

Clinical Practice Guidelines on Menopause: *An Executive Summary and Recommendations: Indian Menopause Society 2019–2020

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*This is a short summary and recommendations from the detailed monogram on Clinical Practice Guidelines on Menopause, available at the **Indian Menopause Society Website:** www.indianmenopausesociety.org.

SECTION I

GENERAL CONSIDERATIONS

1. Menopause is a transition phase from the reproductive to the nonreproductive phase in a woman's life. It is nature's protective phenomenon against reproductive morbidity and mortality in the aging population. It sets the stage for aging and accelerates the process of noncommunicable disorders
2. Menopause is diagnosed retrospectively by history. Markers for diagnosis of menopause are preferably restricted for use in special situations and for fertility issues. Levels of follicle-stimulating hormone (FSH) >10 IU/L are indicative of declining ovarian function. FSH levels >20 IU/L are diagnostic of ovarian insufficiency in the perimenopausal age group with vasomotor symptoms (VMS), even in the absence of cessation of menstruation.^[1] FSH level >40 IU/L done at least 4 weeks apart is a reliable marker

for menopause or impending menopause and associated with low estradiol levels. Anti-Müllerian hormone becomes undetectable, inhibin levels fall, and antral follicular count and ovarian volume decrease at menopause. Menstrual irregularity is the only objective marker to define and establish the menopause transition.^[2]

TERMINOLOGY

3. Natural or spontaneous menopause: It is recognized to have occurred after 12 months of amenorrhea, for which there are no obvious pathological and physiological causes. It occurs due to the depletion of

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ovarian follicles, resulting in near-complete, but natural diminution of ovarian hormone secretion. There is no independent biological marker for menopause^[3]

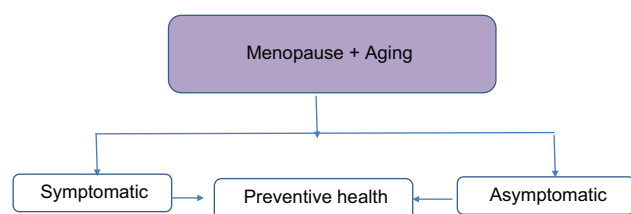
4. Premenopause: It is often used to refer the entire reproductive period, up to the final menstrual period (FMP).
5. Perimenopause: It is the period immediately before and up to 1 year after the FMP. It may last for 3–5 years. The characteristics are increased blood levels of FSH, anovulatory cycles, significantly reduced fertility and erratic menstrual periods, and onset of symptoms. This term is used interchangeably with menopause transition^[4,5]
6. Menopause transition or perimenopause begins on an average 4 years before the FMP and is characterized by irregular menstrual cycles, endocrine changes, and symptoms such as hot flashes that may affect a woman's quality of life (QOL). It may be considered as a biological marker for chronic disease. The biology and symptomatology of menopause are blurred due to its relationship to the underlying aging process. Long-term effects on bone and heart have been related to estrogen deficiency. It is the term coined by the Stages of Reproductive Ageing Workshop (STRAW) group, and during this period, disturbed menstrual cycle and endocrine changes are observed. Anklesaria's staging of menopause has been adopted by the Indian Menopause Society (IMS) after modification^[5-7]
7. Climacteric: Literally, it means the rungs of a ladder. It is interchangeable with perimenopause and menopause transition. When associated with symptoms, it is termed as the climacteric syndrome. This term is preferably not to be used in scientific papers^[4]
8. Postmenopause: It is the span of time dating from the FMP, regardless of whether the menopause was spontaneous or iatrogenic^[4]
9. Senescence: It is the period after the age of 60 years^[3]
10. Premature menopause/premature ovarian insufficiency (POI): POI is replacing the term premature menopause. POI is described as amenorrhea due to loss of ovarian function before the age of 40 years. It is a state of female hypergonadotropic hypogonadism. It can manifest as primary amenorrhea with onset before menarche or secondary amenorrhea. Statistically, it is defined as spontaneous menopause occurring below two standard deviations (SDs) below the mean estimated age for the reference population for 5% level of significance. The estimated average age of menopause in India is reported to be 46 years; hence, we may consider POI as occurring below the age of 38 years. However, we do need to have population-based studies to derive at these cutoff values. The European Society of Human Reproduction and Embryology (ESHRE 2015) laid the following diagnostic criteria for POI-oligomenorrhea/amenorrhea for at least 4 months and an elevated FSH level >25 IU/l on two occasions >4 weeks apart.^[8]
11. Induced menopause: It is cessation of menstruation that follows bilateral oophorectomy or iatrogenic ablation of ovarian function^[4]
12. Temporary menopause: It is a term preferably not to be used since the definition of menopause is complete cessation of menstruation. Rarely, ovarian function is interrupted for a period of time and later resumes^[4]
13. Early menopause: It is the time span between the spontaneous or iatrogenic menopause occurring between the age of 40 years and the accepted typical age of menopause for a given population. The consensus from various guidelines is to treat with hormone replacement therapy (HRT) till the age of menopause
14. Delayed menopause: It is not defined but may be important in terms of increased problems associated with the hyperestrogenism and is used in this guideline. It is two SDs above from the natural average age of menopause in a given population. We may consider it to be beyond 54 years. Population-based studies are needed to derive at these cutoff values
15. Postmenopausal bleeding (PMB): It is bleeding that occurs 12 months after the last normal period. However, it is recommended that any vaginal bleeding that occurs 6 months after the last period (presumed menopause) should be investigated
16. Staging system: The staging system of a physiological event is to improve comparability of strategies and facilitate clinical decision-making. In 1997, Ankelesaria in India published a simple clinical method of staging of menopause to understand and deal with the problems of the transition phase and beyond.^[6,7] STRAW (2001) aimed to classify the woman's life in three phases: (1) reproductive, (2) menopause transition, and (3) postmenopause based on the menstrual cycle, endocrine parameters, and ovarian reserve markers. This was applicable only to healthy women. The 2012 STRAW + 10 provides a greater clarity for menstrual pattern and is applicable to most women, except for those with POI^[9,10]
17. India, with a population of 1.2 billion people, is the second largest emerging economy and second most populated country in the world. According to the latest World Health Organization (WHO) data published in 2018, the life expectancy in India for a

