NARCHI BULLETIN

Sir Ganga Ram Hospital, New Delhi, 2024-25

March 2025, Issue 4

THEME: "THE CHANGE: MENOPAUSE AND BEYOND"

UPDATEKNOWLEDGEUPGRADESKILLSUPLIFTWOMEN'SHEALTH

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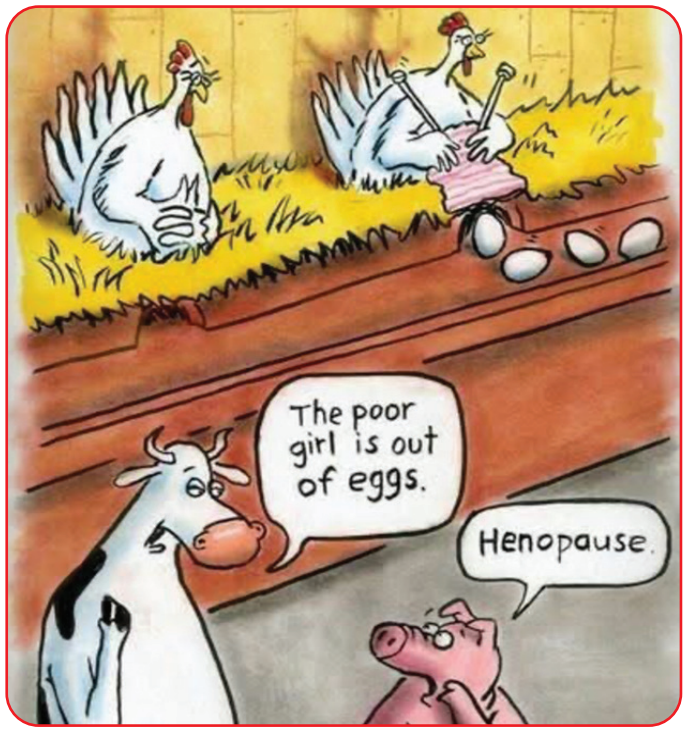
As average lifespans across the world increase, the fact that women live more than a third of their lives without the benefit of their hormones, starts to sink in.

How many of us consider menopause as an issue that, some "highly strung" women unnecessarily make a big deal of? As guardians of women's health and our own, how many of us are aware of the immediate and long-term effects of menopause: the permanent cessation of ovarian activity. That the physical, neurological and psychological symptoms, once considered a result of poor adaptation to ones psychosocial environment, now form a symptom complex of menopause that are known to be the direct effects of hormone cessation.



Generation X is now reaching the menopausal age. Gripped less by the shackles of patriarchy than a generation before them, this generation is more voluble in voicing its concerns and is unwilling to take a casual attitude from health care providers, lying down. They are seeking answers through their phones, through social media and through sharing of information across borders. As women's health care providers, it is our responsibility to ensure they get the right information and the right treatments whenever indicated.

This bulletin aims to do just that: To update ourselves on the various effects of menopause, and to learn a nuanced approach of when and how to intervene with HRT, if at all.

Sincerely,
The editorial team
Mamta Dagar, Ruma Satwik, Sakshi Nayar

Contents

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Warm greetings to everyone !

It is our pleasure and privilege to wish everyone a happy Holi - the festival of colours. Similarly, we also thrive in different and exuberant environment of academics, social, clinical and skill up grading activities. The Institute of Obstetrics and Gynecology at Sir Ganga Ram Hospital organized CME on Adolescent health on International women's day which was a great success. NARCHI Delhi Chapter took pride and an opportunity to felicitate and thank eminent clinicians who have contributed immensely with dedication and commitment for the women's health.

The theme of this bulletin is **"The Change: Menopause and beyond"**. As women's health care providers, we are custodians of her health during menopause and beyond. Due to improved living conditions, the life expectancy of Indian women is 75 years as of 2024. Nowadays, she is spending one third of her life in oestrogen deficient stage. The awareness about the menopausal transition and their consequences is important among the gynaecologists.

The stages of reproductive age have been elaborately described by Dr. Mamta Dagar. The vasomotor symptoms of menopause have been vividly portraid by Dr. Shelly Arora. The menopause and aging bring with it neurocognitive symptoms which has been readily dealt with by Dr. Renuka Malik. The aging process and menopause brings with it various musculo-skeletal syndrome, nicely highlighted by Dr. Geeta Mediratta. The genito-urinary syndrome of menopause has been rightly addressed by Dr. Sonal Bathla. The various management options and medications of MHT has been critically reviewed by Dr. Jyoti Bhaskar, Dr. Meenakshi Ahuja has deliberated on types, preparations and routes of MHT delivery. Dr. Priti Dhamija has adequately dealt with MHT prescription for different metabolic health. Risk types. So, comprehensively, we all will be highly knowledgeable about the physiology, various symptoms and syndromes as well as management options of menopause.

We hope this bulletin adds extra dimensions to our already existing knowledge and information revolving around menopause and mature women's health. The scientific contributions by all eminent writers will be of immense help in adding greater outlook in understanding and management of menopausal problems. We shall be really happy if this bulletins adds as well as widens arena and approach of our members towards menopause and their problems and management. Hope, the shared knowledge benefits them in their day to day clinical practice.

Long live NARCHI Delhi Chapter !!

Stages of Reproductive Aging

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Introduction

Menopausal health is globally gaining significance as longevity in women has increased while the age of menopause has practically remained the same.Though the age at which menopause occurs varies, but menopausal symptoms often begin a few years before the final menstrual period (FMP) and continue several years after or until late into menopause. Ultimately these effects have a large impact on women's physical and psychosocial well-being. The early symptoms and later complications of menopause follow a sequential pattern due to gradual, progressive estrogen deprivation. Throughout her life, a woman plays different social roles, viz. daughter, wife, mother, grandmother and caregiver, which influence the health of her family. While older men have the privilege to retire from work, women are never relieved of their social responsibilities. At this stage, the protective advantage of hormones is lost and women become more vulnerable to certain diseases than men.

Menopause - is it a Disease?

Menopause is a physiological event similar to menarche, pregnancy and the postpartum period. At each stage of the reproductive stage, there is a change in the hormonal milieu which bring about varied changes and challenges in the woman's physical and emotional well-being. Menopause is the most notable event for women at mid-life. Estrogen deprivation associated with menopause, not only causes the undesirable symptoms but also the long-term health consequences. Therefore this natural phenomenon has been listed as a Disease in International Classification of Diseases. A well-managed menopause transition sets the stage for active and healthy aging.

A healthy woman is able to cope with the challenges, for nature brings about physiological changes in the body to compensate for the physical and emotional demands at each life events. Natural biomarkers signal the need to give the additional care in these vulnerable phases of a woman's life to maintain health, prevent complications and give quality of life.

Is Staging Necessary?

Staging systems are primarily used as research and clinical tools. They help in communication, to maintain a common language, understand the progress of disease or physiology and help in clinical management.

Menopause is a physiological event and staging is important in research of midlife women, particularly for studies of menopausal symptoms, aging and the role of reproductive hormones in various diseases. Menopausal status classification is also important to clinicians for treating midlife women. Clinicians need to be able to identify perimenopausal women in order to counsel them, on the ways to reduce their risk for chronic diseases, such as osteoporosis and heart disease. And help them to provide treatment options for menopausal symptoms, such as hot flushes and night sweats. An individual patient develops different needs at various stages of menopause. Therefore, a competent physician will try to alter management according to the individual needs of each patient. Such tailor-made ideal management is easily possible through a simple user-friendly staging system.[1]

Staging Systems

Menopause is described by the World Health Organization (WHO) as "the permanent cessation of menstruation resulting from the loss of ovarian

follicular activity".[2]

- **Menopause:** It occurs with the FMP, which is known with certainty only in retrospect a year or more after the event.
- **Perimenopause:** The term "perimenopause" includes the period immediately prior to menopause and the first 12 months after menopause.
- **Post-menopause:** It refers to the time dating from the FMP, regardless of whether the menopause was natural or brought on (Fig. 1)[3].

The age at which the menopause occurs varies, ranging from late 30s to late 50s, but menopausal symptoms often begin a few years before the FMP and continue several years after.[4]

- **Climacteric:** This refers to the period before and after menopause during which ovarian activity diminishes and gradually ceases. This period may start as early as 2 years prior to menopause and its effect may extend for 2 decades or more after menopause.[4]

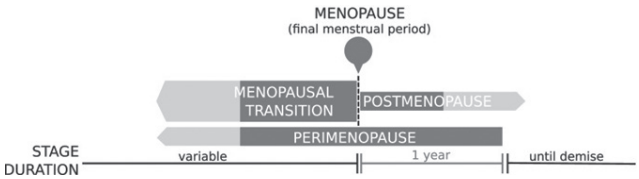

Figure 1: Time periods surrounding the menopause Source[3]

Anklesaria Menopausal Staging[5]

In 1997, Anklesaria published for the first time, a simple staging of menopause to help deal with perimenopausal symptoms and expected postmenopausal complications. This was based on the premise that the symptomatology of menopause comes in a chronological order. Stages may overlap due to individual variation. Dr. Behram Anklesaria in 1996 published this simple three-stage staging system for the menopause transition (Table 1).[5]

This staging of menopause was adopted and utilized for clinical purposes and treatment of menopause. Henceforth, it shall be referred to as Modified Anklesaria's IMS consensus group staging.

Dr. Behram Anklesaria wrote for the Federation of Obstetric and Gynaecological Societies of India (FOGSI) FOCUS in 2010 that individualized management of 40+ women with their diverse cultural and regional needs is not possible without clinical categorization. Individualization of treatment involves another more important aspect. The same "woman" develops different needs at various "stages" of menopause. Hormone therapy and other interventions are now critically "time bound". For example, the "window of opportunity" period for initiation of long-term hormone replacement technology (HRT) happens to correspond exactly with Stage II of this system.[5]

Stage I

From the earliest perimenopausal symptoms (usually vasomotor instability or menstrual irregularity) to menstrual cessation. This stage can last from 3 years to 5 years.

Stage II

Five years after menopause, this stage is further subdivided into stage IIA and stage IIB.

Stage IIA: From the cessation of menstruation up to 1 year (i.e., up to confirmation at menopause by WHO definition).[2,4] The main symptoms of menopause during this are the urethral syndrome and vasomotor instability.

Stage IIB: From end of stage IIA up to 4 years. The symptoms are as follows:

- Atrophic symptoms, vaginitis, dyspareunia
- Urinary symptoms
- Weight gain

Table 1: Anklesaria's stages of menopause

Stage	Time	Events	Action
I	3-5 years before menopause	IA: Menstrual irregularity IB: Vasomotor instability IC: Early psychosomatic	Establish communication
II	IIA: Up to 1 year post menopause IIB: Up to 5 years post menopause	Confirmation Local atrophic changes Late psychosomatic symptoms	Treat
III	Beyond 5 years post menopause	IIIA: Late atrophic changes IIIB: Ischemic heart disease IIIC: Osteoporosis IIID: Very late complication (e.g. cerebrovascular accidents, Alzheimer's disease, etc.)	Prevent

- Skin and hair changes
- Genital prolapse
- Late psychological symptoms
- Sexual disorders

Stage III

From 5 years after menopause up to an indefinite period; probably lifetime.

Stage III A: Residual atrophic symptoms

Stage IIIB: Stage of ischemic heart disease and early osteoporosis

Stage IIIC: Very late complications, e.g. cerebro vascular changes and Alzheimer's disease

The Five-year Rule of Thumb by Anklesaria Staging System

Duration of each stage is highly variable, but a rough 5 years per-stage calculation is clinically useful. Consider a case of a lady who reaches her menopause at the age of 50 years that can lead to the following:

Approximations

- 45 years to 50 years: She is in stage I when she needs initial counseling.
- 50 years to 55 years: She will be in stage II, the window of opportunity for treatment.
- 55 years to 70 years: She will go through the earlier Stage III complications, which can be prevented.
- At above 70 years: She will enter stage IIID and beyond. She will now need very different management than the earlier stages.

Strengths

The system is based on FMP and symptoms and meant for use by the clinician to address and plan the menopause transition and beyond. Moreover, there is a lot of variability in the biomarkers used for diagnosis of menopause. None of them have been validated for use to exclusively determine menopause status. Various studies have demonstrated the onset of early cycles as a hallmark of menopause.

The findings from the Women's Ischemia Syndrome Evaluation (WISE) study suggest that a menstrual status classification algorithm that relies solely on bleeding data can effectively distinguish among premenopausal, perimenopausal and postmenopausal women. Although it is not recommended that hormone levels alone be used to determine menopausal status, the approach used by the WISE algorithm combining hormone measurements with age and bleeding history may be well-suited for study populations and clinical samples in epidemiological studies.[6]

Limitations

The limitations of stage I are retrospective and there can be a recall bias. It cannot be used for premature ovarian insufficiency infertility, or hormone-based research studies.

Straw (2001) Menopausal Staging[7,8]

Stages of reproductive aging workshop members considered a number of potential components of a staging system: menstrual cycles, hormonal factors, fertility, signs and symptoms in other organ systems and uterine and ovarian anatomy. The anchor for the staging system is the FMP. Prior to the FMP there are five stages (Fig. 2); the age range and duration for each of these five stages are variable.

Criteria for STRAW Staging System

An ideal staging system would adhere to the following criteria:

- Use only objective data because symptoms are inherently subjective
- Employ only reliable tests that are relatively inexpensive and readily available
- Allow women to be placed in the appropriate stage prospectively

Inclusion in one stage precludes placement in another stage.

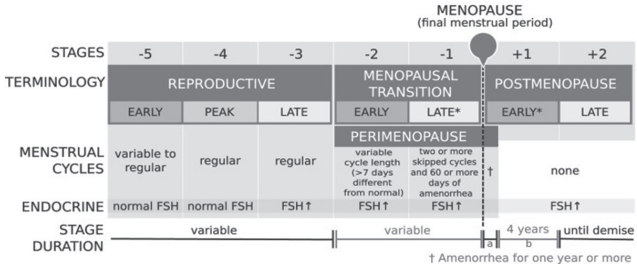

Figure 2 Straw classification source.[7]

This staging system is not applicable in the following circumstances:

- Cigarette smoking
- Extremes of body weight [body mass index (BMI) <18 or >30 kg/m2]
- Heavy exercise (>10 hour/week of aerobic exercise)
- Abnormal uterine anatomy (e.g. fibroids)
- Chronic menstrual cycle irregularity
- Prior hysterectomy
- Abnormal ovarian anatomy (e.g. endometrioma)

The Stages of Reproductive Aging Workshop+10 (Straw+10, 2011)

On September 20 and 21, 2011, a workshop was held in Washington to address the unfinished agenda of menopausal staging started 10 years back in 2001, i.e. STRAW+10.[9]

STRAW+10 simplified bleeding criteria for the early and late menopausal transition, recommended modifications to criteria for the late reproductive stage Stage III and the early postmenopause stage Stage+1, provided information on the duration of the late transition Stage I and early postmenopause Stage +1 (Fig. 3).[10]

The need for restaging:

- To reevaluate criteria for the onset of late reproductive life and early menopausal transition, given new population-based data relating to follicle-stimulating hormone (FSH), antral follicle count (AFC), anti- Müllerian hormone (AMH), and inhibin-B
- To re-evaluate criteria for staging postmenopause, given new population-based data on changes in FSH and estradiol concentrations after FMP
- To reevaluate applicability to women based on variations in body size, lifestyle characteristics and health status To identify remaining gaps in scientific knowledge and
- research priorities

The objectives are:

- Rely primarily on objective data
- Use widely available, reliable, noninvasive and inexpensive tests
- Allow for prospective classification of women
- Permit unambiguous classification of women into a unique stage

In addition, it was concluded that the modified staging system should:

- Retain the same widely accepted nomenclature
- Consider menstrual cycle criteria to remain the most important criteria given the continuing lack of international standardization of biomarker assays as well as their cost and or invasiveness, particularly in the context of resource-poor countries
- Consider biomarker criteria as supportive criteria given the lack of assay standardization (supportive criteria are to be used only as necessary and should not be interpreted as required for diagnosis)
- Use criteria that are independent of age, symptoms and pathology (because no universal menopausal syndrome has been established across ethnic groups, two key symptoms are incorporated only as descriptive additional information that may support other criteria in assessing stage)

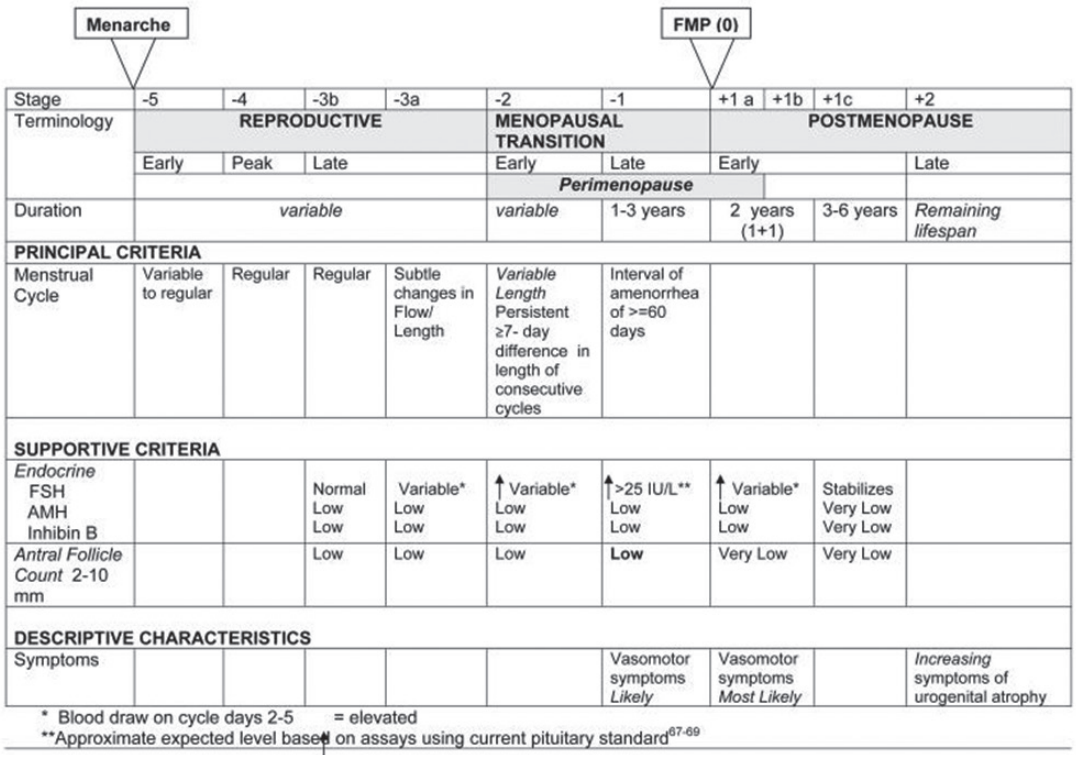

Fig: 3 Source[9]

Strengths

Evidence now supports the applicability of the STRAW+10 recommendations for most women. Epidemiologic and clinical studies have documented that the process of reproductive aging, although influenced by demographic factors, lifestyle and BMI, follows a robust and predictable pattern. Although smoking and BMI influence hormonal levels and the timing of transition, these factors do not alter the trajectory of change in bleeding patterns or hormonal levels with reproductive aging. Therefore, the STRAW+10 staging system is applicable to women regardless of age, demographic, BMI or lifestyle characteristics.

Limitations

Lack of standardized assays for key biomarkers remains an important limitation in efforts to stage reproductive aging and to translate research findings to cost-effective clinical tools. Given the importance of AMH in relation to fertility and its relative stability across the menstrual cycle, the development of an international standard for the assessment of AMH is of paramount importance.

Empirical analysis across multiple cohorts is needed to specify precise menstrual cycle criteria for stages IIIB and -IIIA.

Studies are needed to characterize the hormonal changes of postmenopause from stage +1 to stage +2 because data across these stages are limited; several cohort studies are well-positioned to provide this information. The development of highly sensitive, well- characterized assays is needed.

- Given that the large cohort studies of midlife women were initiated before the STRAW staging system was developed, these cohorts should be supported to apply the STRAW+10 staging criteria to reanalyze key findings on the clinical changes that occur across the menopausal transition.
- Improved characterization of the pattern, timing and level of reproductive biomarkers across nations is necessary, especially to provide data on the experience of women from low-resource countries.
- Research is needed to better understand the process of reproductive aging and appropriate staging criteria for women with polycystic ovary syndrome (PCOS) and primary ovarian insufficiency (POI) and those who have had removal of a single ovary and/or hysterectomy.
- Research is needed to better evaluate staging in women with chronic illness such as HIV infection and those who are undergoing cancer treatment.

