CHAPTER 1

Clinical Symptomatology of Menopause

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Perimenopause or menopausal transition is a period where many physiological changes take place and it occurs on an average four years before the final menstrual period. At this time, menstrual cycles become irregular due to hormonal fluctuations. In some women, it is accompanied by hot flashes, sleep disturbances, mood swings and vaginal dryness. This definitely affects her quality of life. At the same time, changes in lipid profile and bone loss can have long-term health implications. Almost 80% of the women develop hot flashes but surprisingly only 20% seek medical help. Few symptoms vanish after some time and few persist even after menopause and few get worsened in late menopause.[1]

BASIC PATHOPHYSIOLOGY

Menopause is diagnosed retrospectively by history and sometimes it remains symptomless except for history of cessation of menstruation. All changes of menopause are basically due to ovarian failure due to depletion of ovarian follicles. There is rise in FSH level due to absence of negative feedback from the ovary. Due to atresia in the follicular apparatus, there is decreased production of estrogen and inhibin resulting in reduced inhibin levels and elevated FSH levels, a cardinal sign of menopause.[2]

Markers for diagnosis of menopause are not used to diagnose it routinely and are preferably restricted for use in special situations. Levels of follicular-stimulating hormone (FSH) >10 IU/L are indicative of declining ovarian function. Levels >20 IU/L are diagnostic of ongoing ovarian failure in perimenopausal patients with vasomotor symptoms (VMS) even if there is no cessation of menstruation. FSH levels obtained two months apart and >40 IU/L are diagnostic of menopause. Other features are decrease in AMH and inhibin levels and reduction in antral follicular count accompanied by decrease in ovarian volume. Menstrual irregularity is the most important objective marker of menopausal transition.

TERMINOLOGY

- ***Natural or spontaneous menopause:*** It occurs after 12 months of amenorrhea for which there are no obvious pathological and physiological causes. It is a retrospective diagnosis. It occurs due to depletion of ovarian follicles resulting in near complete,

but natural diminution of ovarian hormone secretion. There is no independent biological marker for menopause.

- ***Perimenopause:*** It is usually a period of 3–5 years prior to and one year after the menopause. At this time, due to anovulatory cycles, there is irregularity in menstrual cycles.
- ***Menopause transition:*** It is the term coined by Stages of Reproductive Aging Workshop (STRAW) group, and at this time, usually disturbances in menstrual cycle and hormonal changes are seen (Fig. 1.1).
- ***Post-menopause:*** It is the span of time dating from the final menstrual period, regardless of whether the menopause was spontaneous or iatrogenic.
- ***Premature menopause:*** It is the spontaneous menopause occurring two standard deviations (SDs) below the mean estimated age for the reference population. Traditionally, it is considered to be below the age of 40 years. We may consider it as occurring below 38 years in India.
- ***Surgical/induced menopause:*** It is the cessation of menstruation that follows surgical removal of both ovaries or iatrogenic ablation of ovarian function (by any means like chemotherapy, radiotherapy or treatment with GnRH analogue).
- ***Early menopause:*** It is the time span between the spontaneous or iatrogenic menopause occurring between the age of 40 years and the accepted typical age of menopause for a given population.
- ***Delayed menopause:*** It is not defined but may be important in terms of the increased problems associated with the hyperestrogenism. It is two SDs above from the natural average age of menopause in a given population. It is usually considered to be beyond 54 years.

Menarche — FMP (0)

Stage	-5	-4	-3b	-3a	-2	-1	+1a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*Variable*				*Variable*	1-3 years	2 years (1+1)		3-6 years	*Remaining lifespan*
PRINCIPAL CRITERIA										
Menstrual cycle	Variable to regular	Regular	Regular	Subtle changes in Flow/ Length	*Variable length* persistent ≥7-day difference in length of consecutive cycles	Interval of amenorrhea of >=60 days				
SUPPORTIVE CRITERIA										
Endocrine FSH AMH Inhibin B			Low Low	Variable* Low Low	↑Variable* Low Low	↑>25 IU/L** Low Low	↑Variable* Low Low		Stabilizes Very Low Very Low	
Antral Follicle count			Low	Low	Low	Low	Very Low		Very Low	
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor Symptoms Likely	Vasomotor Symptoms *Most Likely*			*Increasing* symptoms of urogenital atrophy