female is 70.3 years, expected to increase to 77 years by 2050. Noncommunicable diseases account for 60% of the total deaths in India. Currently, approximately 10% of India's population, i.e., more than 100 million, is aged over 50 years^[11]

18. The estimated mean age of menopause is 46 years in India and is lower than that of the Caucasians.^[12-28] From the available Indian data, it is hypothesized that an early age of menopause predisposes a woman to chronic health disorders a decade earlier than a Caucasian woman. It is reported that osteoporotic fractures occur 10–20 years earlier in Indians compared to Caucasians.^[29,30] The first myocardial infarction (MI) attack occurs in 4.4% of Asian women at a younger age than in European women.^[31] In India, type 2 diabetes mellitus (T2DM) occurs a decade earlier than the Caucasians.^[32] Breast cancer is the most common cancer in Indian women, and the incidence peaks before the age of 50 years^[33]
19. The overall prevalence of hypertension in India was 29.8%. Significant differences in hypertension prevalence were noted between rural and urban parts, i.e., 27.6% and 33.8%, respectively. Only 25% of rural and 38% of urban Indians are being treated for hypertension. The burden of cardiovascular disease (CVD) in India is projected to increase by 115% from 1990 to 2020^[34] and cerebrovascular incidence by 104%.^[35] The migrant population from the Indian subcontinent in the UK is known to be at a significantly higher risk of developing diabetes and CVD.^[36] The mean bone mineral density (BMD) in India is about two SDs lower than in women in the Western population.^[29] The prevalence of low bone mass is to the extent of 40% from the age of 40 years and increases to more than 62% by the age of 60 years and 80% by the age of 65 years.^[37-42] The above facts indicate the need to have well-planned cost-effective systems in place to promote a healthy and an active aging population.

INDIVIDUALIZED PLAN FOR MENOPAUSE

20. Each woman needs an individualized health plan management. It is most important to distinguish



Flowchart 1: The physician's role and approach

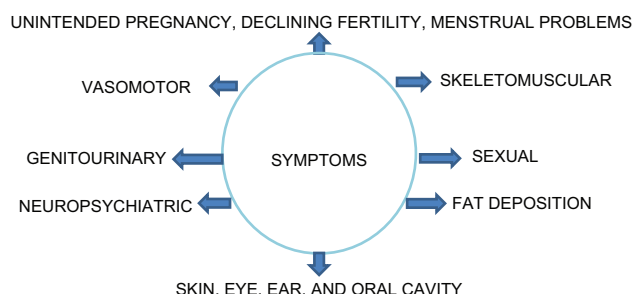
between a symptomatic and an asymptomatic menopausal woman.^[43] Women may present at the menopausal clinic with menstrual problems, menopausal symptoms, or request for a general health checkup or as an opportunistic contact to be picked up by the health professional [Flowcharts 1 and 2].^[44]

SECTION II

SYMPTOMS OF MENOPAUSE, ISSUES RELATED TO MENOPAUSE TRANSITION, AND AGING

Fertility

21. After the age of 30 years, if a woman does not conceive naturally within 6 months, the couple should have an infertility workup (Grade B)
22. In women with a single ovary, previous ovarian surgery, poor response to gonadotropins, previous exposure to chemotherapy or radiation, or unexplained infertility, they should undergo ovarian reserve testing even before the age of 30 years, and in all women, it is done beyond more than or equal to 30 years (Grade B)
23. In women aged >40 years who do not conceive within 1–2 cycles of controlled ovarian hyperstimulation, *in vitro* fertilization (IVF) should be considered (Grade B)
24. The only effective treatment for ovarian aging is oocyte donation. A woman with decreased ovarian reserve should be offered oocyte donation as an option, for pregnancy rates associated with this treatment are significantly higher than those associated with controlled ovarian hyperstimulation or IVF with a woman's own eggs (Grade B)
25. The risk of spontaneous pregnancy loss and chromosomal abnormalities increases with age, and the couple needs to be counseled on this aspect (Grade B)
26. Preconception counseling with an emphasis on optimal general health and screening for medical conditions, such as hypertension, diabetes, and pregnancy-related risks, should be addressed for women aged >40 years (Grade B).



Flowchart 2: Issues in symptomatic women

Contraception

27. Pregnancies in the elderly women are associated with higher maternal and perinatal morbidity and mortality. There is an increased risk of fetal malformations. This can also lead to psychological and potential domestic and social consequences
28. The annual risk of deaths associated with using no method of contraception far exceeds that for use of any method among all age groups [Table 1]^[45]
29. Pattern of contraception use in the age group of 15–49 years is shown in Table 2^[46]
30. Sterilization is a highly effective, safe, and single act; the case-fatality rate with tubectomy is 1–2/100,000 procedures. However, it is a permanent method. Vasectomy is even safer except for minor complications (Grade A)
31. Oral contraceptive pills (OCPs) are effective, easy to use, and reversible. Low-dose OCPs have noncontraceptive health benefits with an increased safety profile (Grade A)^[47–49]
32. For women above the age of 35 years, careful personal and family history, and accurate measurement of blood pressure (BP), breast examination, screening for diabetes, and lipid profile should be performed (Grade A)^[50]
33. Healthy women of normal weight, nonusers of tobacco, and doing well on a combination contraceptive pill can continue this method until the age of menopause and up to a year or 2 years later, after analyzing its risks and benefits (Grade B)
34. If OCPs are continued before major surgery, heparin prophylaxis may be considered (Grade B)
35. Depot medroxyprogesterone acetate (DMPA) is associated with bone loss, which returns to normal, after stopping DMPA. Yet, the caution needs to be exercised in women at a high risk of osteoporosis. Short- or long-term use of DMPA in healthy women should not be considered as an indication for dual X-ray energy absorptiometry or other tests that assess BMD (Grade C)
36. Change over from OCPs to hormone therapy (HT) is carried out at an arbitrary age of 45–50 years, if serum FSH: luteinizing hormone ratio of >1; low estradiol <20 pg/mL; FSH >30 IU/L done twice 6 weeks apart^[51]
37. Progesterone-only contraceptive is an ideal method in women with a history of venous thromboembolism (VTE) and gallstones. Limitations are erratic and scanty periods. The levonorgestrel–intrauterine system, apart from being used as a contraception, is an effective HT for heavy menstrual bleeding and for treating bleeding disturbances associated with endometrial hyperplasia (EH) (Grade B)
38. Intrauterine contraceptive devices are effective but sometimes can cause menorrhagia and dysmenorrhea (Grade B)
39. Emergency contraception is an effective emergency method, but it is not as effective and consistent as the use of other contraceptive (Grade C).

Perimenopausal bleeding

40. It is suggested to incorporate the use of PALM-COEIN (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified) classification for abnormal uterine bleeding (AUB)^[52]
41. The common causes are anovulatory bleeding, leiomyoma, endometrial polyp, EH, and endometrial cancer (EC)^[53]
42. Endometrial tissue sampling may be performed in patients with AUB who are older than 40 years (Grade C). Office hysteroscopy is the preferred method for tissue sampling. Blind sampling procedures are justified if an abnormality is symmetrically “panuterine.” Directed biopsies are preferable, in cases of focal lesions^[54]
43. Pipelle is a safe, accurate, noninvasive, and cost-effective outpatient procedure and may be offered to women at low risk of cancer.^[55] It has a low sensitivity for detecting other intracavitary lesions, including polyps and submucosal fibroids, and small lesions may be missed. Hysteroscopy directed biopsy is the gold standard
44. A meta-analysis by van Hanegem *et al.*, 2016 concluded that a positive test result of endometrial

Table 1: Mortality rates

Age	35-39 years	40-44 years
No method Contraception	11.7/100,000 women	20.6/100,000
With oral contraceptive pills	1/10,000 women	1.9/100,000

Table 2: Unmet need for family planning, and percentage of women currently married women and sexually active women 15-49 years who use any contraceptive method

Criteria	Numbers in percentages
Total unmet need in %	13%
Unmet need for spacing in %	6%
Not using any method	47%
Female sterilisation	37%
Male sterilisation	0.3%
Pill/Injectables	4.1%/0.2%
IUD/PPIUD	1.5%
Condom ;male/female	5.6%/0.1%
Rhythm/withdrawal	3.5%/2.3%

IUD - Intrauterine device; PPIUD - Postpartum Intrauterine device

sampling is very accurate in diagnosing endometrial (pre) cancer or endometrial disease. However, endometrial sampling is not very accurate in ruling out endometrial (pre) cancer and endometrial disease, and therefore, further diagnostic workup for focal pathology is warranted, after a benign result of endometrial sampling in high-risk women. Endometrial sampling methods show good specificity (98%–100%), but the sensitivity is low (76%–90%)^[56]

45. Transvaginal ultrasonography (TVS) is the primary screening test for AUB, and magnetic resonance imaging (MRI) should be considered when the diagnosis is inconclusive (Grade C)
46. Persistent bleeding with a previous benign pathology, such as proliferative endometrium, requires further testing to rule out focal endometrial pathology or a structural pathology, such as a polyp or leiomyoma (Grade B)
47. Management depends on the cause, the cost-benefit analysis of therapy, and the patient's choice (Grade C).

Postmenopausal bleeding

48. PMB is defined as uterine bleeding occurring after at least 1 year of amenorrhea. Its incidence is about 10%–15%^[57]
49. Women with PMB have a 10%–15% chance of having EC. Conversely, 90% of EC in the postmenopausal period presents with PMB. Hence, immediate evaluation is required^[58]
50. The common cause of PMB is due to atrophic changes in the vagina and the endometrium^[59]
51. A detailed clinical and drug history is important as some over-the-counter drugs such as “ginseng” can cause PMB
52. A thorough clinical examination is carried out to rule out cervical, vulval, and vaginal cancer, atrophic vaginitis, and urinary and anal causes for bleeding
53. Women with PMB may be assessed initially with TVS and an endometrial biopsy (Grade A)
54. Endometrial thickness is measured as the maximum anteroposterior thickness of the endometrial echo on a long-axis transvaginal view of the uterus
55. Women with PMB with an endometrial thickness of ≤ 3 –4 mm in the transvaginal scan do not require endometrial sampling unless they are at a high risk for EC or bleeding is episodic. In an asymptomatic early postmenopausal woman, an endometrial thickness of >11 should prompt an endometrial biopsy^[60]
56. An endometrial thickness of more than 3–5 mm in TVS consider endometrial sampling. The sensitivity for detecting EC at 3 mm is 98%, at 4 mm is 95%, and at 5 mm is 90%. In women with homogeneous and normal morphology, those on MHT, and

hypertensive medication, the acceptable combined thickness is 6 mm^[61]

57. A focal increased echogenicity or a diffuse heterogeneity in the endometrium even in a thin endometrium warrants further investigations
58. Outpatient endometrial sampling devices such as Pipelle in low-risk woman and with global pathology may be used. Outpatient hysteroscopy is the preferred method for endometrial sampling
59. If the endometrial biopsy tissue is reported as insufficient for diagnosis, and endometrial thickness on TVS is <4 mm, follow-up is sufficient. Recurrent episode warrants further investigations
60. Saline infusion sonography and three-dimensional (3D) USG play a limited role in PMB evaluation.

Quality of life

61. The WHO defines QOL as an individual's perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards, and concerns.^[62] The two terms in common usage are global QOL and health-related QOL (HRQOL). The WHO-several questionnaires are used to assess the HRQOL
62. QOL as it relates to menopausal women is usually referring to HRQOL, taking into account a woman's symptoms.^[63] Commonly used are Menopause Rating Scale, Greene Climacteric Scale, Women's Health Questionnaire, and Utian QOL Scale
63. When evaluating drug therapies, besides safety and efficacy, it is important to know the effect of drug on QOL
64. Some studies show that menopausal hormone therapy (MHT) significantly improves overall measures of QOL in symptomatic women at menopause
65. Some studies show that low-dose MHT significantly improves overall measures of QOL. MHT had mixed effects on QOL among older women from the Heart and Estrogen or Progestin Replacement Study trial, whereas the Women's Health Initiative (WHI) Trial Investigators found that estrogen plus progestin did not have a clinically meaningful effect on HRQOL
66. An Indian study has shown an improvement in QOL in women receiving tibolone.^[64]

Symptoms of menopause

The symptom complex can be divided into VMS, somatic symptom, genitourinary syndrome of menopause (GSM), and neuropsychiatric symptom.

67. Menstrual cycle: Shortening of cycles that occurs in the late reproductive years is a clinical marker for the onset of menopause. Later, there is usually a lengthening of the intermenstrual interval, and some may have sudden amenorrhea.

68.VMS

- In a multicenter hospital, urban-based study conducted by the IMS, the incidence of VMS was found to be 75%.^[11] There is a wide variation in the prevalence of symptom reporting, ranging from 19% to 75% from various studies conducted in India.^[20,21,65] The prevalence in the UK Asians was reported as 71%^[66] and in the Australian Indians as 33%^[67]
- VMSs present as hot flushes, cold sweats, and night sweats. VMS may be reported in the menopause transition, reaches the maximum intensity during the first 2 years' postmenopause, and then declines over time. VMS generally lasts for 6 months to 2 years although some may experience for 10 years or longer. We need to exclude other causes of flushing before planning treatment
- Grading of VMS is important to plan management, follow-up, and for research. Grades of hot flushes are classified as mild feeling of heat without sweating; moderate feeling of heat with sweating; and severe feeling of heat with sweating and palpitation that disrupt usual activity^[68]
- Lifestyle modifications may be recommended to reduce mild VMS (Grade B)
- The most effective treatment for VMS is MHT (Grade A)
- Low-dose OCPs if not contraindicated may be used at menopause transition phase for contraception and relief of symptoms (Grade A)
- Nonhormonal prescription agents may relieve VMS but have their own side effects. These can be considered when MHT is contraindicated or not desired (Grade B)
- Complementary and alternative treatments should be advised with caution as the data are still insufficient, especially in moderate-to-severe VMS (Grade B).

69.Somatic

- Joint aches and pain are the commonly reported symptoms among women at midlife. While women who are obese or depressed are more likely to experience joint pain, there also appears to be an association with menopausal status, with peri- and post-menopausal women experiencing more joint pain than with premenopausal women
- Body composition – Although women typically gain weight during midlife, it does not appear to be due to menopausal status or stage. In the early postmenopausal years, women typically gain abdominal fat mass and lose lean mass^[69]

- Skin changes – The collagen content of the skin and bones is reduced by estrogen deficiency. Decreased cutaneous collagen may lead to increased aging and wrinkling of the skin, frontal balding, and hirsutism^[70]
- Balance – Impaired balance in the postmenopausal women may be a central effect of estrogen deficiency additional to aging. