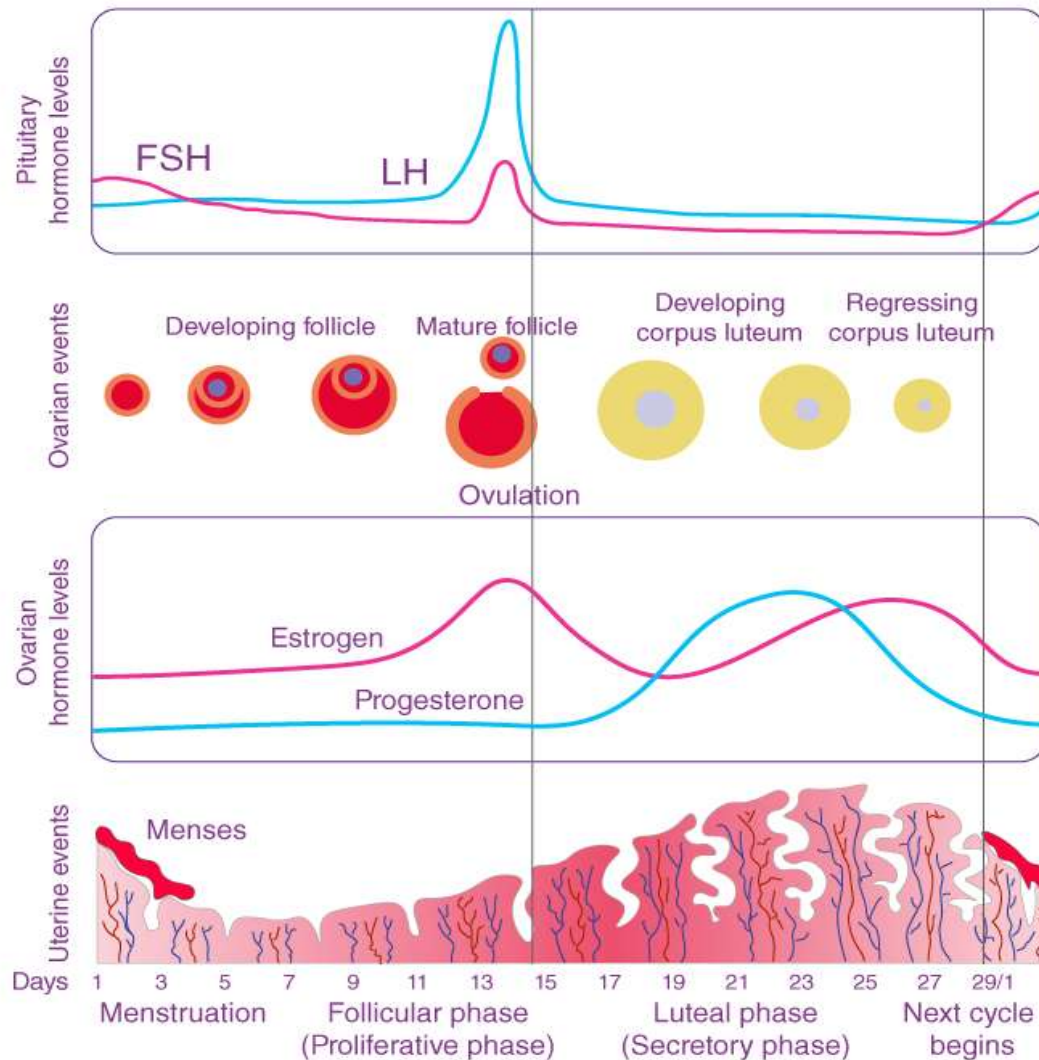
In human females, menstruation is repeated at an average interval of about 28/29 days, and the cycle of events starting from one menstruation till the next one is called the menstrual cycle.

Cyclic menstruation is an indicator of normal reproductive phase and extends between menarche and menopause.

The first menstruation begins at puberty and is called menarche.

Menstrual cycle takes place in four distinct phases :

- 1) Menstruation
- 2) Follicular phase (Proliferative phase)
- 3) Ovulation
- 4) Luteal phase (Secretory phase)



**1)Menstruation-** The cycle starts with the menstrual phase, when menstrual flow occurs and it lasts for 3-5 days. The menstrual flow results due to breakdown of endometrial lining of the uterus and its blood vessels which forms liquid that comes out through vagina. Menstruation only occurs if the released ovum is not fertilised. Lack of menstruation may be indicative of pregnancy. However, it may also be caused due to some other underlying causes like stress, poor health etc.

**2)Follicular phase-** The menstrual phase is followed by the follicular phase. During this phase, the primary follicles in the ovary grow to become a fully mature Graafian follicle and simultaneously the endometrium of uterus regenerates through proliferation. These changes in the ovary and the uterus are induced by changes in the levels of pituitary and ovarian hormones. The secretion of

gonadotropins LH and FSH) Increases gradually during the follicular phase, and stimulates follicular development as well as secretion of oestrogens by the growing follicles. Both LH and FSH attain a peak level in the middle of cycle (about 14<sup>th</sup> day).

**3) Ovulation-** Rapid secretion of LH leading to its maximum level during the mid-cycle called LH surge Induces rupture of Graafian follicle and thereby the release of ovum (ovulation).

[Ovum are released from a woman’s ovaries. Ovum are super tiny – one tenth the size of a poppy seed. Women have two ovaries – one on each side.]

**4)Luteal phase-** The ovulation (ovulatory phase) is followed by the luteal phase during which the remaining parts of the Graafian follicle transform as the corpus luteum . The corpus luteum secretes large amounts of progesterone which is essential for maintenance of the endometrium. Such an

endometrium is necessary for implantation of the fertilised ovum and other events of pregnancy. During pregnancy all events of the menstrual cycle stop and there is no menstruation. In the absence of fertilisation, the corpus luteum degenerates. This causes disintegration of the endometrium leading to menstruation, marking a new cycle.

### PERIMENOPAUSE

Perimenopause means “around menopause”. Perimenopause (also referred to as the menopause transition) is when your body starts transitioning to menopause. During this transition, your ovaries begin producing less hormones, causing your menstrual cycle to become erratic or irregular. The level of estrogen — the main female hormone — in your body rises and falls unevenly during perimenopause. Your menstrual cycles may lengthen or shorten, and you may begin having menstrual cycles in which your ovaries don’t release an egg (ovulate). At this time, your body is moving toward the end of your reproductive years.

Perimenopause may begin as early as your mid-30s or as late as your mid-50s. Some people are in perimenopause for only a short time. But for many, it lasts four to eight years. The term perimenopause simply describes the time when your cycles are no longer predictable.

Other physical changes and symptoms can occur as your body adjusts to different hormone levels. During perimenopause, your fertility is

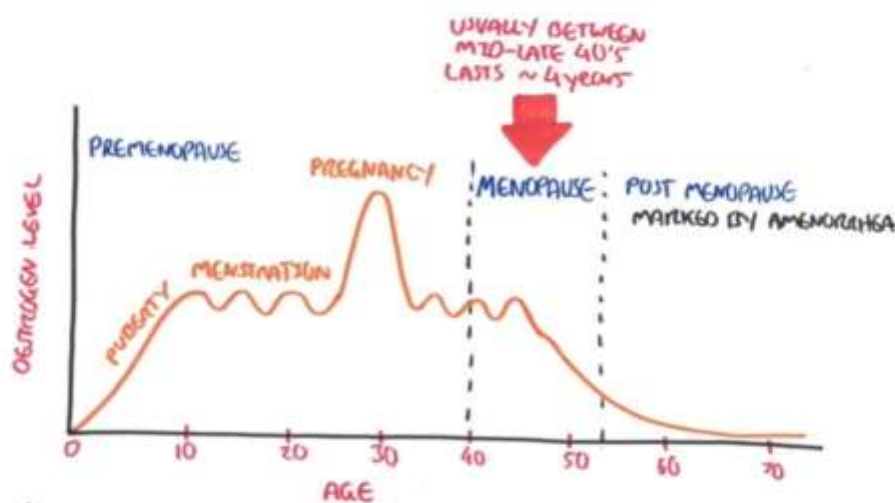
declining, but you still can become pregnant. The symptoms of perimenopause, the age it starts and how long it lasts will vary between women. You’re out of perimenopause and into menopause once you’ve had 12 consecutive months without a menstrual period.

### MENOPAUSE

#### ❖ Natural Menopause

Natural menopause — menopause that’s not caused by surgery or another medical condition — is a normal part of aging. Menopause is defined as a complete year without menstrual bleeding, in the absence of any surgery or medical condition that may cause bleeding to artificially stop such as hormonal birth control, overactive thyroid, high prolactin, radiation or surgical removal of the ovaries.

As you age, the reproductive cycle begins to slow down and prepares to stop. This cycle has been continuously functioning since puberty. As menopause nears, your ovaries make less of a hormone called estrogen. When this decrease occurs, your menstrual cycle (period) starts to change. It can become irregular and then stop. Physical changes can also happen as your body adapts to different levels of hormones. The symptoms you experience during each stage of menopause (perimenopause, menopause and postmenopause) are all part of your body’s adjustment to these changes.



❖ **Premature Menopause**

Menopause, when it occurs between the ages of 45 and 55, is considered “natural” and is a normal part of aging. But, some people can experience menopause early due to various reasons. About 1% of women experience menopause before age 40 (premature menopause). Premature menopause may result from the failure of your ovaries to produce normal levels of reproductive hormones (primary ovarian insufficiency), which can stem from genetic factors or autoimmune disease. But often no cause of premature menopause can be found. For these women, hormone therapy is typically recommended at least until the natural age of menopause in order to protect the brain, heart and bones.

❖ **Surgical Menopause**

Surgical menopause is when surgery, rather than the natural aging process, causes a woman to go through menopause. Surgical menopause occurs after an oophorectomy, a surgery that removes the ovaries.

The ovaries are the main source of estrogen production in the female body. Their removal triggers immediate menopause, despite the age of the person having surgery.

While surgery to remove the ovaries can operate as a stand-alone procedure, it’s sometimes performed in addition to hysterectomy to reduce the risk of developing chronic diseases. A hysterectomy is surgical removal of the uterus.

Periods stop after a hysterectomy. But having a hysterectomy doesn’t lead to menopause unless the ovaries are removed too.

**SYMPTOMS**

When reproductive hormones, like estrogen, slow down, it’s not just your period and ovulation that are affected. Changes in these

hormone levels can lead to a slew of seemingly unrelated symptoms, like sleep disturbances, headaches, and even dry mouth.

This is because estrogen, a hormone produced by the ovaries, doesn’t just regulate your reproductive organs. Estrogen affects and helps regulate many, many organs and systems within the body, including the brain, the heart and vascular systems, bones, skin, hair, and breast tissue, to name a few.

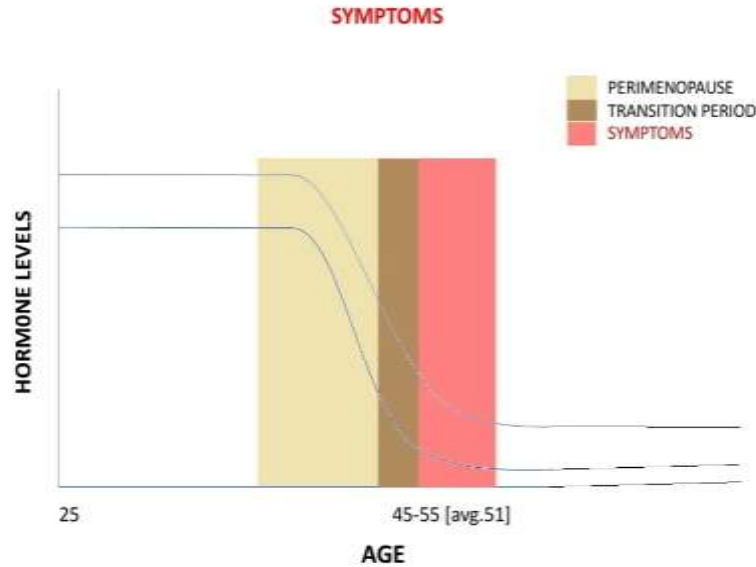
While your adrenal glands and fat cells produce small amounts of estrogen, the ovaries contribute the most of this hormone to the body. As such, during menopause, when the ovaries produce less or stop producing estrogen, the entire body can feel the effects.

For many people, the transition from perimenopause to menopause can last between two and eight years, so it’s a good idea to both learn about possible symptoms and prepare yourself to manage them.

Just because there are many symptoms of menopause doesn’t mean you will have all of them! The experience of menopause is unique to each woman, in much the same way that puberty is unique.

Some women will experience a range of symptoms that affect their lifestyles, while others may sail through perimenopause and into postmenopause without a blip.

So, what percentage of women experience no significant symptoms of menopause? According to Jean Hailes, an Australian non-profit that researches women’s health issues, around: 20% of women will have no menopause symptoms 60% experience will experience mild to moderate menopause symptoms 20% will experience severe menopause symptoms that impact their daily life.



Here are few most common symptoms:

**1. Irregular periods**

A hallmark of oncoming menopause is irregular periods. This is because the natural decline in estrogen means that your ovaries may not release an egg every month or may not release an egg at around the same time each month.

Other changes to your period may include:

Heavier or lighter bleeding

Skipped periods

Getting periods at irregular intervals (even if your period used to arrive every 28 days like clockwork).

**2. Hot flashes**

More than 80% of women will experience hot flashes brought on by menopause. Hot flashes are sudden sensations of warmth, heat, sweating, flushing, anxiety, and chills lasting around 1-5 minutes (though much longer for some people).

**3. Night sweats**

Night sweats are hot flashes that occur at night. Also known as 'sleep hyperhidrosis,' night sweats are generally benign but can affect the quality of your sleep.

During a night sweat, your body temperature rapidly increases, then is followed by excessive sweating. When you wake from a night sweat, you may feel chilled instead of hot, as the intense sweating can soak bed sheets.

**4. Insomnia**

Insomnia means that you may have trouble falling asleep or staying asleep long enough to have a restful night.

Over 50% of perimenopausal and menopausal women experience insomnia. One study even suggests that one in four women with sleep difficulties deal with severe enough symptoms to impact their daytime functioning.

**5. Vaginal dryness**

Vaginal dryness can be a common symptom of changing hormones during menopause. While this irritating symptom is not frequently discussed, it affects more women than you might think!

**6. Mood swings**

Just like you may have experienced with premenstrual syndrome, sudden changes in emotions, also known as mood swings, can also be common during menopause.

Many factors can affect your mood during menopause, including changes in hormones or fatigue brought on by menopausal insomnia.

**7. Weight gain**

Between 45 and 55 years old, women typically gain about half a kilo (a little over a pound) a year.

While hormone fluctuations may contribute to weight changes, hormones alone are not to blame. A drop in muscle mass as we age can also slow your metabolism. In fact, muscle mass is said to decline by 3% to 8% every decade after our 30s.

**8. Common psychological symptoms:**

1. Memory lapses
2. Depression
3. Anxiety
4. Panic disorder
5. Irritability
6. Fatigue
7. Brain Fog

**9. Sexual health changes**

1. Decreased libido

**Other physical symptoms**

1. Paresthesia (Tingling or ‘pins and needles’)
2. Burning mouth
3. Electric shock sensations
4. Itchiness

**10. Aches and pains:**

1. Joint pain
2. Muscle tension and aches
3. Breast tenderness
4. Headaches

**11. Digestive changes:**

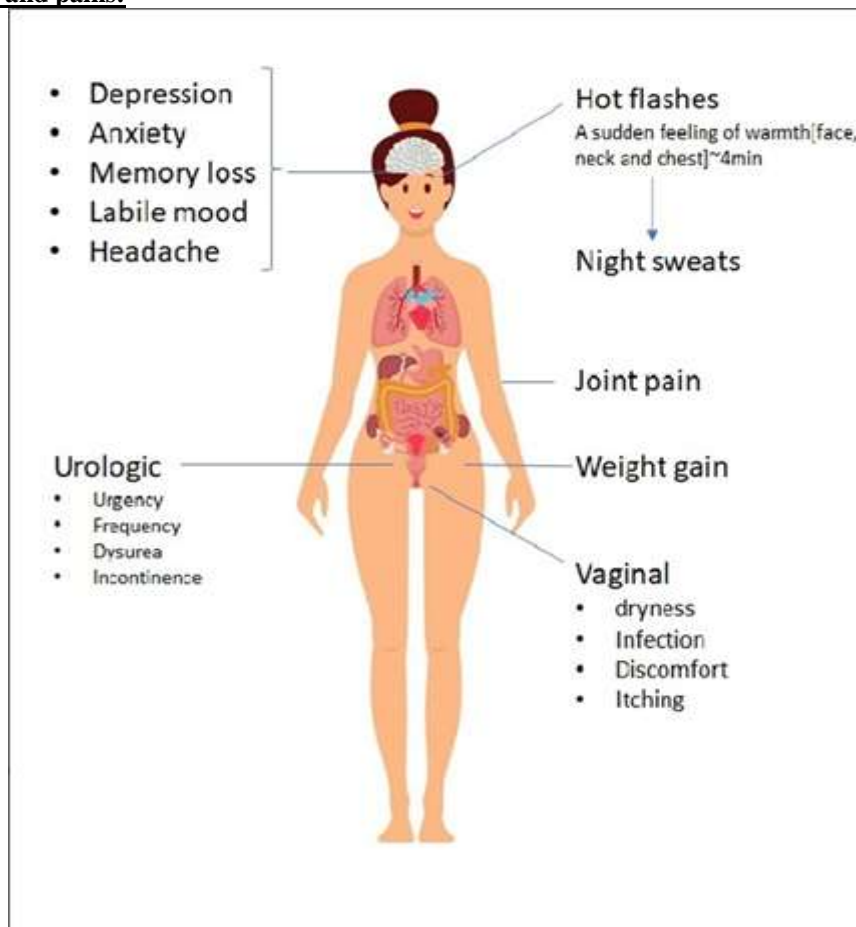
1. Food sensitivities/IBS (Irritable bowel syndrome)
2. Food Cravings
3. Changes in taste
4. Bloating

**12. Physical changes:**

1. Thinning hair
2. Brittle nails

**13. Additional symptoms:**

1. Allergies
2. Osteoporosis
3. Irregular heartbeat
4. Bladder incontinence
5. Dizzy spells



## DIAGNOSIS

A new blood test known as the PicoAMH Elisa diagnostic test was recently approved by the Food and Drug Administration Trusted Source. This test is used to help determine whether a woman has entered menopause or is getting close to entering menopause.

During perimenopause, FSH and estrogen levels fluctuate daily, so most healthcare providers will diagnose this condition based on symptoms, medical history, and menstrual information.

Depending on your symptoms and health history, your healthcare provider may also order additional blood tests to help rule out other underlying conditions that may be responsible for your symptoms.

Additional blood tests commonly used to help confirm menopause include:

- Thyroid function tests
- Blood lipid profile
- Liver function tests
- Kidney function tests
- Testosterone, progesterone, prolactin, estradiol, and chorionic gonadotropin (hCG) tests.

## TREATMENT

Menopause treatment and management revolve around minimizing disruptive symptoms and preventing long-term complications.

### 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. The 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.

### 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 increasing the risk of cancer. SERMs have the same outcome as hormone therapy in preventing

bone loss and promoting beneficial lipoprotein levels. Raloxifene acts as an estrogen agonist (pro-estrogen) on bone and lipids and like an estrogen antagonist (anti-estrogen) on the 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 that 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 flashes 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.

### Nonprescription Remedies

A proper diet can ease symptoms and prevent some complications. 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 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 shown to be effective in treating osteoporosis and high cholesterol.

### **GENERAL FACTORS AFFECTING MENOPAUSE**

The age at natural menopause (ANM) depends on various factors like genetic, environmental, socioeconomic, reproductive, dietary, and lifestyle of which some like nulliparity, vegetarian diet, smoking, high fat intake, cholesterol, and caffeine accelerates; while others like parity, prior use of oral contraceptive pills, and Japanese ethnicity delays the ANM. ANM is an important risk factor for long-term morbidity and mortality; and hence, the need to identify the modifiable risk factors like diet and lifestyle changes.

Although there are many factors that influence the onset of menopause, there is no consensus as to whether these factors are definitive in all women. Studies show that the onset age of menopause is affected by the age at the first menstrual period, the use of oral contraceptives, the number of pregnancies experienced, Body Mass Index (BMI), smoking, drinking alcoholic beverages, blood lead levels, lifestyle, diet, physical activity, genetics, chromosomal issues, autoimmune diseases, epilepsy and other factors. Some of these factors are explained below:

#### **Lifestyle factors :-**

Behavioural or lifestyle factors like smoking,[25,26,27] alcohol consumption, and intake of coffee and tea influence the age at natural menopause (ANM). Smoking and ANM have an inverse consistent relationship such that it accelerates menopause by 1.5-2 years. Polycyclic aromatic hydrocarbons present in cigarette smoke are toxic to ovarian follicles that result in decreased oestrogen levels, and hence menopause. The drug metabolism is enhanced in smokers with the result that oestrogen gets more rapidly metabolized in liver and moreover smoking has an antiestrogenic effect as well. Effect of passive smoking on ANM has not been documented well. There are studies that have documented a dose-response effect on atrophy of ovarian follicles such that heavy smokers have an earlier natural menopause as compared to light smokers. Alcohol consumption and its effect on the ANM has been evaluated in very few studies due to certain social and ethnic

limitations. Moderate alcohol[28,29,30] consumption delays ANM. Regular tea consumption also delays the ANM probably due to the antioxidant and nonsteroidal estrogenic effects of flavonoids that counteract the degenerative processes. However, there are no studies on the effect of various types of tea on age at menopause. Low level of lifelong sun[31] exposure has been found to be associated with early ANM.

#### **Physical activity:-**

Higher BMI at 20 years age, mid-life weight gain moderate-high, exercise participation, and enhanced leisure time physical activity during adulthood and adolescence are associated with late menopause and longer reproductive span; however, severe weight loss or vigorous exercise accelerates ANM by lowering the oestrogen levels. The role of moderate weight gain and physical activity with the onset of menopause has not been studied yet.

#### **Diet:-**

The effect of nutrition on sex hormone levels and reproductive span has been extensively studied in animal models; however, large prospective studies in humans are scarce. Studies on dietary factors and ANM have conflicting results; and hence, the need for further studies. Caloric restriction particularly during early childhood decreases ANM as evidenced by famous 1944-1945 Dutch famine. Dietary factors influence ANM by virtue of their effect on serum estradiol levels. High intake of fruits and vegetables delays the onset of menopause and prolongs the reproductive lifespan because of the presence of antioxidants in fruits and vegetables that counteracts the adverse effects of reactive oxygen species on the number and quality of ovarian follicles. Higher intake of total calories, high carbohydrate, and high protein intake are found to be associated with delayed age at menopause; however, the correlation of carbohydrate diet with ANM has conflicting results with some studies documenting inverse or no relationship. Dietary fibres, soy products, and red meat have inconsistent results in various studies; and hence, the need for larger studies. High intake of polyunsaturated fats accelerates ANM, while total fat and saturated fat intake has no effect on menopause. Current calcium supplementation and lifelong fish consumption influencing ANM need larger studies for confirmation. Thus; apart from genetic, reproductive, socioeconomic, and demographic factors influencing ANM there has been increasing insight and research in modifiable risk factors like



diet and lifestyle, but still larger prospective studies are needed. There is a growing need of menopausal clinics and health awareness campaigns to initiate preventive strategy specially in developing nations like India where the ANM is 2-3 years earlier than the industrialized nations.

#### **Genetics:-**

If there's no obvious medical reason for early menopause, the cause is likely genetic. Your age at menopause onset is likely inherited.

Knowing when your parent started menopause can provide clues about when you'll start your own. If your parent started menopause early, you're more likely than average to do the same.

However, genes tell only half the story.

#### **Chromosome issues:-**

Some chromosomal issues can lead to early menopause. For example, Turner syndrome (also called monosomy X and gonadal dysgenesis) involves being born with an incomplete chromosome.

Women with Turner syndrome have ovaries that don't function as expected. This often causes them to enter menopause prematurely.

Other chromosomal issues can cause early menopause, too. This includes pure gonadal dysgenesis, a variation on Turner syndrome.

In this condition, the ovaries don't function. Instead, periods and secondary sex characteristics must be brought about by hormone replacement therapy, usually during adolescence.

Women with Fragile X syndrome, or who are genetic carriers of the disease, may also have early menopause. This syndrome is passed down in families.

#### **Autoimmune diseases:-**

Premature menopause can be a symptom of an autoimmune disease, such as thyroid disease or rheumatoid arthritis.

In autoimmune diseases, the immune system mistakes a part of the body for an invader and attacks it. Inflammation caused by some of these diseases can affect the ovaries. Menopause begins when the ovaries stop working.

#### **Epilepsy:-**

Epilepsy is a seizure disorder that stems from the brain. Someone with epilepsy is more likely to experience primary ovarian insufficiency, which leads to menopause. Changing hormone

levels due to menopause can affect seizures in people with epilepsy.

An older study from 2001 Trusted Source found that in a group of women with epilepsy, about 14 percent of those studied had premature menopause, as opposed to 1 percent of the general population.

Socioeconomic status, income, and employment. Nine studies (24%, 9/37) examined the relationship between socioeconomic status and the menopausal transition of immigrant women. Higher socioeconomic status was linked to better health. Higher economic attainment was also correlated with higher education and acculturation, which was further linked to healthy habits. Although immigrants' education was rarely acknowledged, having a higher pre-immigration socioeconomic status most often led to further opportunities in their new country. Low education and illiteracy were related to psychological complaints, cognitive impairments, increased odds of reporting negative symptoms, and low overall health status

## **II. CONCLUSION**

As life expectancy increases, so does the time spent in the period of menopause. Women are subjected to the hormonal and biochemical changes that adversely affect their quality of life in this period. Menopause-specific quality of life scales seek to identify and measure the severity of the menopausal symptoms women experience in order to define quality of life during menopause. The quality of life of women entering menopause at earlier ages is thought to be more adversely affected. Ensuring a high quality of life for women in menopause may only be made possible by defining the extent of their quality of life and the factors related to this.

## **ACKNOWLEDGEMENT**

It gives us great pleasure in presenting the review report on 'MENOPAUSE : A MIDLIFE CRISIS'. We would like to take this opportunity to thank our internal guide Mrs. Mugdha Nandedkar for giving us all the help and guidance we needed. We are really grateful for her kind support. The valuable suggestions were very helpful.

## **REFERENCES**

- [1]. Kaur M, Talwar I. Age at natural menopause among rural and urban punjabibrahmin

- females. *Anthropol.* 2009;11:255–8. [Google Scholar]
- [2]. Mishra GD, Cooper R, Tom SE, Kuh D. Early life circumstances and their impact on menarche and menopause. *Women's Health (Lond Engl)* 2009;5:175–90. [PMC free article] [PubMed] [Google Scholar]
- [3]. Joshi S, Khandwe R, Bapat D, Deshmukh U. Effect of yoga on menopausal symptoms. *Menopause Int.* 2011;17:7881. [PubMed] [Google Scholar]
- [4]. Parazzini F. Progetto Menopausa Italia Study Group. Determinants of age at menopause in women attending menopause clinics in Italy. *Maturitas.* 2007;56:280–7. [PubMed] [Google Scholar]
- [5]. Kapur P, Sinha B, Pereira BM. Measuring climacteric symptoms and age at natural menopause in an Indian population using the Greene Climacteric Scale. *Menopause.* 2009;16:378–84. [PubMed] [Google Scholar]
- [6]. Nagata C, Wada K, Nakamura K, Tamai Y, Tsuji M, Shimizu H. Associations of physical activity and diet with the onset of menopause in Japanese women. *Menopause.* 2012;19:75–81. [PubMed] [Google Scholar]
- [7]. Mahajan N, Aggarwal M, Bagga A. Health issues of menopausal women in North India. *J Midlife Health.* 2012;3:84–7. [PMC free article] [PubMed] [Google Scholar]
- [8]. GBD 2019 Collaborators. Global mortality from dementia: application of a new method and results from the Global Burden of Disease Study 2019. *Alzheimer's Dement.* 2021;7:e12200.
- [9]. Mikkola TS, Gissler M, Merikukka M, Tuomikoski P, Ylikorkala O. Sex differences in age-related cardiovascular mortality. *PLoS ONE.* 2013;8:e63347. CAS PubMed PubMed Central Google Scholar
- [10]. McAloon CJ, Boylan LM, Hamborg T. The changing face of cardiovascular disease 2000: an analysis of the world health organisation global health estimates data. *Int J Cardiol.* 2016;224:256–64. PubMed Google Scholar
- [11]. Taylor CM, Pritschet L, Yu S, Jacobs EG. Applying a women's health lens to the study of the aging brain. *Front Hum Neurosci.* 2019. Article PubMed PubMed Central Google Scholar
- [12]. World Health Organization. Research on the menopause in the 1990s: report of a WHO scientific group. Geneva: World Health Organization; 1996.
- [13]. Ambikairajah A, Walsh E, Cherbuin N. Lipid profile differences during menopause: a review with meta-analysis. *Menopause.* 2019.
- [14]. Bhagat M, Mukherjee S, De P. Clustering of cardiometabolic risk factors in Asian Indian women: Santiniketan women study. *Menopause.* 2010.
- [15]. Ghosh A, Bhagat M. Anthropometric and body composition characteristics in pre- and postmenopausal Asian Indian women: Santiniketan women study. *Anthropologischer Anzeiger.* 2010;68:1–
- [16]. Kadam N, Chiplonkar S, Khadilkar A, Divate U, Khadilkar V. Low bone mass in urban Indian women above 40 years of age: prevalence and risk factors. *Gynecol Endocrinol.* 2010;26:909–17
- [17]. Aydin ZD, Erbas B, Karakus N, Aydin O, K-Ozkan S. Sun exposure and age at natural menopause: A cross-sectional study in Turkish women. *Maturitas.* 2005;52:235–48. [PubMed] [Google Scholar]
- [18]. Martin LJ, Greenberg CV, Kriukov V, Minkin S, Jenkins DJ, Boyd NF. Intervention with a low-fat, high-carbohydrate diet does not influence the timing of menopause. *Am J Clin Nutr.* 2006;84:920–8. [PubMed] [Google Scholar]
- [19]. Delavar MA, Hajiahmadi M. Age at menopause and measuring symptoms at midlife in a community in Babol, Iran. *Menopause.* 2011;18:1213–8. [PubMed] [Google Scholar]
- [20]. Singh M. Early age of natural menopause in India, a biological marker for early preventive health programs. *Climacteric.* 2012;15:581–6. [PubMed] [Google Scholar]
- [21]. Valdes A, Bajaj T. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Jul 19, 2022. Estrogen Therapy. [PubMed]
- [22]. Soares CN. Depression and Menopause: An Update on Current Knowledge and Clinical Management for this Critical

- Window. *Med Clin North Am*. 2019 Jul;103(4):651-667. [PubMed]
- [23]. Vishwakarma G, Ndetan H, Das DN, Gupta G, Suryavanshi M, Mehta A, Singh KP. Reproductive factors and breast cancer risk: A meta-analysis of case-control studies in Indian women. *South Asian J Cancer*. 2019 Apr-Jun;8(2):80-84. [PMC free article] [PubMed]
- [24]. Burkard T, Moser M, Rauch M, Jick SS, Meier CR. Utilization pattern of hormone therapy in UK general practice between 1996 and 2015: a descriptive study. *Menopause*. 2019 Jul;26(7):741-749. [PubMed]
- [25]. Polo-Kantola P, Rantala MJ. Menopause, a curse or an opportunity? An evolutionary biological view. *Acta Obstet Gynecol Scand*. 2019 Jun;98(6):687-688. [PubMed]
- [26]. Bansal R, Aggarwal N. Menopausal Hot Flashes: A Concise Review. *J Midlife Health*. 2019 Jan-Mar;10(1):6-13. [PMC free article] [PubMed]
- [27]. Caruso D, Masci I, Cipollone G, Palagini L. Insomnia and depressive symptoms during the menopausal transition: theoretical and therapeutic implications of a self-reinforcing feedback loop. *Maturitas*. 2019 May;123:78-81. [PubMed]
- [28]. Katon JG, Zephyrin L, Meoli A, Hulugalle A, Bosch J, Callegari L, Galvan IV, Gray KE, Haeger KO, Hoffmire C, Levis S, Ma EW, McCabe JE, Nillni YI, Pineles SL, Reddy SM, Savitz DA, Shaw JG, Patton EW. Reproductive Health of Women Veterans: A Systematic Review of the Literature from 2008 to 2017. *Semin Reprod Med*. 2018 Nov;36(6):315-322. [PMC free article] [PubMed]
- [29]. Kling JM, Clarke BL, Sandhu NP. Osteoporosis prevention, screening and treatment: a review. *J Womens Health* (2014) 23(7):563-72. Doi: 10.1089/jwh.2013.4611CrossRef | Google Scholar
- [30]. Krum SA, Brown M. Unraveling estrogen action in osteoporosis. *Cell Cycle* (2008) 7:1348-52. Doi: 10.4161/cc.7.10.5892PubMed Abstract | CrossRef Full Text | Google Scholar
- [31]. Gartlehner G, Patel S, Viswanathan M, Feltner C, Weber RP, Lee R, et al. Hormone therapy for the primary prevention of chronic conditions in postmenopausal women: an evidence review for the US Preventive Services Task Force: Evidence Synthesis No: 155. Agency for Healthcare Research and Quality:2017. AHRQ publication 15-05227-EF-1. Agency for Healthcare Research and Quality (2017)Google Scholar
- [32]. Byun JH, Jang S, Lee S, Park S, Yoon HK, Yoon BH, et al. The efficacy of bisphosphonates for prevention of osteoporotic fracture: an update meta-analysis. *J Bone Metab* (2017) 24(1):37-49. Doi: 10.11005/jbm.2017.24.1.37PubMed Abstract | CrossRef Full Text | Google Scholar
- [33]. MacLean C, Newberry S, Maglione M, McMahon M, Ranganath V, Suttorp M, et al. Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. *Ann Intern Med* (2018) 148(3):197-213. Doi: 10.7326/0003-4819-148-3-200802050-00198CrossRef Full Text | Google Scholar
- [34]. Faubion SS, Kuhle CL, Shuster LT, Rocca WA. Long-term health consequences of premature or early menopause and considerations for management. *Climacteric* (2015) 18(4):483-91. Doi: 10.3109/13697137.2015.1020484PubMed Abstract | CrossRef Full Text | Google Scholar
- [35]. Manson JE, Aragaki AK, Bassuk SS, Chlebowski RT, Anderson GL, Rossouw JE, et al. Menopausal estrogen-alone therapy and health outcomes in women with and without bilateral oophorectomy: a randomized trial. *Ann Int Med* (2019) 171(6):406-14. Doi: 10.7326/M19-0274PubMed Abstract | CrossRef Full Text | Google Scholar
- [36]. Col NF, Kim JA, Chlebowski RT. Menopausal hormone therapy after breast cancer: a meta-analysis and critical appraisal of the evidence. *Breast Cancer Res* (2005) 7:R535-40. Doi: 10.1186/bcr1035PubMed



- Abstract | CrossRef Full Text | Google Scholar
- [37]. The North American Menopause Society. Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society. *Menopause* (2015) 22(11):1155–74.  
Doi: 10.1097/GME.0000000000000546PubMed Abstract | CrossRef Full Text | Google Scholar
- [38]. Faubion SS, Sood R, Kapoor E. Genitourinary syndrome of menopause: Management strategies for the clinician. *Mayo Clinic Proc* (2017) 92(12):1842–9.  
Doi: 10.1016/j.mayocp.2017.08.01CrossRef Full Text | Google Scholar
- [39]. David PS, Kling JM, Vegunta S, Faubion SS, Kapoor E, Mara KC, et al. Vasomotor symptoms in women over 60: results from the Data Registry on Experiences of Aging, Menopause, and Sexuality (DREAMS). *Menopause* (2018) 25(10):1105–1100.  
Doi: 10.1097/GME.0000000000001126PubMed Abstract | CrossRef Full Text | Google Scholar
- [40]. The North American Menopause Society. The North American Menopause Society Statement on Continuing Use of Systemic Hormone Therapy After Age 65. *Menopause* (2015) 22(7):693.  
Doi: 10.1097/GME.0000000000000492PubMed Abstract |