* Blood drawn on cycle days 2–5 ↑ =elevated

** Approximate expected level based on assays using current international pituitary standard

Fig. 1.1: STRAW—menopause transition

- ***Post-menopausal bleeding (PMB):*** It is the occurrence of vaginal bleeding following a woman's final menstrual cycle and not on cyclical hormone therapy. However, vaginal bleeding that occurs 6 months after amenorrhea should be considered suspicious and warrants investigation.[3]

STRAW +10 Criteria

In 2001, Stages of Reproductive Aging Workshop (STRAW) proposed nomenclature and a staging system for ovarian aging including menstrual age and qualitative hormonal criteria to define each stage. It is widely considered the gold standard for characterizing reproductive aging through menopause. These criteria were summarized and updates were recommended in 2011 (STRAW + 10). STRAW + 10 simplified the bleeding criteria for the stages of menopausal transition, recommended a quantitative cut point for FSH levels characteristic of late transition, and recommended application regardless of women's age, ethnicity, body size, or lifestyle characteristics.

SYMPTOMS DURING PERIMENOPAUSE/ MENOPAUSAL TRANSITION

Women in perimenopause have at least some of the following symptoms:

- Hot flashes
- Breast tenderness
- Worse premenstrual syndrome
- Lower sex drive
- Fatigue
- Irregular periods
- Vaginal dryness; discomfort during sex
- Urinary leakage when coughing or sneezing
- Urinary urgency
- Mood swings
- Insomnia

MENOPAUSAL SYMPTOMS

- Vasomotor symptoms
- Genitourinary symptoms
- Sexual dysfunction
- Neurological symptoms
- Sleep disorders
- Impairment in cognitive functions
- Psychological symptoms
- Cardiovascular diseases
- Musculoskeletal symptoms

VASOMOTOR SYMPTOMS

Vasomotor symptoms are the most common symptoms encountered by perimenopausal women. Vasomotor flush is known as the hallmark of the female menopause, also known as "hot flush" or "hot flash" described as a sudden onset of reddening of the skin over the head, neck and chest, accompanied by an increase in heart rate and a feeling of intense body heat. Sometimes it is followed by profuse perspiration. It may last for a few seconds to several minutes. They are more frequent at night. They are fewer, less intense and shorter in cool environment. It may be preceded by headache or a prodromal awareness that a flush is beginning.

Vasomotor symptom is a major feature of post-menopause, peaking in the first year after the last menses. It can also occur in premenopause. Hot flashes usually last for 1–2 years and can continue for 10 years or longer.

It is the commonest symptom where women seek help. Hot flashes not only disturb women at work and interrupt daily activities, but also disrupt sleep. Basic mechanism is not completely understood but it is thought that it is initiated at the central level in the hypothalamus. Due to increase in core body temperature, metabolic rate and increase in skin temperature, there is vasodilation and sweating. Vasomotor symptoms are a consequence of estrogen withdrawal, not simply estrogen deficiency.[2]

Grades of Hot Flashes

- Mild—feeling of heat without sweating.
- Moderate—feeling of heat with sweating.
- Severe—feeling of heat with sweating and palpitation that disrupts usual activity.

GENITOURINARY SYNDROME OF MENOPAUSE

The genitourinary syndrome of menopause (GSM) is a term used to describe genital symptoms and urinary symptoms. Genital symptoms include dryness, burning, irritation, and sexual symptoms such as discomfort or pain due to lack of lubrication. Common urinary symptoms are urgency, dysuria, and recurrent urinary tract infections. All these symptoms are due to estrogen deficiency. GSM has negative impact on the quality of life of post-menopausal women, so they should be made aware of these problems and treated with an appropriate effective therapy.[4]

Urogenital Atrophy

Estrogen and progesterone receptors are present in the urogenital region as well as the pelvic musculature. Estrogen deficiency after menopause causes atrophic changes in the urogenital tract and is associated with urinary symptoms which may co-exist with symptoms of vaginal atrophy.

It has been found that after menopause, the pH becomes more alkaline and the vaginal environment becomes less hospitable to lactobacilli and more susceptible to infection by urogenital and fecal pathogens. pH >4.5 is almost always observed with estrogen deficiency. Atrophic vagina can also cause itching, irritation and burning due to urogenital atrophy. Urethral and bladder mucosal thinning occurs which leads to urethritis with dysuria, urge incontinence and urinary frequency. Infecting organisms can ascend into the urinary system to cause urethritis, urinary tract infections and cystitis.

Sexual Dysfunction

Estrogen deficiency can lead vaginal dryness and dyspareunia. There is reduction in rate of production and volume of vaginal lubricating fluid, and there is some loss of vaginal elasticity and thickness of epithelium. Also there is dyspareunia associated with a feeling of dryness and tightness, vaginal irritation and burning with coitus, and post-coital spotting and soreness. But a woman's sexual response may be significantly related to non-hormonal factors also such as partner's age and health, conflict between partners, insomnia, inadequate stimulation, etc. Life stresses can also lead to sexual dysfunction. So the sexual dysfunction in menopause is multifactorial and needs to be addressed accordingly.

SYMPTOMS RELATED TO CNS SYSTEM

Insomnia

A detailed history of menopausal woman should include questions about sleep pattern. Sleep diaries can be useful to assess sleep in detail.

Medical or psychiatric causes of insomnia should be ruled out and if present, should be treated accordingly.

Psychological Symptoms

It is observed that many menopausal women show depressed mood, anxiety, irritability, mood swings, emotional liability, lethargy and lack of energy have been associated with the menopause. Psychological problems experienced during the menopause are likely to be associated with past problem and current life stresses. Although most women undergo this transition to menopause without experiencing psychiatric problems, some of them have depression at some point during menopause. Studies of mood during menopause have generally revealed an increased risk of depression during perimenopause or menopausal transition with a decrease in risk during post-menopausal years.

Dementia

Dementia is a syndrome which is progressive and chronic. Usually there is deterioration in cognitive function (difficulty in thought process). Here severity is more than expected due to normal aging. It affects thinking,

memory, comprehension, orientation, calculation, judgement and language. It is also accompanied by deterioration in emotional control, motivation as well as social behaviour.

Presence of impairment in any two functions is suggestive of dementia:

- Memory
- Communication and language
- Ability to focus and pay attention
- Reasoning and judgment
- Activities of daily living
- Visual perception.

CARDIOVASCULAR AND METABOLIC EFFECTS ASSOCIATED WITH MENOPAUSE

After the age of 50, almost half of the deaths are due to some form of cardiovascular disease. In women after menopause, cardiovascular disease is the biggest cause of death but still unfortunately there is low level of awareness.

The detailed discussion about cardiovascular system and menopause is dealt with separately in a subsequent chapter.

MUSCULOSKELETAL EFFECTS ASSOCIATED WITH MENOPAUSE

Osteoporosis

The National Institute of Health definition says, "it is a disease characterized by decreased bone strength and propensity to fall". The diagnosis of an osteoporotic fracture, the clinical end-point of osteoporosis is by the presence of fragility fracture (clinical or by investigation) and or by BMD. In the Chapter 10 "Post-menopausal osteoporosis", we have discussed in detail about the approach to its diagnosis and management.

Sarcopenia

Menopause is associated with an increase in visceral adiposity as well as a decrease in bone density, muscle mass and muscle strength. This decline in muscle mass, known as sarcopenia, is frequently observed in post-menopausal women.[5] This topic is discussed in detail in the subsequent chapter.

MENOPAUSE—PAST, PRESENT AND FUTURE

Menopause brings many physiological changes in woman's life which affect her quality of life so it is considered as the most significant event. There have been a lot of speculations about the symptoms that appear before, during and after the onset of menopause.

Menopause is a transition phase from the reproductive to the non-reproductive in a woman's life. It is nature's protective phenomenon against reproductive morbidity and mortality in the aging population. Post-menopause is a relatively long period of a woman's life with changes started from ovaries and accompanied with biological, psychosomatic, psychological and in some cases behavioral symptoms.

Today, we are aware that menopause has much wider implications than simply loss of fertility as it accelerates the process of non-communicable disorders. In 1947, when India achieved independence, the average life expectancy was approximately 32 years and now it is about 72 years. In India, the estimated mean age of menopause is 46.7 years. Women now live one-third of their lives after menopause.

It is important to discuss about clinical signs and symptoms, not only in perspective of menopause transition and early menopause but also for late menopause so that by addressing them, quality of life can be improved. The peri- and post-menopausal women of present era have various important responsibilities. Some may be house makers others may be working women going out and performing their duties. In any case, bothersome menopausal symptoms can affect her performance. Menopause should not pause her from having good quality of life and freedom to live with fitness, strength

and independence. In future era, menopausal women may need to have more independence from various aspects of life including health as one of the major criteria.

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