Conclusion

The health and social status of women beyond reproductive years clearly highlights the need for greater thrust on healthcare activities as well as social security mechanisms which can cater to their special needs. There is a growing need for separate interventions based on simple and scientific clinical staging to ensure the health of such a vulnerable group. In the current scenario, the major concern that arises is the timing of interventions in the management of menopausal symptoms.

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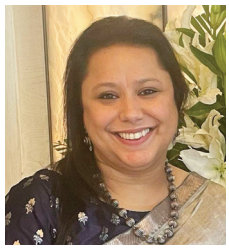
Vasomotor Symptoms of Menopause



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'Menopause' is derived from the Greek term for cessation of the last monthly period. Menopause is a physiological event that is recognised after 12 consecutive months of amenorrhea for which no other obvious pathological or physiological cause is present. The years leading up to and the year beyond menopause are known as 'perimenopause', a phase marked by fluctuating and eventually decreasing levels of estrogen. Although physiological, menopause has important adverse short- and long-term effects on health.

Vasomotor symptoms (VMS) are short-term effects resulting from estrogen deficiency, characterised by hot flashes, cold sweats, and night sweats. They are the most common complaints affecting up to 80% of women, although only 10% to 20% seek medical advice. This chapter explores the pathophysiology, prevalence, clinical presentation, and management strategies for vasomotor symptoms during menopause.

Clinical Presentation

A 'hot flush' is an uncomfortable subjective feeling of warmth in the upper part of the body, typically affecting the face, neck, and upper chest, usually lasting around 3-4 minutes. Flushing is a visible reddening of the skin, particularly on the face and upper body, which can accompany sweating and is sometimes preceded by nausea, anxiety or palpitations. Night sweats may be particularly troublesome, leading to severe insomnia and chronic tiredness.

About 20% of women begin experiencing flushes while still menstruating regularly. Flushes usually subsides as the body adjusts to the new lower estrogen concentrations. The onset and duration of VMS are variable. Findings from the Study of Women's Health Across the Nation (SWAN) show that VMS lasts an average of 7.4 years.[1]

In around 10% of women, symptoms may persist for more than a decade.[1] Vasomotor symptoms may affect quality of life and mood. Early onset and persistently high VMS, have been associated with more adverse health and psychosocial issues than low VMS.[2]

Pathophysiology of Vasomotor Symptoms

The pathophysiology of VMS remains not fully understood and is likely influenced by multiple factors. Hot flashes are mediated by thermoregulatory dysfunction at the level of the hypothalamus and are induced by estrogen withdrawal. A narrowing of the thermoneutral zone has been described, the feeling of warmth results from inappropriate peripheral vasodilatation with increased digital and cutaneous blood flow. Perspiration results in rapid heat loss and a decrease in core body temperature below normal. Shivering may then occur as a result of temperature lowering. The exact mechanisms result from an interplay among the central nervous system, endocrine components, and the peripheral vascular system.[3]

One aspect of the mechanism of VMS involves the interaction of kisspeptin, neurokinin B, and dynorphin (KNDy) neurons within the hypothalamus.[4] These neurons are influenced by low levels of circulating estrogens and gonadotropins and become hypertrophied after menopause. Emerging research suggests that

targeting and blocking the KNDy neuron system may be an effective approach for treating VMS.[5]

Prevalence

The incidence of hot flushes increases typically during perimenopause, reaches the highest during the first 2 years of post-menopause and then declines over time.

Prevalence varies across different ethnic groups. In the SWAN, the highest rate of VMS is seen in African- Americans (46%), followed by Hispanics (34%), Whites (31%), Chinese (21%) and Japanese (18%).[6]

In a study conducted by the Indian Menopause Society (IMS), out of 1801 women, 192 women were asymptomatic, and 1609 reported symptoms. VMS were reported by 75.3%, psychological symptoms by 62%, physical ailments by 32% and genitourinary by 15.5%.[9]

Risk factors

Epidemiologic studies have been conducted to identify risk factors for vasomotor symptoms.

1. Racial and ethnic differences have been found to play a significant role in the reporting of these symptoms in various observational studies. For example, the Study of Women's Health Across the Nation, which assessed menopausal symptoms in 14,906 women aged 40–55 years from diverse ethnic backgrounds in the United States, found that Black and Hispanic women have higher incidences of VMS, followed by White women and Asian women, who have the lowest incidence. [6]
2. Women of lower socioeconomic status and education may be more affected than those with higher incomes and levels of education.
3. Women with obesity, especially those with increased abdominal adiposity, tend to have more VMS than women who are not obese.[7]
4. Smoking
5. Reduced physical activity

Vasomotor symptoms (VMS) are increasingly recognised as more than just bothersome symptoms; they are also a marker for disease. VMS has been independently associated with cardiovascular disease, as women experiencing these symptoms tend to have less favourable cardiovascular risk profiles and a higher burden of subclinical disease. This understanding could eventually lead to a shift in clinical practice, where the focus of VMS treatment moves from merely managing symptoms to preventing disease.[8]

Differential Diagnosis

Most often, the clinical situation points to the diagnosis of menopausal flushing. Flushing can be caused by other pathological diseases and medications.

Medications: Calcium channel blockers, antiestrogens like raloxifene, aromatase inhibitors, bromocriptine, cholinergic drugs, opiates, and alcohol.

Systemic diseases: Thyroid diseases, carcinoid syndrome, pheochromocytoma, Horner's syndrome, anxiety, spinal cord lesions, recurrent UTI

Management of Vasomotor Symptoms

The management of vasomotor symptoms focuses on alleviating the intensity and frequency of hot flashes and night sweats.

General principles for the management of hot flashes include

a) Symptom intensity and frequency.

b) Medical history – Is the patient a candidate for menopausal hormone therapy (MHT)?

c) Personal choice – Is the patient interested in MHT?

d) Coexistence of other menopausal symptoms, such as depression, as these women often require treatment with both MHT and antidepressants (usually selective serotonin reuptake inhibitors [SSRIs])

Treatment strategies can be divided into hormonal and non-hormonal approaches.

Nonpharmacological Options (Behavioural and Lifestyle changes)

Counselling has an important role to play in encouraging lifestyle modification:

- Wear layered clothing
- Use cooling methods such as hand-held fans, drink cold water
- Try relaxation methods such as paced, deep breathing
- Avoid triggers such as caffeine, spicy food, alcohol, tobacco
- Engage in regular exercise especially if overweight

Table 1. Treatment Options for Menopausal Vasomotor Symptoms

Treatment	Dosage/Regimen	Evidence of Benefit*
Hormonal		
Estrogen-alone or combined with progestin		
• Standard Dose	Conjugated estrogen 0.625 mg/d	Yes
	Micronized estradiol-17β 1 mg/d	Yes
	Transdermal estradiol-17β 0.0375-0.05 mg/d	Yes
• Low Dose	Conjugated estrogen 0.3-0.45 mg/d	Yes
	Micronized estradiol-17β 0.5 mg/d	Yes
	Transdermal estradiol-17β 0.025 mg/d	Yes
• Ultra-Low Dose	Micronized estradiol-17β 0.25 mg/d	Mixed
	Transdermal estradiol-17β 0.014 mg/d	Mixed
Estrogen combined with estrogen agonist/ antagonist	Conjugated estrogen 0.45 mg/d and bazedoxifene 20 mg/d	Yes
		Yes
	Depot medroxyprogesterone acetate	No
Progestin		Yes
Testosterone	2.5 mg/d	No
Tibolone		
Compounded bioidentical hormones		
Nonhormonal		
SSRIs and SSNRIS		No
Paroxetine	7.5 mg/d	Yes
Clonidine	0.1 mg/d	Yes
Gabapentin	600-900 mg/d	Yes
Phytoestrogens		No
Herbal Remedies		No
Vitamins		No
Exercise		No
Acupuncture		No
Reflexology		No
Stellate-ganglion block		Yes

(Table 1 courtesy: ACOG Practice Bulletin: Management of Menopausal Symptoms, No.141; Jan 2014.)

- Yoga
- Remove yourself from stressful situations

Despite limited supporting data, the above lifestyle solutions are reasonable measures for the management of mild vasomotor symptoms. Although they may provide other health benefits, cannot be recommended for the treatment of moderate-severe bothersome VMS because of lack of evidence for efficacy.

Cognitive behavioural therapy (CBT) has been shown in several studies as an effective strategy to manage VMS. MENOS1 and MENOS2 are cognitive behaviour therapy protocols that may have a positive effect on VMS. In a recent study, CBT-Meno was effective in reducing the combination of self-reported VMS symptoms, sleep, depressive symptoms, and sexual concerns.[10]

Pharmacological options (HORMONAL)

Menopausal hormone therapy (MHT) is the most effective treatment for managing vasomotor symptoms (VMS). A Cochrane systematic review of randomised controlled trials found that MHT, whether estrogen alone or estrogen combined with a progestogen, significantly reduced the frequency of hot flashes by 75% compared to placebo, as well as decreased symptom severity.[11] MHT can be safely initiated in healthy women under 60 years old or those who are less than 10 years post-menopause,

provided they have no contraindications. VMS can be relieved with standard MHT doses as soon as 2 weeks after beginning therapy.

Data do not support the use of progestin-only medications, testosterone, or compounded bioidentical hormones for the treatment of vasomotor symptoms.

General Principles of Prescribing Hormonal Therapy:

1. In women with a uterus, estrogen is provided along with a progestogen; for women who have had a hysterectomy, estrogen therapy is used alone. The estrogen component serves to alleviate bothersome symptoms, whereas the progestogen component provides endometrial protection.
2. An initial assessment should include screening for MHT contraindications.
3. MHT doses should be titrated to the desired effect when managing VMS, beginning with low to standard estrogen doses. These doses can be modified based on symptom improvement or the occurrence of side effects.
4. There is no specific time frame or duration for systemic MHT use. Periodic re-evaluation of a patient's MHT prescription is recommended.
5. There is no standard recommendation for stopping MHT; the dosage can either be gradually tapered or discontinued abruptly. Discontinuation of HT may be associated with recurrent VMS in approximately 50% of women, regardless of age and duration of use.[12]

Contraindications to systemic MHT

Contraindications to estrogen

- Undiagnosed abnormal vaginal bleeding
- Known, suspected, or history of breast cancer
- Known or suspected estrogen-dependent cancers (i.e. endometrial, ovarian)
- Coronary heart disease
- Active or history of venous thromboembolism
- Active or history of stroke
- Known thrombophilia
- Active liver disease
- Known or suspected pregnancy

Contraindications to progestogen

- Undiagnosed abnormal vaginal bleeding
- Current or history of breast cancer

For **Postmenopausal** women, estrogen-progestogen therapy (EPT) regimens can be either continuous or cyclic. In continuous EPT regimens, both estrogen and progestogen are taken continuously. In cyclic EPT regimens, progestogens are administered 12–14 days per month, while estrogen is taken continuously.

For **Perimenopausal** women, a cyclic regimen of EPT may be preferred to minimise the risk of breakthrough bleeding. Estrogen with LNG-IUS may be preferred in women who need contraception or with heavy vaginal bleeding.

Choice of Estrogen: Estrogen is available in the form of oral pills, transdermal patches and gels, and vaginal applications. It can be formulated as conjugated estrogen, estradiol, and estrone.

Transdermal estrogen may be associated with a lower risk of venous thromboembolism than oral estrogen[13] and may be preferred over oral pills in women who are smokers or who have high triglyceride levels, hypertension, gall bladder disease, migraines, or malabsorption syndromes.

Choice of Progestogen: Medroxyprogesterone, micronized progesterone, norethindrone, dydrogesterone and drospirenone are used in MHT regimens.

Although progestin (specifically depot medroxyprogesterone acetate) demonstrated a greater reduction in vasomotor symptoms (79% versus 55%), there is limited data on the safety of progestin alone compared to combined estrogen and progestin preparations for treating vasomotor symptoms. There is concern that the risk of breast cancer may be related to progestin use. So, it is not considered a first-line therapy for VMS.

Options That Do Not Require a Progestogen: Tissue selective estrogen complex (TSEC) and tibolone

TSEC, a progestogen-free daily oral option, combines conjugated estrogen with a selective estrogen receptor modulator (SERM), **bazedoxifene**. Bazedoxifene has antagonist effects on estrogen receptors in the uterus and, therefore, provides endometrial protection. There is no increased risk of breast cancer in trials up to 2 years. Reduces VMS by 75% compared to 51% by placebo.[15]

Tibolone is a synthetic steroid analogue of the progestin norethynodrel. Tibolone is converted to 3 active metabolites in the body with weak estrogenic, progestogenic, and androgenic properties. It appears to have a beneficial effect on bone density, vasomotor symptoms, and

vaginal symptoms without estrogenic effects on the uterus or breasts. In a recent Cochrane review of randomized controlled trials, tibolone was more effective than placebo, but slightly less effective than EPT, in reducing VMS in postmenopausal women.[14]

NON-HORMONAL PRESCRIPTIONS

For patients with contraindications to hormone therapy or those who prefer alternatives to MHT, non-hormonal prescription options have shown some efficacy in the relief of VMS. These include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine uptake inhibitors (SNRIs), gabapentinoids, clonidine, and oxybutynin. None are as effective as estrogen, and the response rate among women is variable.

SSRIs/ SNRIs: There is increasing evidence that the antidepressant agents SSRIs and SSNRIs are effective for the treatment of VMS associated with menopause. The efficacy of antidepressants for the reduction of hot flashes may vary from 27% to 61%.[16] However, they come with side effects and do not provide the additional health benefits of hormone therapy, such as the prevention of urogenital atrophy and osteoporosis. Paroxetine (7.5 mg/d) is the only non-hormonal therapy that is approved by the FDA for the treatment of vasomotor symptoms.

Gabapentin, an antiepileptic drug, has been found in trials to improve bothersome VMS, reducing hot flash frequency by 45% to 71% from baseline.[17] It may be a good option for women with sleep disturbances from VMS because drowsiness is a side effect. Start gabapentin at 200–300 mg at night and increase the dosage in increments of 100 mg every 3–4 days until a maximum dosage of 900 mg nightly is reached.

Clonidine, a centrally acting alpha 2-agonist, is an anti-hypertensive agent. A systematic review and meta-analysis reported a small benefit of clonidine (0.1 mg/d) compared with placebo but less benefit compared with MHT.[16]

Oxybutynin is an anticholinergic agent, typically used for urinary incontinence, that has also been shown to significantly reduce VMS when taken at a dosage of 2.5 mg or 5 mg twice daily. Adverse effects of oxybutynin include dry mouth, gastrointestinal upset, constipation, and blurred vision.[18]

Complementary and Alternative therapies

Phytoestrogens are plant-derived substances with estrogenic biologic activity. Examples include the isoflavones genistein and daidzein, which are found in high amounts in soybeans, soy products, and red clover. A 2010 Cochrane meta-analysis of 30 placebo-controlled trials of high levels of phytoestrogens for the treatment of vasomotor symptoms found no evidence of benefit.[19]

Herbal treatments that have been studied for the relief of vasomotor symptoms include Chinese herbal medicine, black cohosh, ginseng, St. John's wort, and ginkgo biloba. There is currently insufficient data to support the use of herbal remedies for menopausal–VMS. However, there are reports of adverse effects like photosensitivity and an increased risk of bleeding with Chinese dong quai and Liver toxicity with black cohosh.

Alternative Techniques like acupuncture and reflexology showed no benefit over placebo for VMS.

Conclusions

Vasomotor symptoms can significantly affect a woman's quality of life. New understanding of VMS pathophysiology is paving the way for exciting developments in therapeutic approaches for VMS.

MHT, with estrogen alone or in combination with progestin, is the most effective therapy for vasomotor symptoms related to menopause. MHT is the recommended therapy for the management of VMS in postmenopausal women without contraindications.

Non-hormonal prescription medications can be considered in women who are unable or do not desire to use MHT. Lifestyle measures such as cognitive behavioural therapy may also help manage VMS.

The needs of each woman, as well as their risks and benefits, should be considered when deciding among the treatment options for managing VMS.

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Neurocognitive Decline at Menopause

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Neurocognitive decline in menopause refers to a decrease in cognitive functions of a woman like memory, concentration, and decision-making ability during menopause, often referred to as Brain Fog. It may herald in the menopause transition phase itself. It is primarily owing to the gradual decline in the estrogen levels at menopause. Female gender is a consistent risk factor for dementia.[1] Estrogen plays an essential role in cognitive processing and neuronal function. Menopausal women and also women during the transition phase report experiencing brain fog including, memory lapses, difficult concentration and cognitive decline. Prior to menopause women perform better in cognitive function compared to males in the same age group. But this advantage is lost with the onset of menopause.

Cognitive disorders are classified as cognitive aging, mild cognitive impairment (MCI), and dementia.[2] Cognitive aging is physiologic forgetfulness and represents an erosion of existing abilities, beginning almost imperceptibly in middle age and accelerating during old age.MCI is episodic memory loss without dementia. It is demonstrable memory impairment, but other cognitive abilities are not impaired and daily activities are largely intact.[2] Neurophysiologic changes in the brain begin and clinical manifestations like cognitive decline are present with age, that`s defined as MCI. When these symptoms are persistent with cognitive impairment, it eventually will progress to dementia. Dementia is characterized by severe cognitive decline and might lead to functional disability subsequently. About 50 million people in world suffer from dementia. It is the fifth leading cause of death globally. Menopausal women with early cognitive symptoms are at increased risk of dementia. About 50 million people in world suffer from dementia. The most common cause of dementia is Alzheimer's disease.

Cognitive function comprises of six key domains (Table 1) - complex attention, executive function, learning and memory, language, perceptual-motor control, and social cognition. Cognitive decline may manifest as slowing and difficulty in recalling details and learning new information. It significantly impacts the quality of life.[3]

Table 1. Neurocognitive domains.[4]

NEUROCOGNITIVE DOMAINS
1. Complex Attention ▪ Sustained attention ▪ Divided attention ▪ Processing speed ▪ Selective attention
2. Executive Function ▪ Planning ▪ Decision making ▪ Responding to feedback ▪ Working memory ▪ Inhibition ▪ Flexibility
3. Learning and Memory ▪ Free recall ▪ Cued recall ▪ Recognition memory ▪ Autobiographical and semantic long-term memory ▪ Implicit learning
4. Language ▪ Object naming ▪ Word finding ▪ Fluency ▪ Syntax & grammar ▪ Receptive language
5. Perceptual-Motor Control ▪ Visual perception ▪ Visuoconstructional reasoning ▪ Perceptual motor coordination
6. Social Cognition ▪ Recognition of emotions ▪ Theory of mind ▪ Insight

Neurocognitive Domains

Complex Attention

Complex attention is one's ability to focus on multiple things and the ability to choose what to pay attention to and what to ignore. We do not think about it very often, but our capacity to remain focused, particularly when there are distractions and parallel tasks involved, requires significant effort from our brains. Attention and concentration are a multifaceted construct and is generally divided into two global sub domains: selective attention and sustained attention (or vigilance). Concentration generally falls under the rubric of sustained attention. Divided attention is viewed as falling under the concept of selective attention. Selective attention is the process of attending to information that is relevant and important and ignoring other non-relevant information. Selective attention tasks often provide distracting information and request the examinee to attend specifically to the relevant information.[5]

Executive Function

It refers to high-level cognitive function which is required to control and coordinate other cognitive behaviors. These are functions which help to plan, prioritize, take decisions, respond to one's environment, and move between tasks. It involves sequencing, planning, and organization of tasks. Executive functioning is the definitional set of top-down processes, because effectively using simpler cognitive abilities is required for real-world adaptive success. Thus, executive functioning also requires cognitive flexibility, in that problem solving, particularly of novel tasks, requires consideration of new strategies and rapid rejection of failed efforts.[6]

Learning and Memory

It is the most well-known aspect of cognitive function. It involves the ability to record information, such as facts or events, and retrieve them when required. Memory is one of the most complex and multifaceted cognitive domains composed of sub domains, like working memory, procedural memory, and prospective memory.[5] Working memory is the ability to hold information in consciousness for adaptive use. It can involve information from all sensory modalities along with verbal and nonverbal information. Further, working memory is conceptualized to include two separable components: maintenance of information and manipulation of information.

Language

Itis strongly associated with one's ability to communicate, through writing, reading, or speaking. It involves abilities like naming objects, finding right words, fluidity and flow of speech, grammar, syntax, and receptive language. Language skills involve receptive and productive abilities, ability to understand language, access semantic memory, identify objects and respond to verbal instructions with behavioral acts.

Perceptual-Motor Control

It is one's ability to coordinate body movements in response to what is happening around us. It is the ability to interact with the environment by combining one's senses like vision, touch and motor skills. Sensation refers to the ability to detect a stimulus that occurs in one of the five sensory modalities. The ability to identify a meaningful stimulus falls under perception. Under the domain of perception, sensory information is processed and integrated. One of the concepts of perception is identification of previously experienced objects from sensory information. Perception can be assessed in terms of ability to recognize objects, sounds, and for the intactness of the perceptual fields.

There are several different basic elements of motor activity. They include fine motor abilities, including manual dexterity and motor speed, as well as reaction time, and more global skills such as balance.[5]

Social Cognition

It is the way we process, remember, and use information to explain and predict our behavior as well as the behavior of others in the social context. This includes our ability to control our desires to act on impulses, express empathy, recognize social cues, read facial expressions, and motivate ourselves.

Methods to Assess Cognitive Decline

Identifying cognitive decline during menopause involves using various tools designed to assess different aspects of cognitive function, including memory, executive function, attention, and overall mental sharpness. Some of the widely used tools are Montreal Cognitive Assessment (MoCA) [7], Mini-Mental State Examination (MMSE) [8], Trail Making Test (TMT)[9], Quick Mild Cognitive Impairment (Qmci) screen[10], CANTAB (Cambridge Neuropsychological Test Automated Battery)[11]and Cognitive Failures Questionnaire (CFQ).[12]

A study by Zhu et al.[13] evaluated the Everyday Memory Questionnaire-Revised (EMQ-R) in menopausal women to gain insights into the phenomenon of "brain fog." The researchers focused on assessing the reliability and validity of the EMQ-R in capturing everyday memory lapses reported by menopausal women. They concluded that the EMQ-R can effectively measure subjective memory complaints and provide valuable insights into cognitive challenges during menopause, thereby guiding potential interventions.

The Six Item Cognitive Impairment Test (6CIT)[14] is a widely used test which comprises of seven questions covering three domains (orientation, episodic memory, and attention). It has a total score of 28. A score of more than or equal to 8 is suggestive of cognitive impairment. The authors have been using this questionnaire in their Menopausal Clinic, since last 2 years. It is translated into Hindi, validated and published.[15]The 6CIT is valued for its simplicity and efficiency, taking only a few minutes to administer, and has been validated in various settings, including in the context of cognitive decline during menopause.

Relationship Between Menopause and Cognitive Decline

Changes affecting cognition at menopause:

The decrease in estrogen level during menopause affects cognition. Estrogen has neuroprotective role. It enhances synaptic plasticity, reduces inflammation and increases cerebral flow. The common symptoms of cognitive decline are memory lapse, mainly verbal memory. The other features are difficulty in concentration, slow processing, and executive function decline.

After adjusting for age, cognitive performance at menopause is lower than in reproductive years, particularly verbal delayed memory, and executive function, which is estrogen dependant.[16] Mild cognitive impairment represents a transition between normal cognition and dementia so prevention and treatment of MCI is essential to prevent its development into dementia.

Younger age at menarche, increased age at menopause, age at birth of first child more than 20 years, and extended reproductive period had better cognitive performance after menopause.[16] Few studies have documented increased risk of dementia up to 23 %with late menarche, early menopause, and short reproductive period.[17]

Key Research and Research Findings on Neurocognitive decline:

- SWAN Study (Study of Women's Health across the Nation): It inferred that women in the menopause transition phase often experience memory loss especially those with vasomotor symptoms.
- KEEPS Study18 (Kronos Early Estrogen Prevention Study): It investigated the effect of early hormone treatment on cognitive function, with mixed results.
- WHIMS Study (Women's Health Initiative Memory Study): It found that women above 65 years of age who started hormone therapy had an increased risk of dementia. It thus highlighted the importance of timing of MHT use.
- Some research studies suggest that menopausal transition is associated with transient cognitive changes especially verbal memory and attention.
- Longitudinal studies have shown that while some cognitive changes may stabilize after menopause, others may persist or increase the risk of cognitive disorders like Alzheimer's disease in later life.
- Women suffering with severe vasomotor symptoms like hot flashes and night sweats seem to have higher cognitive decline possibly due to change in sleep hygiene and hormonal changes.
- Recent studies are investigating the role of gut-brain interaction, inflammation and genetics in cognitive decline at menopause.

Prevention of cognitive decline

There are various hormonal and non-hormonal interventions which help in the prevention of cognitive decline:

A. Hormone therapy:

Estrogen therapy especially when started early in the menopause transition phase may preserve cognitive function and decrease the risk of developing Alzheimer's disease later on. However, if started late it can increase the risk of Alzheimer and dementia. In cases of premature ovarian failure, it is seen as per as research that the cause of cognitive decline is genetic rather than estrogen deficiency. More research is required to see the benefit of menopausal hormonal therapy (MHT). The findings of MHT Studies on Neurocognitive functions are shown in Table 2. At present there is no current guideline promoting MHT for prevention or treatment of neurocognitive decline at menopause.

Table 2. Randomized clinical trials on hormone therapy and cognition in women[1]

S. No.	Name of Study	Country	N (%)	Age (year)	Hormone treatment	Findings	Reference
1.	Women's Health Initiative Memory Study-WHIMS	USA	HT users: 2229. Placebo: 2303	≥ 65	CEE + MPA	HT increased dementia risk	Shumaker et al, 2003
2.	Women's Health Initiative Memory Study-WHIMS	USA	HT users: 1464. Placebo: 1483	65 - 79	CEE alone	Estrogen alone did not decrease incidence of mild cognitive impairment/ dementia	Shumaker et al, 2004
3.	Randomized, double-blind study.	USA	HT users: 187. Placebo: 186	≥ 65	CEE with or without MPA	HT did not affect cognition	Green-span et al, 2005
4.	Randomized, placebo-controlled, double-blind trial	USA	HT users: 208. Placebo: 209	60 - 80	Ultra–low dose unopposed transdermal estradiol	Transdermal estradiol did not affect cognition	Yaffe et al, 2006
5.	Women's Health Initiative Study of Cognitive Aging-WHISCA	USA	HT users: 1125. Placebo: 1179	65 - 80	CEE with or without MPA	HT was associated with worsening global cognitive decline and few specific cognitive domains which persisted after the interruption of HT	Espeland et al, 2010
6.	Women's Health Initiative Memory Study of Younger Women-WHIMSY	USA	HT users: 696. Placebo: 630	50 - 55	CEE with or without MPA	HT did not alter global cognitive function or any specific domain of cognition	Espeland et al, 2013
7.	Cognitive and Affective Study-KEEPS-Cog	USA	HT users: 431. Placebo: 262	Mean: 52.6	CEE + micronized progesterone OR Transdermal estradiol + micronized progesterone	HT did not affect cognition	Gleason et al, 2015
8.	Early vs Late Intervention Trial with Estradiol Cognitive endpoints-ELITE-Cog	USA	HT users: 284. Placebo: 283	Early post-menopause: 55.6. Late post-menopause: 64.9	Estradiol with or without micronized progesterone	HT did not affect verbal memory, executive function, and global cognition, regardless of whether it was started < 6 year or ≥ 10 year after menopause	Hender-son et al, 2016
9.	WHIMSY extended + Women's Health Initiative Memory Study of the Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO)	USA	WHIMSY-HT users: 701. Placebo: 635. WHIMS-ECHO-HT users: 1402. Placebo: 1478	Two groups: 50 –54&65 - 79	CEE with or without MPA	HT prescribed to younger women had no significant effect on cognition in the long term while in older women produced decreased global cognitive function, executive function, and working memory	Espeland et al, 2017
10.	Kronos Early Estrogen Prevention Study (KEEPS)-Cog trial	USA	HT users: 292. Placebo: 387	Early post-menopause	Oral CEE,tE2both with micronized progesterone or placebo pills and patch	No long-term cognitive effects of short-term exposure to HT started in early menopause versus placebo.	Gleason CEet al, 2024

CEE: Conjugated equine estrogen; MPA: Medroxyprogesterone acetate; HT: Hormone therapy, tE2, transdermal 17β-estradiol.

B. Lifestyle modification

Healthy lifestyle with adequate exercise, avoidance of obesity, mental and physical stimulation, control of stress, treatment of medical illnesses and depression, and control of vascular risk factors such as diabetes, hypertension, and hyperlipidemia is suggested to prevent cognitive decline.

Exercise- Regular exercise, especially aerobics improves cognition, brain plasticity and decreases the risk of dementia. There is a marked potential for physical activity and exercise training to improve cognitive function .Women with higher levels of baseline physical activity were less likely to develop cognitive decline. Keeping the brain active by continuing to learn new skills is helpful to build cognitive reserve.

Diet-Mediterranean diet rich in fruits, vegetables, grains, nuts and unsaturated fats is considered to be healthy for brain function. Free radical damages can accelerate the brain aging, so by consuming antioxidants such as vitamin E will help the body quench free radical associated changes. A healthy diet helps prevent hypertension (via reduced saturated fats and sodium), prediabetes (reduce sweets and caloric intake and consume more fiber), and stroke (dietary change to reduce cholesterol).

There is evidence that individuals whose diets are high in omega-3 fatty acids, especially docosahexaenoic acid (DHA), have a 50% reduction in their risk of developing dementia. DHA180 mg daily intake is suggested and this amount can be achieved by eating the fish about three times per week. However, the evidence is mixed. Optimal Vitamin D level is essential for brain health and may benefit women with cognitive decline.[6]

Control of hypertension- Key end-organ pathological mechanisms, for which hypertension is proposed to be causative, include acute and covert cerebral ischemia and hemorrhage, accelerated brain atrophy, cerebral micro vascular rarefaction and endothelial dysfunction, disruption of blood-brain barrier and neuroinflammation that affects amyloid pathologies. In addition to the direct-effect of hypertension on brain structure and microvasculature, hypertension is a risk factor for other diseases associated with an increased risk of dementia, most notably chronic kidney disease and heart failure. Mid-life hypertension increases the relative risk of life-time dementia by 20–54%.[19]

Sleep hygiene-Improving the quality of sleep via behavioral modification and or medical therapy may help in cognitive function.. A regular sleep schedule, a calming nighttime ritual, and an idealized sleeping environment are all examples of good sleep hygiene techniques. Establishing a sleep schedule, creating a sleep-inducing environment by ensuring the bedroom is dark, quiet, and cool with comfortable bedding and practicing relaxation techniques like reading, meditation, or taking a warm bath can help signal the body to wind down. Limiting exposure to electronics and reducing screen time before bed helps maintain melatonin production and circadian rhythm. Avoiding stimulants and heavy meals with regular physical exercise helps in falling asleep faster and enjoy deeper sleep but vigorous activity should be avoided close to bedtime. Managing stress and anxiety also helps to sleep better.

Cognitive training- Staying mentally active via activities like solving puzzles, reading and learning new skills helps in cognition.

C. Pharmacological aids

Antidepressants: Menopausal women suffering with mood-related cognitive symptoms may benefit with taking antidepressants.

Several studies have shown that acetyl-L-carnitine and choline alphoscerate are able to increase the synthesis and the release of Ach in patients with MCI, Alzheimer-related dementia, cerebrovascular damage and aging.

Certain drugs especially anti hypertensive drugs can cause cognitive decline. The opposite evidence of antihypertensive to delay cognitive decline also exists. A study found antihypertensive medications that stimulate (thiazides, dihydropyridine calcium channel blockers, angiotensin type I receptor blockers) vs. inhibit (angiotensin-converting enzyme inhibitors, beta-blockers, non-dihydropyridine calcium channel blockers ,type 2 and 4angiotensin II receptors) had lower rate of cognitive impairment.[19]However, there are no large randomized controlled trials comparing different antihypertensive agents with clinical syndrome of dementia or cognitive impairment as the primary outcome.

D. Reduction of stress and improvement of Mental health:

Mindfulness-based stress reduction (MBSR) and Cognitive behavioral therapy (CBT): improves overall well being and cognitive function.

Conclusion

Cognitive decline at menopause is a multifaceted issue which requires early diagnosis and treatment. It is influenced with hormonal changes and lifestyle factors. Neurocognitive decline may be transient or long lasting. Preventive strategies like lifestyle modifications, regular exercise, stress management and pharmacotherapy may help in improving cognitive decline.

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Musculoskeletal Syndrome of Menopause

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Introduction

As per stats, almost 2 million women in the United States and over 47 million women globally will experience menopause every year. On average, they will reach this transition between the ages of 45 and 55, with symptoms lasting two to ten years.[1,2]

Numerous symptoms are associated with menopause like, hot flashes, sleep disorders, brain fog, decreased libido and anxiety. However, musculoskeletal symptoms are less frequently identified by patients or physicians and can be quiet, debilitating, and irreversible if left untreated.

Musculoskeletal syndrome of menopause refers to symptoms caused by sudden fall in estrogen at the menopause transition.

Musculoskeletal syndrome compromises of, musculoskeletal pain, loss of lean muscle mass, arthralgia, increased tendon and ligament damage, decreased bone density with an increased risk of fracture, adhesive capsulitis, and cartilage matrix fragility with the advancement of osteoarthritis.

Postmenopausal women's quality of life may be significantly impacted by the musculoskeletal syndrome of menopause.

Musculoskeletal syndrome of menopause

Imaging results of these patients may not reveal any structural abnormalities, but it's crucial to be aware of the hormonal changes that take place in this group, particularly those involving estrogen.

In the early stages, before onset of musculoskeletal symtpoms, primary care physicians and obstetrics and gynaecology professionals could be the initial point of contact. In these situations, it may be helpful to address the musculoskeletal syndrome of menopause with women during routine check-ups or talks about other typical perimenopausal problems, such as hot flashes, in order to provide preventive care.

Women's bone mineral density decreases by 10% on average during the perimenopause.[3] Moreover, during menopause, women's muscle mass decreases by 0.6% per year.[4]

Since estradiol, the most physiologically active form of estrogen, affects almost every type of musculoskeletal tissue, including muscle, bone, cartilage, tendon, ligament and adipose tissue, musculoskeletal problems can be linked to its decline.[5,6] Five primary changes can be seen due to fall in estrogen levels (table 1): An increase in inflammation, decreased bone mineral density leading to osteopenia/osteoporosis, arthritis, sarcopenia and a decrease in the proliferation of satellite cells (muscle stem cells).

Table 1. Musculoskeletal syndrome of menopause: processes and signs.

Process	Signs
Inflammation	Arthralgia, joint pain, joint discomfort, frozen shoulder
Sarcopenia	Poor balance, falls, decreased muscle mass, loss of stamina, walking slowly
Decreased satellite cell proliferation	Decreased muscle mass, inability to gain muscle
Osteoporosis	Loss of height, back pain, stooped posture, low-impact fracture
Arthritis	Arthralgia, joint pain, joint stiffness

Inflammation

17β-estradiol, by inhibiting the release of inflammatory cytokine tNF-α [7], can lead to degradation of muscle proteins and reduced ability of muscles to control to damage.[8] Adipocytes release tNF-α and can lead to the accumulation of fat and impaired muscle function.[9, 10] Lean muscle loss and fat accumulation can be prevented by estrogen replacement therapy[11,12], with evidence that estrogen uses the estrogen receptor-α to act on and affect adipose tissue.[9]

Sarcopenia

Sarcopenia, refers to age-related loss of lean muscle mass, and it is characterized by atrophy of fast muscle fibers, decreased number of motor units, loss of type ii fibers and increased intra- muscular adipose tissue.[13]

To reduce the effects of sarcopenia, it has been suggested that nutritional interventions, such as consumptions of proteins, vitamin D and creatinine, and exercise including resistance training, can lead to improved strength and muscle mass, although further high-quality research is required.[14]

Estrogen plays a significant role on strength and muscular mass. It has been found that animals that undergo ovariectomy, and subsequent decline in estrogen, have a decreased mitochondrial function, complex I and I + iii activity and membrane microviscosity.[15] Additionally, the reduced estrogen leads to increased production of mitochondrial H2O2 [16], low antioxidant protein levels[16,17] and impairment of insulin sensitivity.[15] The ability of estrogen to restore glucose homeostasis and cellular redox in skeletal muscle is linked to these changes.[15,18,19] In various animal models, it has been found that estrogen is beneficial for muscle strength and mass.[20,21] In one such experiment, a 10% reduction in strength after 24 weeks of estrogen shortage was accompanied by an 18% drop in fiber cross-sectional area.[20] Another experiment using ovariectomized mice showed that muscle is more vulnerable to damage and has limited growth when estrogen is not present.[21] MHt is a reasonable approach, particularly when combined with resistance training.[22,23]

Satellite cell proliferation

Satellite cells are the stem cells on muscle fibers, and promote regeneration and plasticity.[24] type i oxidative fibers have a better blood supply and hence possess relatively more number of satellite cells.[24] In a steady state, satellite cells are dormant[25,26], but in chronic inflammatory situations, they become active in response to damage or anabolic stimulation to repair muscle tissue.[27, 28] Through estrogen receptors, estradiol promotes the activation and proliferation of satellite cells.[29], and it seems that the binding of estradiol to estrogen receptor-α determines a part of the force produced by skeletal muscle.[30,31] Muscle strength and post-injury recovery are compromised when the stimulus to estrogen receptor-α by estrogen is lost.

In addition to lowering risk, guidelines for management of postmenopausal osteoporosis comprise strengthening the muscles surrounding weaker bone regions, particularly the lower legs, hips, and back

Bone density

Osteoporosis affects around 200 million post-menopausal women and is a serious problem in this group.[32] it can be prevented and treated but is usually underdiagnosed. Around 70% of hip fractures occur in women, and 30% to 50% of women experience a clinical fracture at some point in their lives.[32]

Significant bone loss is linked to estrogen deficiency[11], which increases fragility and fracture risk. Osteoporosis can be prevented by removing risk factors, exercising, and a healthy diet. Additionally, it has been demonstrated that MHT was sufficient and successful in preventing osteoporotic fractures in women who were at risk.[33] Hence, for the prevention and treatment of osteoporotic fractures MHT should be recommended because of its proof of effectiveness, safety and cost.[34]

Cartilage damage and osteoarthritis

cartilage is made up of highly specialized chondrocytes which are partially regulated by estrogen and a dense extracellular matrix.[35] Incidence of osteoarthritis in women rises sharply around menopause and recent literature shows that women have more incapacitating arthritic pain than men.[36–37]

Role of MHt is controversial in the prevention and treatment of postmenopausal osteoarthritis. Evidence suggests that estrogen has both mitogenic and protective effects on intervertebral disks [38], and that the decline in estrogen after menopause causes alterations in the connective tissue matrix that can be prevented with estrogen replacement treatment.[39]

Moew studies are needed to ascertain if there is a particular age range or dosage for which MHT may be helpful for osteoarthritis.

Clinical applications

Because estrogen depletion during menopause has a number of detrimental effects on women's health, particularly the musculoskeletal system, it is critical that patients and practitioners understand preventative and management strategies. Exercise, diet, and testing are examples of conservative strategies. According to updated guidelines, women 65 years of age or older and those between the ages of 50 and 64 who have certain risk factors, such as a positive family history of osteoporosis, should get screened for the disease.[40]

It has been demonstrated that dietary vitamin D can significantly increase hip bone mineral density in postmenopausal women and lower the risk of falls.[41,42] Nine months of 1000 IU of vitamin D3 was linked to lower bone turnover indicators. Vitamin D levels were markedly elevated after receiving 500 mg of magnesium daily.[43]

Vitamin K2 is another vitamin supplement that may help treat and slow the onset of osteoporosis. Zhou et al.'s recent meta-analysis of nine randomized controlled trials involving 6853 postmenopausal patients with osteoporosis revealed a markedly elevated change in lumbar and forearm bone mineral density without any evidence of serious side effects.[44]

Exercise is the only non-controversial method of menopause prevention and treatment available. Reduced power, which has been proposed as the primary measure for doing everyday tasks, is linked to the loss of type II muscle fibers caused by declining estrogen.[45–46] Resistance training with larger weights in lower repetition sets is generally accepted to be more effective at increasing muscle power than training with lighter weights in higher repetition sets.[47]

Resistance training and dietary modifications, such as consuming more protein and the vitamins, may be essential for postmenopausal women to reduce their risk of fractures and falls.

When it comes to treating postmenopausal women in general and the musculoskeletal syndrome of menopause in particular, MHT may be the next big thing. MHt provides a novel way to lessen the potentially disastrous musculoskeletal symptoms of estrogen withdrawal by decreasing the pace of estrogen depletion, facilitating a more seamless physiological transition.

Orthopedic surgeons, who might be less familiar about the musculoskeletal symptoms of menopause than general physicians and obstetrics and gynecology specialists, should not undervalue their role as clinicians in addressing the musculoskeletal syndrome of menopause. For instance, a skilled doctor should explain the musculoskeletal syndrome of menopause and support the patient's agency in therapy when midlife women exhibit signs of adhesive capsulitis, atraumatic joint pain, or recent loss of muscle or height.

By telling patients that their state is normal due to anticipated biochemical changes and, more importantly, that these changes are treatable and that appropriate action may be done right away to prevent additional manifestations, this may psychologically improve patient satisfaction.

Conclusions

Joint discomfort, inflammation, sarcopenia, osteoporosis, and cartilage degeneration are among the prevalent musculoskeletal symptoms associated with estrogen deficiency that have been dubbed the "musculoskeletal syndrome of menopause." When used in isolation, these phrases fail to adequately explain to patients the significance of estrogen reduction or how treatment with resistance training, correct nutrition, vitamin consumption, and/or MHt may significantly improve quality of life, prevent falls, and lower frailty mortality. In order to provide patients with more comprehensive care, doctors should use this terminology as a way to communicate, in still agency that may improve patient satisfaction, and provide appropriate active therapy.

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Genitourinary Syndrome of Menopause: Understanding, Diagnosis, and Management

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Introduction

Menopause marks a significant biological transition in a woman's life, characterized by a decline in **estrogen and other sex hormones**. These hormonal changes lead to several physiological alterations, including **Genitourinary Syndrome of Menopause (GSM)**.

GSM, a term introduced by the **International Society for the Study of Women's Sexual Health (ISSWSH)** and the **North American Menopause Society (NAMS)**, replaces **vulvovaginal atrophy (VVA)** to reflect the **broad spectrum of symptoms affecting both the genital and urinary systems**.[1]

Women suffering from GSM often experience **vaginal dryness, irritation, dyspareunia (pain during intercourse), recurrent urinary tract infections (RUTIs), urinary incontinence, and pelvic organ prolapse (POP),** significantly impacting **sexual function and quality of life**.[2]

Prevalence and Indian context

GSM affects **40-50% of postmenopausal women**, but only **25% seek medical attention**, mainly due to **lack of awareness and cultural stigma**.[3]

Pathophysiology of GSM

Estrogen plays a crucial role in maintaining the structure and function of the urogenital tract. Declining levels of estrogen in menopause leads to decreased vaginal lactobacillus, increased pH, altered epithelial morphology, reduced vascular flow and reduced fluid secretion in the vagina, which subsequently cause symptoms of urogenital atrophy.

Symptoms of GSM

GSM presents with **genital, sexual, urinary, and pelvic symptoms**, progressively worsening if left untreated.

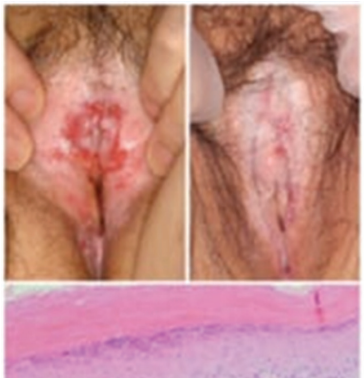
Table 2: Symptoms of GSM

Category	Common Symptoms
Genital	Vaginal dryness, irritation, burning, increased infection risk
Sexual	Dyspareunia, reduced arousal, reduced lubrication and decreased sexual satisfaction
Urinary	Urgency, frequency, dysuria, recurrent UTIs and incontinence
Pelvic	Sensation of pressure, vaginal bulging, difficulty emptying bladder or bowels, discomfort during sex

Unlike **hot flashes and mood swings**, which improve over time, **GSM is progressive and requires medical intervention**.

Differential Diagnosis[4]: GSM shares symptoms with several dermatological conditions. Following are few common conditions.

1. **Lichen Sclerosus(LS):** LS causes intense itching, white plaques, and scarring, while VVA presents with dryness and dyspareunia without scarring. Diagnosis of LS often requires a biopsy (Toulidine blue guided) to confirm histopathological features. Treatment involves high-potency topical corticosteroids.



2. **Vaginal Infections:** Vaginal infections cause discharge and odor, while VVA presents with minimal discharge and an elevated pH. Diagnosis of vaginal infections involves identifying specific pathogens through laboratory tests. Treatment includes appropriate antimicrobial agents.
3. **Lichen Planus:** It often affects more than one part of body and many patients with oral manifestations also have genital involvement. Vulvar symptoms include pain, burning and scarring. Diagnosis requires Biopsy. First line treatment is similar to Lichen sclerosus.
4. **Vulvodynia:** It presents with vulvar pain without an identifiable cause that persists for atleast 3 months. Physical examination should incorporate pressure point testing using a cotton swab in a circumferential fashion along vulvar vestibule, which will elicit pain even with light touch. Treatment includes vulvar hygiene, stress reduction, pelvic floor physical therapy and psychological interventions.

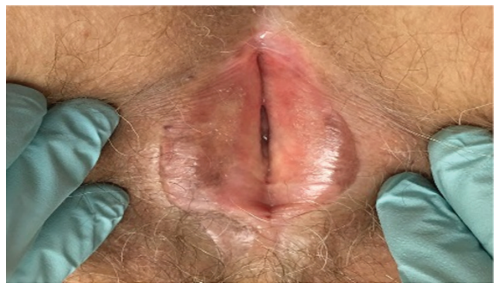
Diagnosis of GSM

A comprehensive medical history and pelvic examination are essential for diagnosis. Key questions include:

- "Do you experience vaginal dryness or irritation?"
- "Is intercourse painful?"
- ''Is the desire for intercourse decreased?''
- "Do you frequently suffer from urinary infections?"

Pelvic Examination Findings: The classic appearance of vaginal atrophy includes

- Loss of rugae and a pale thin vaginal epithelium
- Tenderness to palpation
- Reduced vaginal elasticity
- Vaginal narrowing and an increased susceptibility to trauma and irritation
- The epithelial tissues are friable and submucosal petechial hemorrhages may be there.



Laboratory Tests: The two primary objective measures of vaginal atrophy include a change in vaginal pH and VMI.

- Vaginal pH test: A pH >5.0 suggests atrophy.
- Vaginal Maturation Index (VMI): Measures the proportion of epithelial cells. A detailed vaginal health index is useful for documentation and follow-up (Table 3).
- Urine analysis & culture: To rule out infections.

Table 3: Vaginal Health Index

Score	Overall Elasticity	Fluid secretion type and consistency	pH	Epithelial mucosa	Moisture
1	None	None	6.1	Petechiae noted before contact	None, mucosa inflamed
2	Poor(scant)	Thin yellow	5.6-6.0	Bleeds with light contact	None, mucosa not inflamed
3	Fair (Superficial)	Thin white	5.1-5.5	Bleeds with scraping	Minimal
4	Good (Moderate)	Thin white	4.7-5.0	Not friable, thin mucosa	Moderate
5	Excellent	Normal white flocculent	≤4.6	Not friable normal mucosa	Normal

Lower score corresponds to greater urogenital atrophy.

Management of GSM

GSM treatment aims to **relieve symptoms, restore vaginal health, and improve quality of life**.

Table 4: Management of GSM

Treatment Approach	Description
Lifestyle Modifications	**Quit smoking**, maintain **regular sexual activity**, and practice **pelvic floor exercises** (Kegels) to strengthen vaginal and bladder muscles.
Non-Hormonal Therapies	**Vaginal lubricants**: used only at the time of sexual activity. They can be water-based (K-Y Jelly), silicone-based, Oil-based.[5] **Vaginal moisturizers:** For routine use, typically two or three days per week, not just during sexual activity. It restores hydration and pH balance.[5] **Pelvic floor Physical therapy** for Bladder control.
Local Estrogen Therapy (LET)	Available as **vaginal creams, tablets, or rings** (Described in Table 5). LET improves **vaginal elasticity, lubrication, and urinary symptoms.**[6] Clinical safety data are limited to 1 year.
Systemic Hormone Therapy (SHT)	**Oral or transdermal estrogen therapy** for women with **additional menopausal symptoms**, helping improve GSM along with vasomotor symptoms.
Selective Estrogen Receptor Modulators (SERMs)	**Ospemifene (Osphena 60mg daily)** provides **estrogen-like benefits to vaginal tissues**.[7] Not recommended in women with known or suspected breast cancer.
Emerging Therapies	**Intravaginal DHEA (Prasterone 6.5mg vaginal suppository daily)** stimulates estrogen and androgen receptors, improving vaginal health.[8] (FDA approved) **Laser therapy (fractional CO_2 laser, Erbium: YAG laser)** helps rejuvenate vaginal tissue.[9] (Not FDA approved)
Surgical Management	**For severe cases** with **pelvic organ prolapse** or **persistent urinary incontinence**, surgical options such as **vaginal reconstructive surgery or urethral sling procedures** may be required.

Table 5: Local Estrogen Therapy[4]

Preparations	Common formulations	Dosing
Vaginal Creams Conjugated estrogen (Premarin)	0.625mg per 1g of cream	Apply 0.5 to 2g of cream intravaginally once per day for 21 days, then stop for seven days or apply 0.5g intravaginally twice per week (generally start with 0.5g dose)
17 beta Estradiol (Estrace)	0.1mg per 1g of cream	Apply 0.5 to 4g of cream intravaginally once per day for 2 weeks, then reduce to 0.5g twice per week
Estriol (Evalon)	0.5mg per 1g of cream	Apply 0.5 to 1mg of cream intravaginally once daily for 3 weeks followed by 1 week off. For maintainence twice a week.
Vaginal tablet Estradiol (Imvexxy, Vagifem, Yuvafem)	Vagifem and Yuvafem:10mcg per tablet Imvexxy: 4 or 10 mcg per tablet	Insert tablet into vagina once per day for 2 weeks, then reduce to twice per week
Vaginal ring Estradiol (Estring)	2mg ring, released as 7.5mcg per day over 90 days	Insert ring into vagina; replace every 90 days

Pretreatment investigations: Complete physical and gynaecological examination is mandatory. Suggested investigations prior to hormone replacement therapy are complete haemogram, urine culture, blood sugar, lipid profile, Pap smear, TVS, mammography and DEXA scan.

Follow Up: A follow-up visit is scheduled after 1 and 3 months. If, in 3 months, she shows improvement in her signs and symptoms, the patient will be advised to taper off. Routine endometrial surveillance is not recommended in low-risk women using low-dose vaginal ET.[10] Any spotting or bleeding requires a

thorough evaluation that may include transvaginal ultrasound and/or endometrial biopsy.

Special situations:

1. **History of Venous Thromboembolism:** Local estrogen has minimal systemic absorption and may be used with caution under medical supervision.[11]
2. **Patients on Aromatase Inhibitors:** Some studies suggest that vaginal estrogen with close monitoring may be an option for those with debilitating GSM symptoms.[11]
3. **Estrogen receptor-positive Breast cancer survivors:** The use of vaginal estrogen in patients with a history of breast cancer does not appear to be associated with an increased risk of breast cancer recurrence, breast-specific mortality, or overall mortality.[12]
4. **Cervical cancer survivors:** Among women with and without hormone therapy (HT) exposure, no significant difference in survival or recurrence of cancer was noted. A significant decrease in post-radiotherapy complications was seen in women who had received HT.[13]
5. **Endometrial cancer survivors**: The available retrospective and observational studies fail to show an increase in recurrence or death among women with early stage cancers who used HT compared to those who did not. Therefore, it is reasonable to offer a short course of estrogen-based HT after surgical management, but, the treatment should be individualized, taking into account woman's symptoms and preferences, and the uncertainty of evidence for and against HT use.[14] Non hormonal therapies are recommended for women with more advanced endometrial cancer.
6. **Ovarian cancer survivors:** A meta-analysis (largely cohort studies) found no increased risk of recurrence or death in women receiving HT after treatment for ovarian cancer. Concern has been raised regarding HT in tumours that are likely to contain ERs, such as low-grade serous and endometroid carcinomas, and sex cord stromal malignancies, such as ovarian granulosa cell and Sertoli-Leydig ovarian tumours, but data are very limited.[15]

Urinary Incontinence

Urinary incontinence (UI) is a **common but distressing** symptom of GSM, occurring due to **loss of estrogen-related bladder and urethral support**.

Table 6: Types and Management of Urinary Incontinence

Type	Description	Management
Stress Urinary Incontinence (SUI)	Involuntary leakage of urine during coughing, sneezing, or physical activity, due to weakened pelvic floor muscles	**Conservative:** Pelvic floor exercises (Kegel*), vaginal pessaries. **Drugs:** Duloxetine **Surgery:** Midurethral sling surgery (TVT, TOT, TVT-O), Colposuspension, Urethral bulking agents, Artificial urinary sphincter.
Urge Urinary Incontinence (UUI) (Overactive Bladder - OAB)	Sudden, intense urge to urinate, often leading to leakage before reaching the toilet. Caused by overactive bladder muscles	**Lifestyle intervention:** Caffeine reduction, Weight loss in Obese, Moderate physical activity, Smoking cessation. **Behavioral Therapy:** Bladder training**. **Physical Therapy:** PFMT TENS, PTNS. **Drug Therapy:** Anticholinergics (oxybutynin 2.5-10 mg BD to QID), beta-3 agonists (mirabegron), Vaginal estrogen, Desmopressin (for Nocturia). **Surgery:** Intravesical injection of Botulinum toxin A, Sacral nerve stimulation, Augmentation cystoplasty, Urinary diversion.
Mixed Urinary Incontinence (MUI)	A combination of stress and urge incontinence	Combination of pelvic exercises, medications, and lifestyle changes
Overflow Incontinence	Inability to fully empty the bladder, leading to continuous dribbling	Catheterization, bladder training, surgical correction if necessary
Functional Incontinence	Urine leakage due to cognitive or physical impairments preventing timely toilet access	Environmental modifications, scheduled voiding, assisted toileting

TOT: Transobturator tape; **TVT:** Tension-free vaginal tape; **TVT-O:** Tension-free vaginal tape obturator; **PFMT:** Pelvic floor muscle training; **PTNS:** Percutaneous tibial nerve stimulation; **TENS:** Transcutaneous electrical nerve stimulation

***Kegels Exercises:** It strengthen the pelvic floor by contracting and relaxing the puborectalis muscle and external anal sphincter. To perform them, tighten the pelvic floor muscles for 3-5 seconds, then relax for the same duration. Repeat 10-15 times per session, three times daily, gradually increasing the hold to 10 seconds. Regular practice improves bladder control and reduces urinary incontinence.[16]

****Bladder Training:** It is an attempt to restore central control over the bladder. The bladder diary (shown in image) will tell how long a woman can go before she senses urgency and/or leaking. The training interval is set shorter than this time interval. For example, if a woman leaks if she waits 2 hours between voids, the training interval is set at one-and-a-half hour while awake. This retrains the bladder to void in response to central command. The training interval is then increased by 15 minutes each week until a satisfactory time interval is reached. Usually the training interval is not set shorter than 1 hour. The patient should discontinue training during sleep.[3]

Bladder Diary

Date ..... **Name** Jane Jones

Day 1 **DoB** ...20/09/57

Fluid In			Urine out		Comments		
Time	**Type of drink**	**Amount of drink (ml)**	**Time**	**Amount** in ml	**How urgent** 1-3 3 = most urgent	**Activity at the time** e.g. reaching front door	**Leakage** damp / wet / soaked
			02.30	370	2	Woke to use toilet	None
			05.30	200	3	Woke to use toilet	Wet
07.30	Orange juice Coffee	150 300	07.45	150	2	Brushing teeth	Damp
08.00	Coffee	250	08.20	110	3	Waited too long	Wet
09.00	Water Diet	100 330					

Pelvic Organ Prolapse (POP)

Pelvic organ prolapse (POP) occurs when **pelvic organs (uterus, bladder, or rectum) descend into or protrude from the vaginal canal** due to **loss of estrogen, weakened pelvic floor muscles, and increased intra-abdominal pressure.**

Table 7: Types and Management of Pelvic Organ Prolapse

Type	Description	Management
Anterior wall (cystocele)	The bladder drops into the vaginal wall, causing urinary urgency and incomplete emptying.	Pessary support, pelvic floor exercises, Anterior colporrhaphy (central) Paravaginal repair (lateral)
Posterior wall (rectocele)	The rectum bulges into the vagina, causing constipation and difficulty passing stool	Stool softeners, dietary fiber, Posterior colporrhaphy
Uterine or vaginal vault Prolapse	The uterus/vault descends into the vaginal canal, leading to pressure, back pain, and vaginal bulging	Pessary, hysterectomy with pelvic reconstruction if severe. Sacrospinous ligament fixation/Uterosacral ligament fixation/ High uterosacral Pectopexy/Abdominal colposacropexy/Colpocleisis (vaginal closure)

The **POPQ** system is the **gold standard** for evaluating pelvic organ prolapse[17]. It provides an **objective** measurement of vaginal and pelvic organ descent, helping guide treatment decisions.

Conclusion

GSM is a **common yet often overlooked** condition that significantly affects postmenopausal women's health and quality of life. **Early diagnosis** and **appropriate treatment**, including lifestyle changes, hormonal and non-hormonal therapies, can effectively manage symptoms. **Raising awareness** and encouraging **open discussions** can help more women seek timely medical support.

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Critical Evaluation of the Indications of Menopause Hormone Therapy

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Introduction

The use of hormone therapy (MHT) in menopausal women has, in last 3 decades, been one of the most debated topics in women's health. Very few therapeutic medical interventions have generated as much controversy, and very few have waxed and waned in popularity as much as MHT.[5] This pendulum of MHT use appears to be driven not just by the sociocultural trends as by the emerging evidence from clinical trials.

The abundance of observational data has shown that HT is not only effective against common menopausal symptoms such as hot flushes and night sweats, vaginal dryness and atrophy but also offers benefit against chronic disorders such as osteoporosis, coronary artery disease, dementia, and even all-cause mortality.

In this article today, we aim to critically evaluate the indications for the Menopause replacement therapy based on evidence.

Current Core Indications:

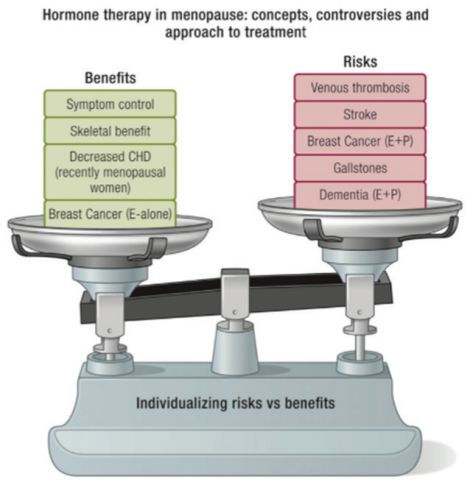
- Menopausal symptoms (Vasomotor symptoms)
- Genito urinary symptoms of Menopause (GSM)
- Premature ovarian insufficiency (premature menopause, oophorectomy)
- Postmenopausal osteoporosis (Accepted indication by few societies only)

Proven additional preventive benefits – Risk Reduction

- Coronary heart disease
- Colorectal cancer
- Diabetes mellitus

Presumed additional preventive benefits to reduce risks

- Metabolic syndrome, Alzheimer's disease, various atrophic-degenerative diseases (skin, mucous membranes, connective tissue), rheumatic diseases, certain forms of schizophrenic psychoses, Breast cancer (E alone)



Core Indications

1. Menopausal Symptoms

The cardinal symptoms causally associated with menopause are vasomotor symptoms (VMS), menstrual changes, disrupted sleep, and genitourinary symptoms. For Asian women, physical symptoms such as body aches and joint pains as well as psychological symptoms are recognized to be more prevalent than VMS. A recent systematic review and meta-analysis of prevalence data globally found

that joint and muscular discomfort were the most prevalent menopause related symptoms at 65.43%.[1]

In addition, many women describe new onset mood and cognitive symptoms, fatigue, palpitations, changes in body habitus, and sexual dysfunction

- Hot flashes are the most common reason for postmenopausal estrogen therapy, affecting 85% of women during late menopause and early post menopause, yet only 25% seek treatment despite impacts on sleep, quality of life, and daily function.
- MHT is considered the most effective currently available treatment for menopause symptoms with strong international consensus. MHT in healthy symptomatic women during a natural timed menopause transition is associated with symptomatic benefits, and low risks.
- Coexistence of other menopausal symptoms, such as depression, sleep disturbances, in these women often require treatment with both MHT and antidepressants (usually selective serotonin reuptake inhibitors [SSRIs].
- **Women with mild hot flashes:** Women with mild flashes usually do not need pharmacotherapy. Instead, simple behavioural measures, such as lowering room temperature, using fans, dressing in layers of clothing that can be easily shed, and avoiding triggers (such as spicy foods and stressful situations), can help reduce the number of hot flashes.
- **Women with moderate to severe hot flashes —** Hormonal or other pharmacotherapy is usually needed for women with more bothersome hot flashes. Women with an intact uterus need both estrogen and a progestin, while those who have undergone hysterectomy can receive estrogen only
- **Consider the initiation of MHT** to be a safe option for healthy, symptomatic women who are within 10 years of menopause or younger than age 60 years and who do not have contraindications to MHT[3]
- For women who choose estrogen or combined estrogen-progestin therapies, short-term use has been suggested (generally for not more than five years) based on the original interpretation of the Women's Health Initiative (WHI) data
- However, several expert societies, including the Endocrine Society, the American College of Obstetrics and Gynecology, the North American Menopause Society, and the International Menopause Society **no longer recommend a specific duration of treatment in symptomatic women, based upon revised safety data and the observation that hot flashes persist well beyond five years in many women**

2. Genito-Urinary Symptoms

The primary indication for treatment of GSM is to relieve symptoms that cause distress in a patient who has diminished ovarian estrogen production due to menopause or other etiologies. Vulvovaginal symptoms include vaginal dryness, burning, pruritus, dyspareunia, vaginal discharge, bleeding, or spotting. Urinary tract symptoms include dysuria, urinary frequency, urethral discomfort, or, infrequently, haematuria.

Management is guided by the patient's symptoms, overall medical health, and goals.

- **Initial therapy –** For most patients with GSM, nonhormonal vaginal moisturizers and lubricants are the preferred approach to initial therapy. Pelvic floor muscle (Kegel) exercises should be encouraged.
- Subsequent therapy[3] - Vaginal ET is most effective in the treatment of urogenital atrophy. Low-dose vaginal preparations are as effective as systemic therapy.

  Treatment should be started early to prevent irreversible atrophic changes and may need long-term treatment to maintain benefits. Regular sexual activity, including vaginal coitus, should be encouraged to maintain vaginal health
- Limited data are available on the use of vaginal ET in women with breast cancer and EC
- Recurrent urinary tract in this age after ruling out other causes may benefit from the local application of ET
- Progesterone supplement for endometrial protection is not needed along with the use of vaginal estrogen
- Endometrial surveillance is not necessary in low-risk asymptomatic woman

- Low-dose vaginal estrogen formulations reported no incidence of increase in CHD, stroke, and VTE.
- There are no contraindications for use in non-estrogen-dependent cancers

3. Premature Ovarian Insufficiency or Early Menopause

Menopause occurring at an age less than 2 SD below the mean estimated age for the reference population is called as POI. It is a spectrum ranging from occult to overt POI

The NFHS of 2015-16 collected information from a sample of more than 90,000 married women aged between 15 and 49 years and covering 99% of the India's population living in 26 states; 3.7% of the women are already in menopause by the age of 30–34 years; and the incidence rises to 8% for the age bracket of 35–39 years.[3]

Women with untreated premature menopause are at increased risk of developing osteoporosis, CVD, dementia, cognitive decline, and Parkinson's and all-cause mortality.

- Appropriate counselling, lifestyle modification, and HT form the mainstay of treatment. HT should be started as early as possible in women with POI and continued till the age of natural menopause.
- Emerging evidence suggests that physiological dose of HT is superior to hormone contraceptives. HT has bone protection effect.
- Androgen replacement may be considered for women with persistent fatigue and loss of libido, in spite of estrogen replacement.
- Counsel women that HT is not a contraceptive, and erratic ovulation and pregnancy may occur in POI
- MHT should be considered in women aged <50 years who have undergone surgical menopause
- Younger women may require higher doses for symptom relief or protection against bone loss
- There is no evidence that HT increases risk of breast cancer, CVD, or dementia, over and above that found in menstruating women with a normally timed menopause

4. Osteoporosis

A meta-analysis of RCTs found that oral and transdermal estrogen (with or without progestogen) reduces hip, vertebral, and total fracture risk by 20%–37%.[7] ET/EPT prevents all osteoporotic fractures even in low-risk population; it increases lumbar spine BMD up to 7.6% and femoral neck BMD up to 4.5% over 3 years.[3]

- All preparations including low-dose, nonoral routes of estrogen are effective in preserving bone mass
- Estrogen–progesterone therapy (EPT) or ET may be used for the prevention and treatment of osteoporosis in the early post menopause in symptomatic women unless there is a contraindication.
- MHT is included in postmenopausal osteoporosis guidelines, with greater fracture risk reduction seen in women starting before age 60.
- MHT should not be started solely for bone protection after 10 years of menopause. Extended use of MHT in women with reduced bone mass is an option after considering the risk–benefit analysis compared to the other available therapies for osteoporosis
- While protection decreases after stopping MHT, there is no rebound fracture risk .

  Although not universally approved for bone protection, MHT should be considered as a first option for bone protection in women with early or natural menopause over antiresorptive or osteoanabolic therapies, unless there are over-riding reasons for bone-specific therapy use such as glucocorticoid associated bone loss.8 Furthermore, MHT may be continued long-term if the benefits for bone health and menopause symptoms continue to outweigh the side effects and risks.

Additional Preventive Benefits: Future probable Indications

1. Cognitive function and Alzheimer's disease

Midlife women commonly experience changes in their cognitive function as they transition through menopause and are often concerned if these symptoms may be initial stages of a more serious cognitive disorder.

FACTS

- Menopause brain fog refers to the

constellation of cognitive symptoms experienced by women around menopause, frequently manifesting in memory and attention difficulties like forgetting names, numbers and unable to multitask.

- Cognitive difficulties at midlife are linked to changes in E2, VMS, sleep and mood.
- Treating these symptoms may benefit cognition, although clinical trial data are not yet available to definitively recommend that approach

MHT role in Cognition function[2]

- Based on current guidelines, MHT is not recommended at any age to treat cognitive concerns at menopause or prevent cognitive decline or dementia.
- Use of MHT early in post menopause appears safe for cognitive function.
- Use of ET in women with early menopause may be helpful in maintaining cognitive function and lowering risk of dementia.
- Use of ET even late in post menopause appears to be safe for cognitive function.
- Use of MHT late in post menopause is risky if the formulation is CEE/MPA but appears to be neutral if the formulation is oral E2 plus vaginal progesterone.
- The magnitude of the effect of MHT on dementia, whether beneficial or adverse, in the literature is small.
- There is no reliable finding in the literature to guide treatment decisions about MHT formulation or duration of use on dementia risk.
- Clinical counselling should focus on a multi-pronged approach to reducing dementia through such modifiable risk factors as obesity, hypertension, diabetes, physical activity, smoking, cognitive activity, social interaction, hearing impairment and depression.

2. Primary prevention of CVD risk and all-cause mortality[4]

FACTS

- Incidence of CHD in women lags behind men by 10 years and incidence of MI and sudden death in women lags behind men by 20 years. This delay in onset of CVD appears due to the cardioprotective effects of endogenous estrogen.
- While premenopausal, women are protected from clinical manifestations of CVD relative to men, after menopause, CVD complications exceed those of men.
- Although there is an age-associated increase in CVD incidence for women as there is for men, age-specific CVD incidence is two- to six-fold greater for postmenopausal than premenopausal women across the age range <40–54 years.

Benefits of MHT for reducing CVD risk

A Cochrane review in 2015 of RCTs of HT showed an overall reduction in risk of CHD and all-cause mortality in women who started HT within 10 years of menopause.

The safety of HT used **early in menopause** is further supported by the ELITE and KEEPS study.[6]

MHT has favourable or neutral effects on CHD risk when started in women younger than 60 years old or within 10 years of menopause, in the absence of contraindications.

Arguments in Favour

- It causes reduction of all-cause mortality and CVD in younger women on menopausal HRT
- Lack of effectiveness of other primary prevention strategies for reduction of all-cause mortality and CVD in women
- Additional benefits beyond reduction of all-cause mortality including
  - o reduction in menopausal symptoms,
  - o potential reductions in CVD, cancer and other mortalities
  - o prevention of new onset diabetes mellitus, osteoporosis and bone fracture prevention
  - o improved quality of life
  - o cost-effectiveness and reduced economic burden

HRT is a sex-specific and time-dependent primary CVD preventive therapy that concomitantly reduces all-cause mortality as well as a diversity of other aging-related diseases with an excellent risk profile.

Despite this, no society guidelines have as yet recommended MHT for primary prevention of CVD.

It is time to recognize that HRT reduces all-cause mortality and CVD, and that it is all about timing.

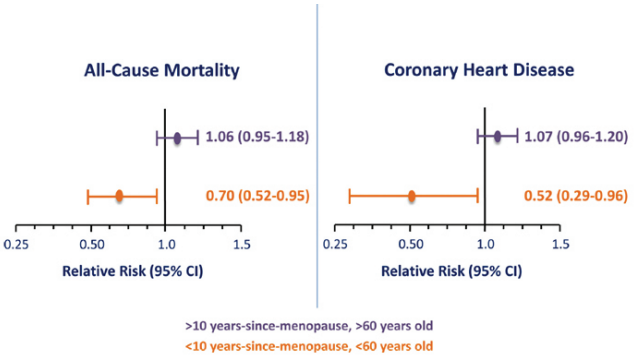


Figure 1. Cochrane meta-analysis validates the Salpeter et al., meta-analyses (Fig. 6) showing similar reductions in all-cause mortality and coronary heart disease in women initiating HRT <60 years old and/or <10 years-since-menopause relative to placebo (26). Nineteen randomized controlled trials of 40.410 women comparing hormone replacement therapy of estrogen with or without progestogen with placebo. CI = confidence interval

Should women without valid indications be prescribed MHT?[1]

- Although MHT is primarily indicated for the relief of distressing menopause symptoms, it is often incorrectly promoted to women as an 'elixir of youth'. It should not be given beyond prescribed core indications.
- It is important to counsel women from the outset that menopause symptoms such as VMS and sleep disturbances, mood swings and brain fog will usually improve with time and may not require treatment.

Conclusion/ Key Practise Points

The ultimate goal is to empower women with evidence-based information to make an individualized choice that is right for them.

- In healthy women less than 10 years since menopause onset, or younger than 60 years, hormone therapy is a safe, effective treatment option for menopausal symptoms; the benefits extend beyond the control of vasomotor symptoms and genitourinary syndrome of menopause to include reductions in risk of fracture and type 2 diabetes.
- MHT is the First line treatment for symptoms causally linked with menopause: VMS & related fatigue, sleep & mood changes. Urogenital atrophy related symptoms •
- For those experiencing loss of ovarian function at an earlier age than the average population norms, consideration for initiation of hormone therapy is advisable not only to mitigate the symptoms resulting from hypoestrogenism, but also to prevent the long-term health consequences n CVS and bone, associated with premature onset of estrogen insufficiency
- There is good evidence that MHT reduces the incidence of osteoporosis and risk of osteoporosis-related fractures, and in some countries – for example, in the USA and Australia – this is also a primary indication for MHT.
- There are also good data supporting its use for reducing the risk of cardiovascular disease, thereby having a positive impact on life expectancy, but MHT is not currently licensed anywhere globally for these indications.
- The research findings regarding the impact of MHT on cognition and dementia are considerably less reliable and require further research.
- **Prior to prescribing, the predominant symptoms should be identified, and realistic goals set as to the degree of improvement expected, and also over what timeline a response to treatment is expected**.

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Types, Preparations and Routes of MHT Delivery

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According to the Indian Menopause Society (IMS) guidelines, **menopause** is defined as the **permanent cessation of menstruation** resulting from the loss of ovarian follicular activity. It is confirmed after a woman has had no menstrual periods for **12 consecutive months**, without any other obvious pathological or physiological cause. Typically, menopause occurs between the ages of 45 and 55, with the average age being around 46-47 years in India. The transition period leading up to menopause, known as **perimenopause**, may involve fluctuating hormone levels and the onset of various symptoms, such as hot flashes, mood changes, and irregular periods.

MHT, also known as hormone replacement therapy (HRT), is used to restore hormones to their pre-menopausal levels to alleviate these symptoms. However, MHT is not a one-size-fits-all solution, as it requires careful selection based on individual health needs and risk factors. Recent research has contributed to a better understanding of the optimal use of MHT and its role in postmenopausal women.

Window of Opportunity Concept in MHT:

1. **Timing of Initiation**: Research suggests that starting MHT early in the menopausal transition—ideally within **10 years** of menopause or before the age of **60**—can provide significant benefits for symptom management (like hot flashes, night sweats, and vaginal dryness) and improve long-term outcomes related to bone health and cardiovascular disease . The idea is that the sooner MHT is started after menopause, the more it mimics the body's natural hormonal environment and has protective effects, particularly on the heart and bones.
2. **Cardiovascular Health**: Studies have shown that early initiation of MHT may have a protective effect on the cardiovascular system, potentially lowering the risk of heart disease, especially if therapy is started during the early postmenopausal years. However, starting MHT later, particularly after age 60 or more than 10 years post-menopause, may have a neutral or potentially harmful effect on cardiovascular health. This has been attributed to the way estrogen impacts the vascular system and endothelial function when given early.
3. **Bone Health**: MHT initiated within the window of opportunity has also been shown to be effective in preserving bone density and preventing fractures. Estrogen's effect on bone resorption is most effective when administered soon after menopause, when bone loss is rapid .
4. **Breast Cancer Risk**: One of the main risks of MHT is an increased risk of breast cancer, especially with long-term use. However, studies suggest that the risk is lower when MHT is started early and used for a shorter duration. Delaying the initiation of MHT until later in life, particularly after age 60, may increase the risk of breast cancer .
5. **Cognitive Function**: Some research indicates that initiating MHT closer to menopause may

have positive effects on cognitive function and help prevent dementia. However, this evidence is still under investigation, with studies showing mixed results on the role of estrogen in brain health.

Types of Menopause Hormone Therapy

MHT consists of two main types: **estrogen-only therapy** and **combined estrogen and progesterone therapy**. These two types are determined by whether the patient has undergone a hysterectomy (surgical removal of the uterus).

1. **Estrogen-Only Therapy**: Estrogen-only MHT is typically prescribed to women who have undergone a hysterectomy, as they no longer have a uterus and do not need progesterone to protect the endometrial lining from hyperplasia (abnormal growth). Estrogen alone is effective in treating hot flashes, vaginal dryness, and other symptoms of menopause.
2. **Combined Estrogen and Progesterone Therapy**: For women who still have a uterus, estrogen is generally combined with progesterone (or its synthetic counterpart, progestin) to reduce the risk of endometrial hyperplasia and subsequent endometrial cancer, which can be a side effect of unopposed estrogen. The combination of estrogen and progesterone is typically administered in one of two ways:
    - **Continuous Combined Therapy**: Both estrogen and progesterone are taken every day.
    - **Cyclic or Sequential Therapy**: Estrogen is taken every day, and progesterone is added for a certain number of days per month (usually 10-14 days) to allow for a regular withdrawal bleed, mimicking the natural menstrual cycle.
3. **Bioidentical Hormones**: Bioidentical hormone therapy refers to hormones that are chemically identical to those the body produces naturally. Bioidentical estrogen and progesterone are often marketed as a "natural" alternative to synthetic hormones, although they are not necessarily safer. The use of bioidentical hormones is popular in some alternative medicine circles, but the long-term safety of compounded bioidentical hormones has not been conclusively proven in large clinical trials. These hormones may be formulated in a pharmacy in specific doses and combinations, often in customized preparations.
4. **Tibolone**: Tibolone is a synthetic steroid that has estrogenic, progestogenic, and androgenic effects. It is used in some countries as an alternative to traditional MHT. Tibolone can provide relief from menopausal symptoms, including hot flashes and vaginal dryness, while also offering potential benefits for bone health. It is not approved for use in all countries, but it is recognized as an option for some postmenopausal women who cannot take estrogen-based therapies.

Preparation and Dosing of MHT

The preparation of MHT depends on the type of therapy being administered and the individual's specific health considerations. When considering MHT, healthcare providers take into account factors such as the severity of menopausal symptoms, any contraindications (such as a history of certain cancers, thromboembolism or liver disease), and the patient's preferences.

Estrogen Preparations

Estrogen is a primary hormone used in Menopause Hormone Therapy (MHT) to alleviate menopausal symptoms. It can be delivered through various forms, each with its own set of advantages, considerations, and methods of administration. The most common preparations include oral tablets, transdermal patches, topical gels/creams/sprays, and vaginal estrogen. These different routes allow healthcare providers to tailor treatment to an individual's needs, taking into account factors such as the severity of symptoms, existing health conditions, and the risks of systemic absorption.

1. Oral Tablets

Oral estrogen is one of the most common forms of estrogen therapy. The most frequently used oral preparations include **estradiol** (a synthetic form of estrogen) and **conjugated equine estrogens** (derived from the urine of pregnant mares). Oral estrogen tablets are typically taken once daily, offering a simple and convenient method of administration.

Advantages:

- **Ease of use**: Oral tablets are widely available and simple to take, making them a popular choice for many women.
- **Systemic effects**: They provide systemic estrogen, which can address a broad range of symptoms, such as hot flashes, night sweats, and vaginal dryness.

Considerations:

- **Thromboembolic risk**: Oral estrogen is metabolized in the liver, which can increase the risk of venous thromboembolism), especially in women who have other risk factors (e.g., obesity, smoking, or a history of clotting disorders).
- **Liver metabolism**: Since oral estrogen passes through the liver, it may be associated with a higher incidence of liver-related side effects or increased clotting factors.

For women who are at a higher risk of thromboembolism or have liver disease, oral estrogen may not be the best option.

2. Transdermal Patches

Transdermal estrogen patches are a popular alternative to oral tablets. These patches are applied to the skin, typically on the lower abdomen or buttocks, and deliver a continuous supply of estrogen through the skin into the bloodstream. The patches are typically replaced once or twice a week, depending on the specific product.

Advantages:

- **Reduced risk of thromboembolism**: Since transdermal estrogen bypasses the liver, it avoids the liver's first-pass metabolism, which is associated with a lower risk of blood clot formation (venous thromboembolism) compared to oral estrogen.
- **Stable hormone levels**: The continuous release of estrogen provides more stable and consistent hormone levels, which can lead to more effective symptom management.
- **Convenience:** Patches require fewer replacements compared to daily oral administration, offering a more convenient option for some women.

Considerations:

- **Skin irritation**: Some women may experience skin irritation or allergic reactions at the site of the patch.
- **Adherence**: There is a need to ensure that the patch stays on securely, which may be challenging for women with active lifestyles or during activities like bathing or swimming.

3. Topical Gels, Creams, and Sprays

Topical estrogen preparations, including gels, creams, and sprays, are applied directly to the skin, typically on the arms, legs, or abdomen. These forms deliver estrogen through the skin and are absorbed locally, reducing the systemic absorption of the hormone.

Advantages:

- **Localized effects**: These preparations are often used to treat symptoms that are confined to specific areas, such as vaginal dryness or skin-related menopausal symptoms. This localized effect minimizes the risk of systemic side effects.
- **Lower thromboembolic risk**: Since the estrogen is absorbed through the skin and not metabolized in the liver to the same extent as oral estrogen, there is a reduced risk of thromboembolic events.
- **Ease of application**: Gels and creams are easy to apply and can be incorporated into daily routines.

Considerations:

- **Messy application**: Some women may find the application of gels or creams to be somewhat messy or inconvenient.
- **Potential for skin irritation**: Like transdermal patches, these preparations may cause skin irritation or allergic reactions at the application site.
- **Absorption variability**: The absorption of estrogen can be influenced by factors like skin type and the area of application, which may affect the consistency of the therapy's effectiveness.

These topical treatments can be especially useful for managing symptoms such as hot flashes or vaginal dryness, particularly in women who prefer non-oral therapies.

4. Vaginal Estrogen

Vaginal estrogen is a highly effective form of treatment for women who primarily experience vaginal dryness, urinary incontinence, or other localized symptoms of menopause. This preparation is available in various forms, including **creams**, **tablets**, and **rings**, which are inserted directly into the vagina.

Advantages:

- **Localized relief**: Vaginal estrogen works locally within the vaginal tissues, providing targeted relief for symptoms like vaginal dryness, itching, burning, and painful intercourse. It also improves

urinary symptoms in some women.

- **Minimal systemic absorption**: Because the estrogen is absorbed primarily in the vaginal area, it has minimal systemic effects. This makes vaginal estrogen an attractive option for women who may be at higher risk for side effects related to systemic hormone therapy (e.g., thromboembolism or breast cancer).
- **Convenience**: Vaginal tablets and creams can be used on a regular basis, often with flexible dosing schedules. Vaginal rings, on the other hand, can remain in place for several months before needing replacement, offering long-term convenience.

Considerations:

- **Initial discomfort**: Some women may experience mild irritation or discomfort when starting vaginal estrogen therapy, although these side effects are usually temporary.
- **Not for systemic symptoms**: Vaginal estrogen is most effective for addressing localized symptoms, so it may not provide relief for broader menopausal symptoms like hot flashes, mood swings, or night sweats.

Vaginal estrogen is considered a first-line therapy for women experiencing genitourinary symptoms related to menopause. For many women, it can be used in conjunction with other forms of MHT to address both systemic and localized symptoms.

Here's an overview of the main types of estrogen and typical dosages:

1. Oral Estrogen (Pill Form)

- **Common preparations:**
  - **Conjugated equine estrogens** (e.g., Premarin)
  - **Estradiol** (e.g., Estrace)
- **Typical doses:**
  - **Premarin**: 0.3 mg to 1.25 mg daily
  - **Estradiol**: 1 mg to 2 mg daily

2. Transdermal Estrogen (Patch or Gel)

- **Common preparations**:
  - **Estradiol patch** (e.g., Vivelle-Dot, Alora, Climara)
  - **Estradiol gel** (e.g., EstroGel, Divigel)
- **Typical doses**:
  - **Patch**: 0.025 mg/day to 0.1 mg/day (the patch dose varies by brand)
  - **Gel**: 0.75 g to 1.5 g daily (which delivers 0.25 mg to 0.5 mg of estradiol)

3. Vaginal Estrogen (Cream, Tablet, or Ring)

- **Common preparations**:
  - **Estradiol vaginal cream** (e.g., Estrace cream)
  - **Estradiol vaginal tablet** (e.g., Vagifem)
  - **Estring** (estradiol vaginal ring)
- **Typical doses:**
  - **Estradiol cream**: 1 to 2 grams daily for the first 2 weeks, then reduced to 1 gram 2–3 times per week
  - **Estradiol tablet**: 10 mcg to 25 mcg daily (usually for vaginal dryness and discomfort)
  - **Vaginal ring:** Estring provides continuous release of 7.5 mcg/day, and is typically replaced every 3 months

4. Injection or Implantable Estrogen

- **Common preparations:**
  - **Estradiol cypionate** (e.g., Delestrogen) – an intramuscular injection
  - **Estradiol implant** (rare, used in some countries)
- **Typical doses**:
  - **Estradiol cypionate**: 1–5 mg every 1–4 weeks, depending on needs

Progesterone and Progestin Preparations:

When progesterone is included in MHT, it is typically administered in the following forms:

1. **Oral Progestins**: Synthetic progestins (such as dydrogesterone,medroxyprogesterone acetate or norethindrone acetate) are taken orally, usually in combination with estrogen. They help protect the endometrial lining and reduce the risk of endometrial hyperplasia.
2. **Intrauterine Device (IUD)**: A progestin-releasing intrauterine device (IUD) can also be used as part of combined hormone therapy for women with a uterus. The IUD releases progestin directly into the uterus, which helps protect against endometrial hyperplasia without the need for oral progestin.
3. **Vaginal Progestin**: Vaginal progesterone is also available and can be used for women who cannot tolerate oral progestins. This preparation delivers progesterone directly to the uterus and may be an alternative for some patients.

Dydrogesterone in Menopausal Hormone Therapy (MHT)

Dydrogesterone is a synthetic progestin that is commonly used in menopausal hormone therapy (MHT). It is structurally similar to natural progesterone, and its use in MHT has been studied for its safety and efficacy profile. Dydrogesterone is often used in combination with estrogen to protect the endometrial lining from hyperplasia, particularly in women with a uterus.

Benefits of Dydrogesterone:

1. **Endometrial Protection**: Like other progestins, dydrogesterone helps protect against endometrial hyperplasia, which is a potential side effect of estrogen therapy. This protection is crucial for women with an intact uterus.
2. **Lower Risk of Adverse Effects**: Dydrogesterone has a more favorable safety profile compared to some other synthetic progestins, such as medroxyprogesterone acetate (MPA). It has been associated with a lower risk of adverse metabolic effects, including lipid profile changes and insulin resistance .
3. **Fewer Androgenic Effects**: Compared to other synthetic progestins, dydrogesterone has a lower androgenic effect, meaning it is less likely to cause side effects such as acne, hair loss, and weight gain.
4. **Breast Cancer Risk**: Some studies suggest that dydrogesterone may have a more favorable impact on breast tissue compared to other synthetic progestins. While long-term studies on breast cancer risk are still ongoing, it is generally considered to have a lower risk compared to MPA .
5. **No Significant Impact on Coagulation**: Dydrogesterone does not seem to significantly affect blood clotting parameters, which makes it a safer choice in terms of thromboembolic risk compared to other progestins, such as MPA.

Limitations and Considerations:

- **Limited Data on Long-Term Use**: While dydrogesterone is considered safe in the short-to-medium term, there is still a need for further studies regarding its long-term safety, particularly regarding its impact on breast cancer risk over many years of use.

Tibolone in Menopausal Hormone Therapy

Tibolone is a synthetic steroid used in menopausal hormone therapy (MHT) that has both estrogenic, progestogenic, and androgenic effects. It is often prescribed to women who experience menopausal symptoms, particularly when estrogen alone is not sufficient to address all their symptoms or when a progestogen is needed for endometrial protection. Tibolone is primarily used in postmenopausal women and is known for its convenience, as it does not require the addition of a separate progestogen when treating women with a uterus.

Mechanism of Action:

Tibolone is a unique compound in MHT because it acts through three different mechanisms:

1. **Estrogenic Effects**: It binds to estrogen receptors in tissues such as the bone and vagina, providing relief from common menopausal symptoms like hot flashes, vaginal dryness, and osteoporosis.
2. **Progestogenic Effects**: Tibolone also has progestogen-like activity that helps protect the endometrium from hyperplasia, meaning it can be used in women with an intact uterus without requiring an additional progestin.
3. **Androgenic Effects**: Tibolone has some androgenic properties, which may improve libido and energy levels in some women, but it may also increase the risk of androgenic side effects, such as acne and hair thinning.

Benefits of Tibolone in MHT:

1. **Symptom Relief**: Tibolone is effective in treating a broad range of menopausal symptoms, including hot flashes, night sweats, mood changes, and vaginal dryness. It has been shown to be as effective as traditional estrogen therapy in many cases.
2. **Bone Health**: Tibolone has beneficial effects on bone mineral density (BMD), helping to prevent osteoporosis and reduce fracture risk in postmenopausal women. This is particularly important for women at high risk of osteoporotic fractures.
3. **Convenience**: Tibolone offers the advantage of not requiring the addition of a separate progestogen for endometrial protection, making it a more straightforward treatment option compared to traditional combined therapies that require both estrogen and progestin.

4. **Sexual Function**: Tibolone has been associated with improvements in sexual desire and arousal, which may be beneficial for women who experience sexual dysfunction after menopause.

Risks and Considerations:

1. **Thromboembolic Risk**: While tibolone does not seem to increase the risk of venous thromboembolism (VTE) to the same degree as some other forms of hormone therapy, it is still associated with a slightly elevated risk. Women with a history of VTE or other risk factors should use tibolone with caution.
2. **Breast Cancer**: Tibolone's impact on breast cancer risk is still being studied. Some evidence suggests a small increased risk of breast cancer with long-term use, particularly in women over 60 years of age, though the risk is generally lower compared to estrogen-progestin combinations . As with any hormone therapy, the decision to use tibolone should be based on individual risk factors.
3. **Mood and Mental Health**: While tibolone may help improve mood and reduce depressive symptoms in some women, it has been associated with mood swings and irritability in others. Its androgenic effects may also contribute to these mood changes.

Latest Recommendations:

- **Use in Early Postmenopausal Women**: Tibolone is generally recommended for use in women within 10 years of menopause or those who are under 60 years old, as the benefits for bone health and symptom relief are more pronounced in this group. It may be less suitable for women with a higher cardiovascular risk or a history of breast cancer .
- **Not First-Line for Women with High Cardiovascular Risk**: Tibolone is not recommended for women with a history of heart disease or high cardiovascular risk, due to its potential impact on lipid profiles and the slight increase in VTE risk .
- **Alternative for Women Seeking Libido Improvement**: Tibolone may be a useful option for women who seek improvement in sexual function, as its androgenic effects may help boost libido . However, its use should be carefully considered in women with a history of androgenic side effects.
- **Endometrial Protection**: Tibolone does not require an additional progestogen for endometrial protection, making it an attractive option for women who have an intact uterus and are at risk of endometrial hyperplasia or carcinoma when taking estrogen .

Here's a simple chart outlining the typical doses of various progestins and tibolone used in menopausal hormone therapy (MHT):

Drug/Type of Therapy	Typical Dose	Formulation	Use
Micronized Progesterone	100-200 mg daily (oral), 200 mg for 12 days per cycle	Oral tablet, Vaginal gel/insert	Protects the endometrium from hyperplasia in women with a uterus.
Norethindrone Acetate	0.5 to 1.0 mg daily	Oral tablet	Combined with estrogen to protect the endometrium.
Medroxyprogesterone Acetate (MPA)	2.5 to 10 mg daily or 5-10 mg cyclically	Oral tablet, Injection	Progestogen used with estrogen to prevent endometrial hyperplasia.
Dydrogesterone	10 mg daily (for 12-14 days per cycle)	Oral tablet	Progestogen used for endometrial protection in combination with estrogen.
Tibolone	2.5 mg daily	Oral tablet	For overall menopausal symptom relief, including osteoporosis.

The choice of therapy and specific dosing should always be tailored to the individual's health history and symptoms, and it's essential to follow a healthcare provider's guidance when using MHT.

Benefits and Risks of MHT

Benefits:

MHT is effective in alleviating many of the symptoms of menopause. It has been shown to:

- Significantly reduce hot flashes and night sweats.
- Alleviate vaginal dryness and urinary symptoms.
- Improve mood and decrease depression associated with menopause.
- Protect against bone loss and reduce the risk of osteoporosis.
- Improve sleep quality in some women.

Risks:

Despite its benefits, MHT is not without risks. Long-term use of MHT has been associated with several potential health risks, including:

- **Breast Cancer**: The use of combined estrogen and progestin therapy has been linked to an increased risk of breast cancer. The risk appears to increase with the duration of use.
- **Cardiovascular Disease**: Studies have shown that MHT may increase the risk of heart disease and stroke, especially when started in older women or those with existing cardiovascular risk factors.
- **Venous Thromboembolism**: Oral estrogen has been linked to an increased risk of thromboembolism and deep vein thrombosis.
- **Endometrial Cancer**: For women who have not had a hysterectomy, estrogen-only therapy can increase the risk of endometrial cancer if used without progesterone.

Recent research, however, suggests that the risk of these complications may be lower if MHT is initiated close to the time of menopause and used for a limited duration.

Current Trends and Considerations

Recent guidelines from health organizations such as the North American Menopause Society (NAMS) and the American College of Obstetricians and Gynecologists (ACOG) emphasize individualized care and a shared decision-making approach when prescribing MHT. Women with significant menopausal symptoms may benefit from short-term MHT, while those with fewer symptoms may consider non-hormonal alternatives or lifestyle changes.

1. **Timing of Initiation**:
    - **Ideal window**: MHT should be initiated **within 10 years of menopause** or before the age of **60** to maximize benefits and minimize risks. This is referred to as the "window of opportunity" for optimal cardiovascular and bone health outcomes .
2. **Type of Therapy**:
    - **Estrogen-only therapy** is suitable for women who have had a hysterectomy, as they do not require progestin for endometrial protection.
    - **Combination estrogen-progestin therapy** is recommended for women with a uterus to reduce the risk of endometrial hyperplasia and cancer.
    - **Transdermal estrogen** (patches, gels, or creams) is considered to have a safer profile than oral estrogen, particularly regarding VTE risk.
3. **Duration of Therapy**:
    - **Short-term use**: MHT is generally recommended for **short-term use** (up to 5 years) to manage moderate to severe menopausal symptoms.
    - **Long-term use**: If MHT is used beyond 5 years, it should be reassessed regularly for ongoing symptom relief and risks, especially for cardiovascular and breast cancer risks.
4. **Individualized Approach**:
    - MHT should be tailored to the individual based on personal health risks, including cardiovascular health, cancer history, and the severity of menopausal symptoms. Close monitoring and ongoing risk assessment are essential.

Research continues into the long-term safety of MHT, with newer studies focusing on personalized approaches and understanding how factors like age, timing of initiation, and underlying health conditions impact the benefits and risks of therapy.

Conclusion

Menopause hormone therapy remains a cornerstone treatment for managing the symptoms of menopause. With a range of hormone types,

preparations, and routes of administration, MHT can be tailored to meet the needs of individual women. However, it is essential to balance the benefits of symptom relief with the potential risks, particularly when considering long-term use. As research progresses, clinicians will continue to refine their approaches to MHT, offering women safer and more effective treatments that improve their quality of life during the postmenopausal years.

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MHT Prescription for Different Metabolic Health Risk Types

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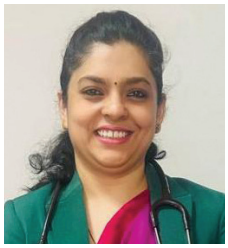

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Menopausal transition is a complex physiological phase which involves several endocrine and cardiometabolic changes. It is now a well-established fact that premenopausal women are less predisposed to cardiovascular and metabolic diseases as compared to their age matched male counterparts due to the protective benefits of estrogen. At menopause, there is a sharp decline in estrogen production leading to adverse changes in many risk enhancing factors which results in accelerated physical, physiological, and neuroendocrine aging in women such that cardiovascular diseases (CVD) are the leading cause of death in this age group of women. The mortality rates due to ischemic heart disease, stroke, peripheral vascular disease and venous thromboembolism (VTE) are higher in postmenopausal women as compared to age controlled men.[1]

What changes at Menopause?

The Study of Women's Health Across the Nation (SWAN) study[2] revealed that menopause was associated with changes in body composition, namely increase in fat mass and decrease in lean mass. Estrogen promotes the accumulation of gluteofemoral fat, however there is accumulation of central fat due to the loss of estrogen and relative hyperandrogenism that is associated with menopause. Reduction of lean body mass and decline in oxygen consumption by the muscles, leads to decrease in exercise capacity and thereby, energy expenditure. This combined with age related decline in metabolic rate and increase in appetite stimulant ghrelin, often tips the balance towards obesity in the postmenopausal years. Though the weight and Body Mass Index (BMI) are not disturbed in the early menopausal years, there is a definite change in the waist : hip ratio.

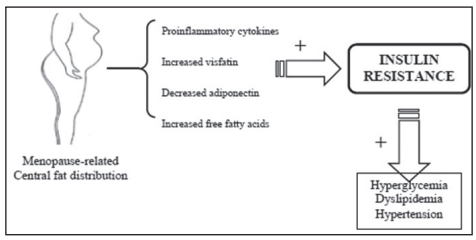

Figure 1: A summary of the major pathogenetic mechanisms underlying the relationship of menopause with metabolic syndrome.

Another noticeable change at menopause due to the indirect genomic effects of estrogen deficiency is the change in lipid dynamics and profile. Dyslipidemias with increase in total and Low Density Lipoprotein (LDL) cholesterol, triglycerides (TG) and Lipoprotein A (Lp(a) and a decrease in High Density Lipoprotein (HDL) cholesterol as a result of decline in circulating estradiol levels, are the hallmarks of this stage. This along with the lower levels of sex hormone binding globulin (SHBG) and resultant increased circulating androgen levels, lead to greater risk of blood coagulability making postmenopausal women vulnerable for formation of intravascular thrombi and atherogenesis. The other effects are loss of beneficial vasodilatation, loss of Nitric oxide (NO) synthesis in vessels and increase in inflammatory markers. It is seen that, in most women, the pathophysiology of cardiovascular disease involves endothelial dysfunction, small vessel and diffuse atherosclerosis as a major cause of ischemia without evidence of blockade in the coronary arteries.

Link between Menopause & CVD

The increasing waist circumference and androgen-to-estrogen ratio are independent predictors of insulin

resistance and ultimately metabolic disease risk in postmenopausal women. By definition, abdominal girth > 88cm, BP>130/90, Fasting blood sugar > 110 mg%, TG>150 mg/dl and HDL cholesterol < 50 mg/dl constitute the components of metabolic syndrome[3] (METS) with a prevalence of 42% in postmenopausal women compared to 16% in premenopausal women. The worldwide prevalence of METS is also on the increase, affecting nearly 20-25% of the adult population (approximately 31% women and 18% men). Simultaneously, there is rise in prevalence of insulin resistance also which may be explained partially by the 'thrifty gene' hypothesis.[4]

The Interheart Study[5] evaluated potentially modifiable risk factors associated with Acute myocardial infarction (AMI) and suggested principles for basing strategies to prevent it. Fifty percent of cardiovascular events occurred in those with metabolic syndrome which had nearly similar risk factors. Many of these "risk enhancers to cardiovascular disease" seen in menopausal women are reversed by oral hormone replacement therapy which can also play a role in preventing cardiovascular morbidity by mechanisms such as vasodilatation of blood vessels, increased LDL clearance and insulin sensitivity and reduced lipid peroxidation and vascular smooth muscle cell proliferation.

Effect of hormone therapy on CVD risk factors

The need of the hour is to tailor menopausal hormone therapy (MHT) as per need and risk assessment. The commonest prescribed estrogen preparations are conjugated equine estrogens (CEE), 17-β estradiol, estradiol valerate and ethinyl estradiol (synthetic and most potent derivative). **(TABLE 1)** Oral preparations result in stimulation of certain proteins, renin substrate and angiotensin and increase HDL and SHBG levels. Oral estrogen is also associated with about a 25% increase in TG and stimulates hepatic coagulation factors and inflammatory markers such as C-Reactive Protein (CRP) and matrix metallopeptidase 9, with implications for CVD. In contrast to oral therapy, transdermal and topical preparations of estrogen have the advantage of not increasing circulating TG but the disadvantage of not increasing HDL cholesterol. As there is less liver exposure, transdermal and topical estrogen therapy may have less effect on gallbladder disease, CRP and coagulation factors. Transdermal estrogen has negligible effects on SHBG and thus less negative effect on sexual functioning. Progestogen therapy is required for all women taking estrogen unless they have had a hysterectomy. Progestogens include micronized progesterone and synthetic progestins which may be combined with estradiol in a tablet or patch, or taken in addition to the estrogen therapy. The 52 mg LNG-IUD is an alternative to systemic progestogen therapy. In the combination HT, the androgenic progesterones (Medroxy progesterone acetate, Norethisterone, Levonorgestrel) were found to blunt the beneficial effects of estrogens. Selecting a metabolically neutral progestogen such as micronized progesterone or dydrogesterone, is recommended to maintain higher plasma high-density lipoprotein (HDL) cholesterol.

Table 1: An approximate equivalence of doses and routes of different formulations of estrogens

Oral	Dose equivalent (mg)
Conjugated equine estrogens	0.625
17beta-estradiol	1
ethinyl estradiol	0.005-
Transdermal	Dose equivalent (mg)
17beta-estradiol Patch	0.05
17beta-estradiol gel	1.5 mg / 2 metered doses
Vaginal	Dose equivalent (mg)
Conjugated equine estrogens	0.3125
17beta-estradiol	0.5

Source: Powers MS, Schenkel L, Darley PE. Pharmacokinetics and pharmacodynamics of transdermal dosage forms of estradiol: comparison with conventional oral estrogens used for hormone replacement. Am J Obstet Gynecol 1985;152:1099– 106.

Effects of MHT on atherosclerosis and related clinical events are dependent on when MHT was initiated in relation to menopause and age. The Women's Health Initiative (WHI) study and its aftermath proved that Estrogen Replacement Therapy (ERT) when started soon after menopause or around mean age of 50 years, confers cardiovascular benefits, whereas delaying initiation of ERT to more than 10 years after menopause had adverse cardiovascular outcomes. This was in agreement to the "timing hypothesis" first described by Clarksons.[6] The timing of initiation of hormone therapy relative to age and time since menopause is crucial. This bidirectional outcome was later supported by several trials such as Early versus Late Intervention Trial with Estradiol (ELITE) study[7],

Kronos Early Estrogen Prevention Study (KEEPS).[8] The utilization of the "window of opportunity" of starting menopausal therapy earlier has shown benefits in protection of cognitive function, glucose metabolism, bone strength and endometrial physiology also, possibly explained by the density and response of available estrogen receptors (ER) in various tissues.

Similar to the timing, the dose, route and type of MHT have also been analysed. Identification of red flags such as early menopause, adverse obstetric events and outcomes like abortions, stillbirths, abruption, premature delivery, low birth weight, presence of excessive weight gain, autoimmune disorders, diabetes mellitus or hypertensive disorders during pregnancy is important as these factors make these women more prone to metabolic syndrome in future life.[9] Likewise manifestations of polycystic ovarian disease (PCOD), heavy menstrual bleeding or hypothalamic amenorrhea, presence of sarcopenia, depressive and vasomotor symptoms in midlife are also associated with adverse cardiovascular risk profile. Hence a rational clinical approach needs to be adopted for managing menopausal symptoms in women who are suffering from metabolic syndrome or are prone to developing cardiovascular morbidity. These women should be identified and comprehensively evaluated, categorized into risk categories using various tools such as WHO/ISH risk prediction charts for SEAR(South east Asian region) or ASCVD (atherosclerotic cardiovascular disease) risk calculator and their comorbidities if any, should be treated and optimized. According to risk stratification, non hormonal, modified or standard MHT should be advised for their menopausal symptoms along with lifestyle interventions (LSI).

Over the years, it has been found that transdermal estradiol preparations are useful for treating menopausal symptoms in women with venous thromboembolism, obesity, hypertension, diabetes or dyslipidemia and/or those who are at mild to moderate risk of developing CVD. This subset of patients also benefit from use of natural progestogens such as dydrogesterone or micronized progesterone to maintain higher plasma HDL cholesterol.

MHT should not be recommended for the sole purpose of lipid profile improvement or cardiovascular disease risk reduction and should be prescribed for a clear indication such as relief from intractable vasomotor symptoms, genitourinary syndrome of menopause (GSM), poor bone density and its associated complications, besides women with premature ovarian insufficiency (POI).

Treatment has to be individualised in order to optimise outcome and keeping the patient's choice in mind. The right dose (least dose which is fully effective) **(TABLE 2)** should be started at the right time and right age in the right woman through the right route and for the shortest possible duration after balancing pros and cons, risks and benefits. Shared decision making is important in continuing MHT and there should be no abrupt stops or arbitrary age limits at which to stop MHT. Annual review of patients who are on MHT is a must in order to ascertain patient safety and dose should be modified as per need to maintain efficacy. A holistic review of custom compounding MHT in various metabolic health conditions is essential.

Table 2 Dosage and types of systemic estrogens

Estrogens	Ultralow	Low	Standard	High
Conjugated equine estrogens -oral-mg	0.15	0.3, 0.45	0.625	1.25
17-β Estradiol – oral - mg	0.5	1	2	4
17-β Estradiol – Transdermal patch-mg	0.014	0.025	0.05	0.1
17-β Estradiol – Transdermal gel-mg	0.375	0.75	1.5	3
Estradiol valerate – oral - mg		1	2	4

MHT in CVD:

A reanalysis of WHI data trends suggested that MHT did not increase heart disease if MHT was started in younger women <60 years old or less than 10yrs from the initiation of menopause. MHT significantly reduced all-cause mortality and cardiovascular disease whereas other primary CVD prevention therapies such as lipid-lowering fail to do so. The ACC (American College of Cardiology) committee advises to take a risk-stratified approach to MHT.
MHT is considered high risk in women with existing CVD or 10-year CVD risk ≥10%, in the setting of uncontrolled cardiac risk factors including blood pressure ≥180/110 mmHg, total cholesterol >7.8 mmol/L and triglycerides > 4.5 mmol/L . Non-hormonal therapy is indicated as first-line therapy for management of vasomotor symptoms in these women . For women with established CVD and persisting vasomotor symptoms despite non-hormonal therapy, shared decision-making regarding the use of transdermal estradiol at doses

of ≤50µg (especially if previous hysterectomy) with concurrent statin use could be considered. Systemic MHT is best avoided where CVD and diabetes coexist with the potential for more rapid progression of coronary artery disease with MHT. In the combination HT, the androgenic progesterones blunted the beneficial effects of vasodilatation brought about by the estrogens. Selecting a metabolically neutral progestogen for EPT, such as micronized progesterone or dydrogesterone, is recommended. However at present, MHT is not recommended for the purpose of secondary prevention of cardiovascular events.

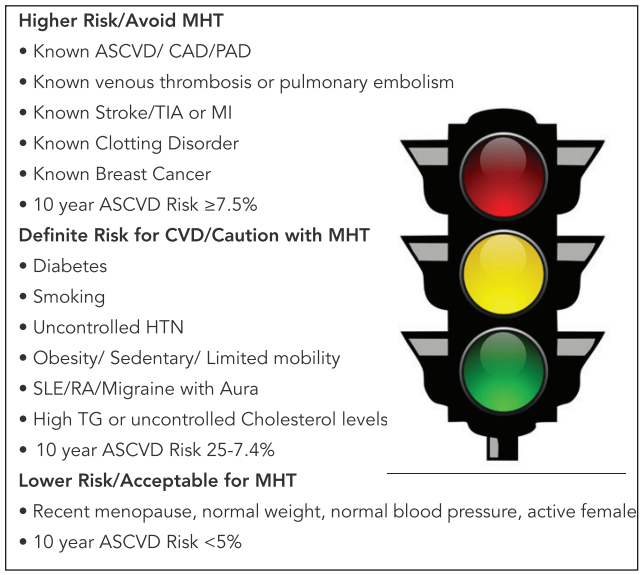

Figure 2: Assessing Women for Menopausal Hormone Therapy

Obesity & MHT:

Obesity is a chronic relapsing progressive disease that has the potential to act as a gateway to a range of other non communicable diseases (NCD). Fifty percent of the postmenopausal women are overweight, of whom a quarter are obese. Specific caution is required for obese women because of their increased risk of thromboembolic disease. Transdermal MHT given at standard therapeutic doses has less potential for thromboembolic disease than oral MHT which is equivalent to the baseline population risk. Tibolone therapy carries a lower risk of thromboembolic disease, but it has been associated with weight gain . Low-dose vaginal oestrogens have not been associated with alterations in coagulation factors or increased thromboembolic risk .

As a general principle, the lowest effective dose of oestrogens [25–50 µg oestradiol transdermally or 0.3–0.4 mg conjugated equine oestrogens (CEE) or 0.5–1 mg oestradiol orally daily] should be used. The use of a metabolically neutral progestogen, such as natural progesterone, dydrogesterone or transdermal norethisterone, is recommended.[10] There is evidence that the use of MHT does not cause weight gain and may promote weight reduction. But there are no recommendations regarding the use of MHT for the prevention or treatment of obesity during perimenopause.

T2DM & MHT:

Oestrogens in MHT have been proven to promote glucose-dependent insulin secretion, increase insulin sensitivity, and correct fasting hyperinsulinaemia in postmenopausal women diagnosed with type 2 diabetes mellitus (DM). Studies have also shown that MHT in menopausal women significantly delays the onset of type 2 DM compared to the control group. Therefore, it seems that women at risk of developing or suffering from type 2 DM should not be denied MHT when exhibiting menopausal symptoms. At the same time, it should be emphasized that this therapy has not been approved as an official prevention of type 2 DM in women.[11]

Table 3 T2DM & MHT

Women with T2DM	MHT use
> 60 years old	NO
or	
> 10 years in menopause	
or	
High CVD risk	
Obese women	YES
or	Prefer transdermal 17ß-oestradiol
Moderate CVD risk	Prefer neutral progestogen
Peri- or recently postmenopausal	YES
and	Prefer oral oestrogens
Low CVD risk	Prefer neutral progestogen

MHT has a favourable effect on glucose homeostasis in both women without and with T2DM. In older women with T2DM (>60 years old or>10 years in menopause), MHT should not be initiated, because it may destabilise mature atherosclerotic plaques, resulting in thrombotic episodes. In obese women with T2DM or in women with moderate CVD risk, transdermal 17β-oestradiol could be used. In any case, a progestogen with neutral effects on glucose metabolism should be used, such as natural progesterone, dydrogesterone or transdermal norethisterone. Although in the past

women with T2DM would be excluded from MHT, nowadays there is strong evidence to support an individualised approach after careful evaluation of their CVD risk.[12,13] However MHT is best avoided in type 1 diabetics and those with end organ damage.

Hypertension & MHT

MHT is not contraindicated in well controlled hypertensive patients and there is no effect on the control in these patients. However it is contraindicated in uncontrolled hypertension. Micronized progesterone appears to have neutral or beneficial effects on blood pressure in postmenopausal women. It has been shown to antagonize the effect of aldosterone, causing natriuresis and a reduction in blood pressure.

VTE &MHT

Different progestins have varied VTE risk. The activation of the thrombin receptor by thrombin may stimulate the extrinsic coagulation and facilitate the development of atherosclerosis. Treatment with progestogens with glucocorticoid effects like the medroxyprogesterone acetate, gestodene, 3-Keto- desogestrel may, therefore, stimulate thrombin induced expression of the tissue factor and upregulate the procoagulatory and vasoconstrictory activity of lesioned arterial walls. In this regard, progestins with androgenic activity, e.g. LNG or NET, are more favorable along with transdermal estrogen. They may also antagonize the reversible estrogen-induced resistance to activated protein C.

Stroke & MHT

Standard-dose oral MHT increased stroke risk by about one-third in generally healthy postmenopausal women. The risk increased with estrogen dose, age and body mass index and was greater during the first years of therapy. Low-dose ERT, transdermal route may not increase the risk of stroke. According to the PEPI.[14] trial, use of transdermal estrogen and natural progestins did not increase the risk of stroke or VTE in women studied. Tibolone and Selective Estrogen Receptor Modulators (SERMs) have lower thrombosis risk.

Conclusion

The clouds of controversy around MHT have gradually been lifted after reanalysis of data from old studies. Today it is considered the best form of treatment for relief from vasomotor symptoms and genitourinary symptoms of menopause in carefully selected populations, for primary prevention of postmenopausal osteoporosis and for preventing the onset of cardiovascular and other morbidities in women experiencing premature menopause. The changing diet and the lack of exercise among today's generation has led to increased prevalence of obesity, which is a slowly evolving pandemic and paves the way for metabolic syndrome and cardiovascular disease. So, increasingly higher number of women are entering menopause with associated morbidities and giving standard MHT to them will not be the correct approach. Hence starting MHT in the early menopausal or perimenopausal stage; individualising MHT as per risk stratification, using more bioidentical hormones and natural products and making them more bioavailable by modifying drug delivery systems can enhance the safety profile as well as the metabolic benefits making menopause a golden age to prevent CVD. This is possible only by creating awareness among general population and clinicians about importance of healthy lifestyle in the prime years, setting up of menopausal clinics that use quick tools for screening and risk assessment, ensuring availability of efficacious MHT drugs and easy access to healthcare for regular review of red flag signs in patients on MHT, thus making postmenopausal women a part of a multimodal plan.

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Colorectal Cancer with Enterocutaneous Fistula in Pregnancy: A Case Report

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Introduction

Colorectal cancer during pregnancy presents an estimated incidence of 0.8 per 100,000 pregnancies. It is associated with diagnostic and therapeutic challenges.[1] A delayed diagnosis during pregnancy may be due to overlapping symptoms with that of normal physiological changes during pregnancy, until an obstruction or perforation happens.[2,3] The relationship between pregnancy and colorectal cancer (CRC) is complex, and while the exact mechanisms behind carcinogenesis during pregnancy remain unclear, there is evidence suggesting that hormonal changes could influence the development and progression of colon cancer. Estrogen and progesterone, which rise significantly during pregnancy, can interact with hormone receptors present in colon cancer cells, potentially stimulating tumor growth.[4,5]

However, treatment options for pregnant women with cancer are limited due to potential risks to fetal health. Systemic chemotherapy should be avoided during the first trimester because it poses a high risk of miscarriage and congenital malformations, but it can be safely administered during the second and third trimesters.[6] Surgery, however, can be performed safely at any time during pregnancy. Radiotherapy should be delayed until after childbirth, regardless of the treatment site, due to the significant risks it poses to the fetus, including childhood cancers, fetal death, and developmental delays. Depending on the stage of pregnancy and the severity of the cancer, treatment plans may vary. Options could include surgery, chemotherapy, or a combination of both. This treatment approach requires a multidisciplinary team, including obstetricians, neonatologists, gastrointestinal surgeons, and oncologists, to manage both maternal and fetal health.[7]

Here, we present a case of colon adenocarcinoma in pregnancy with surgery, and chemotherapy occurring during pregnancy.

Case Report

A 25-year-old female, G2A1, was referred to SGRH at 28 weeks of pregnancy with a history of pain, swelling, and discharge in the left flank area. Ultrasound findings revealed a hyperechoic mass with cystic spaces (11x11x6 cm) in the left lumbar region, displaying internal vascularity and calcifications, abutting the bowel, and with an abscess tract extending to the skin surface, highly suggestive of a neoplastic mass with a fistula. MRI further confirmed the presence of a frond-like mass within the descending colon, with a large extraluminal component, likely indicative of a mucinous tumor of the descending colon. The MRI also highlighted a hyperintense area in the left quadratus lumborum and erector spinae muscles on T2-weighted imaging, with postoperative changes and a subcutaneous fistulous tract in the left posterior abdominal wall. Additionally, elevated levels of CEA and CA19-9 were observed, further supporting the suspicion of malignancy.

A multidisciplinary team, including

obstetricians, gastroenterologists, general surgeons, and medical oncologists, was involved in her care. Sigmoidoscopy performed by the gastroenterologist revealed a polypoidal growth 25 cm from the anal verge, raising concerns about malignancy. A biopsy of the lesion confirmed the diagnosis of well to moderately differentiated adenocarcinoma arising from a background of tubulovillous adenoma. Given the complex nature of the case and the gestational age, a transverse colostomy was performed at 30 weeks of gestation to divert the bowel. Chemotherapy with oxaliplatin and capecitabine was promptly initiated and continued until 33 weeks of gestation. Throughout this period, regular fetal-maternal surveillance was carried out to monitor both maternal and fetal well-being.

Prof. Dr. Kanwal Gujral (Mrs. Nayar)

At 34 weeks of gestation, the patient spontaneously went into labor and had a vaginal delivery of a female baby weighing 1515 grams, with an APGAR score of 8/10, indicating good health at birth. The postpartum period was uneventful, and both mother and baby were stable. The case highlights the importance of a multidisciplinary approach and timely intervention in managing colorectal cancer during pregnancy, ensuring both maternal and fetal health are carefully monitored.

Discussion

Colorectal cancer (CRC) during pregnancy is exceptionally rare, with an incidence ranging from 0.002% to 0.008%. Common symptoms include hematochezia, melena, abdominal pain, unexplained iron deficiency anemia, and changes in bowel habits. Less frequently, patients may experience abdominal distension, nausea, and vomiting, which could signal an obstruction. The diagnosis of CRC in pregnant women is often delayed, as its symptoms can overlap with common pregnancy-related changes, and the occurrence of CRC in younger pregnant women is rare.[2,3] Concerns about potential risks to the fetus often lead to reluctance among healthcare providers to perform necessary diagnostic tests, which further delays the diagnosis and complicates treatment, adversely affecting prognosis.

Non-ionizing imaging techniques, such as ultrasound and magnetic resonance imaging (MRI), are preferred during pregnancy as they avoid exposure to ionizing radiation. While serum tumor markers such as CA 125, CA 15.3, AFP, and SCC are generally not reliable during pregnancy, markers like AMH, CEA, CA 19-9, and HE4 typically do not show elevated levels during pregnancy, making them potentially useful for diagnostic purposes.[8]

Colonoscopy is considered the most accurate diagnostic tool for colorectal cancer, as it allows for the localization and biopsy of lesions throughout the large bowel. Endoscopy is indicated during pregnancy in cases of significant or persistent bleeding, severe or refractory nausea and vomiting, abdominal pain, or when there is a strong suspicion of a colon mass. The optimal time for performing advanced endoscopic procedures is during the second trimester. However, if postponing the procedure could result in harm to the mother or fetus, a multidisciplinary approach should be adopted to ensure the best outcome. Gastrointestinal endoscopy in pregnant patients carries inherent risks, as the fetus is vulnerable to maternal hypoxia and hypotension, both of which can lead to fetal demise.[9]

Treatment is influenced by several factors, including tumor location and stage at presentation and gestational age. If diagnosis is made later in pregnancy (> 20 weeks), surgery can be postponed until fetal pulmonary maturity is reached (28–32 weeks) or after delivery. However, waiting until after the fetus is delivered does pose risks to the mother.[7] Antineoplastic drugs are typically contraindicated in first trimester of pregnancy due to the high risk of major malformations, including those involving the heart, neural tube, limbs, eyes, palate, and ears, which can occur during organogenesis. Standard chemotherapy regimens for advanced colorectal carcinoma, such as FOLFOX (5-FU, leucovorin, and oxaliplatin) or FOLFIRI (5-FU, leucovorin, and irinotecan), are considered feasible during the second and third trimesters but are associated with an increased incidence of small for gestational age fetuses.[10] Chemotherapy is generally avoided after 35 weeks of pregnancy. A minimum three-week interval between the final chemotherapy cycle and delivery is important to to reduce the risk of chemotherapy-related complications, such as bone marrow suppression, bleeding, and maternal or fetal death during delivery.[11] Radiation therapy (RT) is contraindicated during pregnancy because of the location of the tumor and proximity of the fetus. Radiation therapy can be used postoperatively due to the potential risks to the fetus as fetus cannot be protected from RT directed to the pelvic wall because of the anatomic proximity of the uterus to the colon and it should only be used postoperatively after delivery or elective abortion. Consideration of future fertility is crucial, as radiation therapy may lead to permanent ovarian damage and infertility.

Colorectal cancer is a common cause of large bowel obstruction. Patients with acute malignant colorectal obstruction may need emergency

surgery, especially if they are clinically unstable (e.g., experiencing tachycardia, hypotension, or acidosis) or at risk of perforation. Perforation usually happens at the obstruction site due to tumor invasion or inflammation, rather than in the dilated part of the colon. The decision to carry out a staged or single surgery depends on various factors, including the location of the blockage, the condition of the proximal colon, the patient's overall health, life expectancy, care preferences, and whether there is a perforation in the proximal colon.

In our case, patient underwent surgery during pregnancy and received chemotheraphy in second and third trimester

Conclusion

Colorectal cancer is a rare but devastating event during pregnancy. Due to overlapping symptoms with pregnancy, patients often present with advanced disease. That is why, it is essential to be aware of the early symptoms of CRC in order to distinguish between the characteristics of normal pregnancy and those patients showing signs of CRC that will require further assessment. Diagnostic interventions and treatment should not be delayed due to the pregnancy but a balance between maternal and fetal wellbeing must always be kept in mind.

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JOURNAL SCAN

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Treatment of Genitourinary Syndrome of Menopause in Breast Cancer and Gynecologic Cancer Survivors: Retrospective Analysis of Efficacy and Safety of Vaginal Estriol, Vaginal Dehydroepiandrosterone and Ospemifene

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Genitourinary syndrome of menopause (GSM) describes the symptoms and signs resulting from the effect of estrogen deficiency on the female genitourinary tract. It affects approximately 27% to 84% of postmenopausal women. Principal symptoms include vaginal dryness, painful sex, burning, and dysuria.

Hormone replacement therapy (HRT) is widely considered the most effective treatment for the management of menopausal symptoms. However, its use in patients with a history of breast cancer or gynecologic cancer is controversial, because many malignancies are hormone-dependent and HRT possibly increases the risk of recurrence .

First-line therapies for GSM include non-hormonal vulvar and vaginal lubricants with sexual activity and long-acting vaginal moisturizers used regularly (several times a week).

In breast cancer and gynecologic cancer survivors with symptoms unresponsive to non-hormonal options, low-dose vaginal hormones may be considered with shared decision-making in conjunction with patients' oncologists . Specifically, off-label use of local estrogens and vaginal dehydroepiandrosterone (DHEA) may be acceptable due to minimal systemic absorption.

An alternative option to vaginal estrogen and DHEA is ospemifene. Ospemifene is a systemically administered selective estrogen receptor modulator (SERM) approved for the treatment of moderate to severe dyspareunia associated with GSM, with favorable effects on vaginal epithelium and bone density, antiestrogenic effects on the breast, and negligible endometrial and cardiovascular safety concerns.

The aim of the study was to assess the efficacy and safety profile of local hormonal therapy and ospemifene in treating GSM in breast cancer and gynecologic cancer survivors.

Material and Methods

A retrospective comparative analysis was performed among 185 cancer survivors (including breast, endometrial, ovarian, cervical, and vulvar cancer) affected by GSM from 1st January 2017 to 31st December 2023 attending Sandro Pertini Hospital in Rome. Three groups of patients were obtained according to the prescribed therapy: the first group of patients was prescribed estriol 1 mg 1 vaginal tablet per day for 30 days then 3 tablets per week for another 5 months. The second group was prescribed DHEA ovules 1 ovule per day for 6 months. The third group had taken ospemifene 60 mg orally, 1 tablet per day for 6 months. Safety and efficacy of therapies were assessed over a 6-month follow-up. Improvement in symptoms was compared using the following questionnaires: Female Sexual Function Index, Female Sexual Distress Scale, Visual Analogue Scale (VAS)-dyspareunia, VAS-vulvar pain, Short Form (36) Health Survey, and Patients' Impression of Global Improvement. Cancer recurrence was evaluated according to oncological protocol.

Results

After the 6-month follow-up, no significant endometrial thickening or cancer recurrence was observed in any group (from 4.23 mm to 3.67 mm in the estriol group, from 3.98 mm to 3.33 mm in the DHEA group, from 4.10 mm to 3.64 mm in the ospemifene group; P value was not significant). The rate of sexually active women significantly increased in all groups, as well as the frequency of sexual intercourse. Scores on questionnaires assessing women's sexual function significantly improved in all patients. Women also complained of less vulvar pain and dyspareunia. Safety and efficacy of treatment were comparable between the three groups for all items except for dyspareunia. Patients taking ospemifene complained of less dyspareunia than those receiving local hormone treatment.

Conclusion

Vaginal estriol, vaginal DHEA, and ospemifene were effective in improving symptoms of GSM in cancer survivors and were not associated with cancer recurrence over the 6-month follow-up. Ospemifene was more effective than local hormones in treating dyspareunia.

Fezolinetant impact on health-related quality of life for vasomotor symptoms due to the menopause: Pooled data from SKYLIGHT 1 and SKYLIGHT 2 randomised controlled trials

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Up to 80% of women report hot flushes and night sweats (vasomotor symptoms [VMS]) during menopausal transition. Moderate-to-severe VMS are associated with sleep disruption, anxiety, mood disturbances, fatigue, cognitive impairment and cardiovascular disease, which can negatively affect health-related quality of life (HRQoL).

Hormone therapy (HT) remains the principal treatment for VMS associated with menopause. However, HT may not be appropriate for all women, depending on underlying medical conditions, risk factors, age and time since menopause. Non-hormonal alternatives have been tested in a number of randomised trial, but are not always well tolerated and are only partially effective versus HT. Moreover, until recently, only paroxetine was approved by the U.S. Food and Drug Administration (FDA) for treatment of VMS. Additionally, many women try complementary and alternative medicine options to alleviate VMS and improve HRQoL, including cognitive behavioural therapy, nutritional, physical and herbal remedies; however, evidence concerning their efficacy is conflicting.There is therefore a clinical need to identify additional effective pharmacological approaches to treat VMS.

Fezolinetant is a novel selective non-hormonal neurokinin 3 receptor antagonist approved, at a once-daily 45 mg dose, by the FDA for treatment of moderate-to-severe VMS due to menopause and by the European Medicines Agency for treatment of moderate-to-severe VMS associated with menopause. The thermoregulatory centre in the hypothalamus is innervated by kisspeptin-neurokinin B-dynorphin (KNDy) neurones, whose action is inhibited by oestrogen and stimulated by neurokinin B (NKB) via NK3R. With declining oestrogen levels during menopause, NK3R-mediated activation is unopposed, leading to hypertrophy of KNDy neurones; this increases heat dissipation mechanisms, leading to hot flushes and night sweats. Fezolinetant blocks NKB binding on KNDy neurones, thereby reducing the frequency and severity of VMS associated with menopause.

SKYLIGHT 1 (NCT04003155) and SKYLIGHT 2 (NCT04003142) were identical, double-blind, placebo-controlled phase 3 studies evaluating the safety and efficacy of fezolinetant versus placebo on the frequency and severity of VMS associated with menopause. Fezolinetant was efficacious and well tolerated, with a favourable safety profile confirmed by SKYLIGHT 4 (NCT04003389). The objective of prespecified analysis was to assess the effect of fezolinetant treatment on HRQoL using pooled data from SKYLIGHT 1 and 2 via three patient-reported outcome measures (PROMs).

Materials and Methods

SKYLIGHT 1 and 2 were conducted at multiple sites throughout North America (USA and Canada) and Europe (Poland, Czech Republic, Spain, UK; Hungary [SKYLIGHT 1 only] and Latvia [SKYLIGHT 2 only]) from July 2019 to August 2021 (SKYLIGHT 1) and July 2019 to April 2021 (SKYLIGHT 2). 1022 women aged ≥40 to ≤65 years with moderate-to-severe vasomotor symptoms (VMS; minimum average seven hot flushes/day), seeking treatment for VMS were randomised to 12-week double-blind treatment with once-daily placebo or fezolinetant 30 or 45 mg. Completers entered a 40-week, active extension (those receiving fezolinetant continued that dose; those receiving placebo re-randomised to fezolinetant received 30 or 45 mg). Outcome

measures were mean changes from baseline to weeks 4 and 12 on Menopause-Specific Quality of Life (MENQoL) total and domain scores, Work Productivity and Activity Impairment questionnaire specific to VMS (WPAI-VMS) domain scores, Patient Global Impression of Change in VMS (PGI-C VMS); percentages achieving PGI-C VMS of 'much better' (PGI-C VMS responders). Mean reduction was estimated using mixed model repeated measures analysis of covariance.

Results

A total of 1022 women were randomised and received at least one dose of study drug across both studies (placebo, n = 342; fezolinetant 30 mg, n = 339; fezolinetant 45 mg, n = 341) . Mean (SD) age was 54.3 (5.0) years and the majority of the women were white (828, 81.1%).

Fezolinetant 45 mg mean reduction over placebo in MENQoL total score was −0.57 (95% confidence interval [CI] −0.75 to −0.39) at week 4 and −0.47 (95% CI −0.66 to −0.28) at week 12. Reductions were similar for 30 mg. MENQoL domain scores were also reduced and WPAI-VMS scores improved. Twice as many women receiving fezolinetant reported VMS were 'much better' than placebo based on PGI-C VMS assessment.

Conclusion

Fezolinetant treatment for moderate-to-severe VMS was associated with improvement in overall QoL, as measured by the MENQoL, and in self-reported work productivity, as measured by the WPAI. Additionally, a high proportion of women treated with fezolinetant felt their VMS were 'much better' (responders), as measured by the PGI-C VMS

QUIZ TIME

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1. What is the best time to start MHT ?

A) Within 10 years of menopause
B) Within 15 years of menopause
C) Within 20 years of menopause
D) Within 25 years of menopause

2. WHI acronym stands for

A) Women's health of India
B) Women's health initiative
C) Women's health international
D) Women's health of Ireland

3. What is the percentage of Indian menopausal women affected by Genitourinary syndrome of menopause ?

A) 20-30%
B) 30-40%
C) 40-50%
D) 50-60%

4. Which is not a part of cognitive disorders in menopausal women ?

A) Cognitive decline
B) Cognitive aging
C) Mild Cognitive Impairment
D) Dementia

5. During menopause women's muscle mass decrease by what percentage annually?

A) 0.4%
B) 0.5%
C) 0.6%
D) 0.7%

6. Vasomotor symptoms of menopause involve Kisspeptin, neurokinin B and dynorphin (KNDy) neurons:

A)True
B) False

7. Which medication does not causing flushing as side effect ?

A) Calcium channel blockers
B) Bromociptine
C) Angiotensin receptor blockers
D) Aromatase inhibitors

8. Hot flushes occur in what percentage of post menopausal women ?

A)25%
B)50%
C)75%
D)100%

9. According to Anklesaria Menopausal staging , which stage is ideal to start long term hormonal treatment ?

A)Stage I
B)Stage II
C)Stage III
D)Stage IV

10. The age of menopause is affected by all of the factors except :

A) Maternal menopausal age
B) Age at menarche
C) Smoking
D) Exposure to chemotherapeutic agents

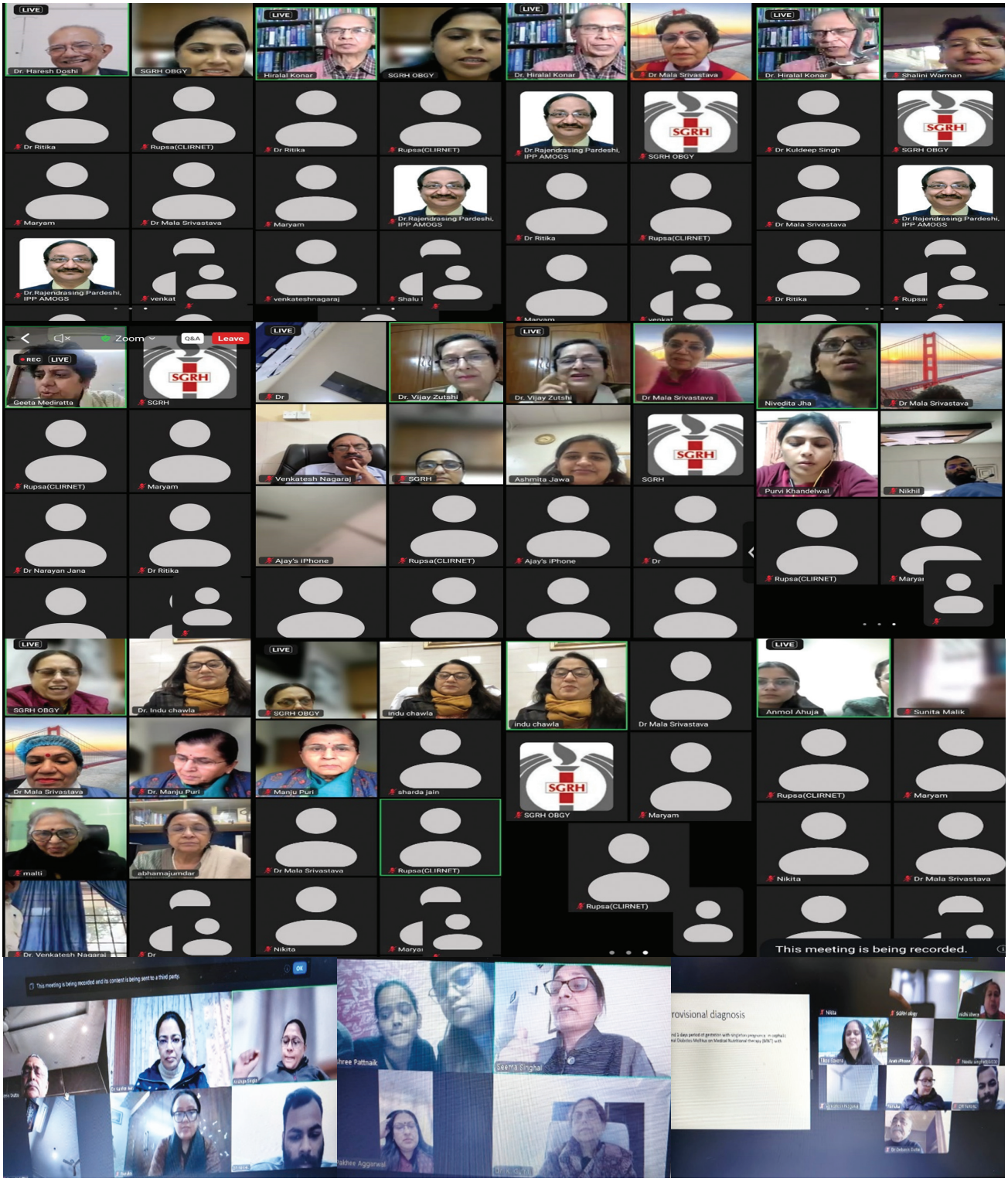
Ans 1: A, Ans 2: B, Ans 3: C, Ans 4: A, Ans 5: C, Ans 6: A, Ans 7: C,
Ans 8: C, Ans 9: B, Ans 10: B

Activities Held Under NARCHI in January 2025

GURUKUL CLASSES HELD ON 2nd – 5th JANUARY, 2025

Virtual Gurukul classes, organized by Institute of Obstetrics & Gynaecology under the aegis of NARCHI Delhi Chapter were held for post graduate students at Sir Ganga Ram Hospital from 2nd to 5th January, 2025. The Gurukul was attended by approximately 70 delegates.

It was an interactive session with lots of take home messages.



PUBLIC AWARENESS CAMP ON THE THEME "SWASTHYA SEWA RASHTRA SEWA" HELD ON 12TH JANUARY, 2025

To commemorate 162nd Swami Vivekanand Jayanti on 12th January, 2025, a PUBLIC AWARENESS CAMP was organized by Institute of Obstetrics and Gynaecology, Sir Ganga Ram Hospital under the aegis of NARCHI Delhi Chapter.

Camp was attended by Dr. Chandra Mansukhani, Dr Kanika Jain, Dr Sakshi, Dr. Payal Hooda, Dr. Nikhil Ritolia, Dr. Maria and Dr Rishabh Dubey

PUBLIC AWARENESS LECTURES ON RESPECTFUL MATERNITY CARE HELD ON 14TH JANUARY, 2025

NARCHI DELHI CHAPTER - Together with Institute of Obstetrics & Gynaecology and Institute of Anaesthesiology, Pain & Perioperative Medicine, Sir Ganga Ram Hospital, New Delhi organized Public Awareness Lectures on Respectful Maternity Care at **Sir Ganga Ram Hospital, New Delhi on 14th JANUARY, 2025**.

It was attended by 8 antenatal patients along with their husbands, an interactive session was held where basics of "Pregnancy and labour" was taken by Dr. Sharmistha Garg, "Introduction to Labour Analgesia" was taken by Dr. Anjeleena Gupta, "Dietary Management" was taken by Dr. Faria, "Physiotherapy in ANC" was taken by Dr. Deepti Pandey, "Breast Feeding" was taken by Dr. Priya Gandhi & "Labour Care Bundle" was taken by S/N Sarita Samul. The topics were discussed in detail and all the related queries were answered. This sessions of Public Awareness Lectures were highly appreciated.

It was an interactive session and all the delegates really appreciated the event.

WORKSHOP ON MOOT COURT (DOCTOR KI MAUT) ON 25TH JAN 2025

Workshop on "Moot Court (Doctor ki Maut)" was held on 25th January, 2025, organized by Institute of Obstetrics & Gynaecology, Sir Ganga Ram Hospital under the aegis of NARCHI Delhi Chapter.

We were blessed by our Chief Guest: Dr. Jayashree Sood and Guest of Honor : Dr. Kanwal Gujral. We were happy to have Senior and experienced chairpersons Dr Geeta Mediratta, Dr Chandra Mansukhani & Dr Kanika Jain. We were lucky to have star speakers Dr Jasmine Chawla Sharma and Dr Sonali Sharma With their law students (Yatharth Khatana, Keshav Narang, Nehal Ahuja , Khushi Ahuja & Sidh Jain) who enlightened us on topics of Moot Court (Doctor ki Maut) and they presented the skit. The CME was attended by approximately 60 delegates.

It was an interactive session with lots of take home messages.

PUBLIC AWARENESS CAMP ON "HPV–SAFE PROJECT" HELD ON 31ST JANUARY, 2025

NARCHI DELHI CHAPTER along with Institute of Obstetrics & Gynaecology, Sir Ganga Ram Hospital conducted school programme on 31st January 2025 on "HPV-Safe Project" at Swami Dayanand SKV School, Old Rajinder Nagar, New Delhi. It was attended by students of class 8th and 9th all sections with their class teachers. The sessions were taken by Dr Mala Srivastava, Dr Neeti Tiwari & Dr Latika Bhalla . These sessions of Public Awareness Lectures were highly appreciated.

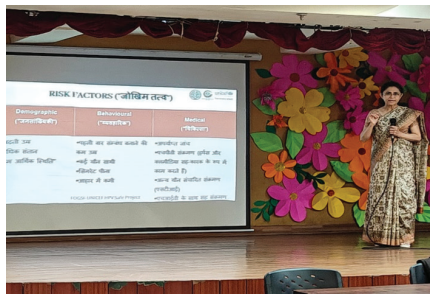
It was a great interactive session.

Activities Held Under NARCHI in February 2025

PUBLIC AWARENESS CAMP ON "HPV–SAFE PROJECT" HELD ON 4th FEBRUARY, 2025

NARCHI DELHI CHAPTER along with Institute of Obstetrics & Gynaecology, Sir Ganga Ram Hospital conducted school programme on 4th February, 2025 on "HPV-Safe Project" at St. Peters School Vikaspuri, New Delhi. It was attended by students of class 8th and 9th all sections with their class teachers. The sessions were taken by Dr Chandra Mansukhani. This session of Public Awareness Lecture was highly appreciated.

It was a great interactive session.



PUBLIC AWARENESS LECTURES ON RESPECTFUL MATERNITY CARE HELD ON 14TH FEBRUARY, 2025

NARCHI DELHI CHAPTER - Together with Institute of Obstetrics & Gynaecology and Institute of Anaesthesiology, Pain & Perioperative Medicine, Sir Ganga Ram Hospital, New Delhi organized Public Awareness Lectures on Respectful Maternity Care at Sir Ganga Ram Hospital, New Delhi on 14th February, 2025.

It was attended by 4 antenatal patients along with their husbands, an interactive session was held where basics of "Pregnancy and labour" was taken by Dr. Sharmistha Garg, "Introduction to Labour Analgesia" was taken by Dr. Anjeleena Gupta, "Dietary Management" was taken by Dr. Faria, "Physiotherapy in ANC" was taken by Dr. Deepti Pandey, "Breast Feeding" was taken by Dr. Priya Gandhi & "Labour Care Bundle" was taken by S/N Sarita John. The topics were discussed in detail and all the related queries

were answered. This sessions of Public Awareness Lectures were highly appreciated.

It was an interactive session and all the delegates really appreciated the event.

Activities Held Under NARCHI in March 2025

CME ON "OPTIMISING HEALTH OF ADOLESCENTS" HELD ON 8th March, 2025 to celebrate National women's day Under the aegis of NARCHI Delhi chapter at Sir Ganga Ram Hospital, New Delhi.

We were blessed by our Chief Guest : Dr. Manju Puri, Guest of Honor : Dr. Jayashree Sood & Dr. Achla Batra (Past National President NARCHI). Co-ordinator : Dr. Mala Srivastava. We had inputs from experienced chairpersons like – Dr. Kanwal Gujral, Dr. Geeta Mediratta, Dr. Kanika Jain, Dr. Shweta Mittal Gupta, Dr. Harsha Khullar, Dr. Chandra Mansukhani, Dr. Sunita Kumar. We were lucky to have star speakers who enlightened us on topics of "PCOS Life Style" by Dr. Neeti Tiwari, "HPV DNA Vaccination" by Dr. Mala Srivastava & "Adolescent Health" by Dr. Latika Bhalla. The CME was attended by approximately 60 delegates.

It was an interactive session with lots of take home messages.


Dr. MANJU


Remember girls ...

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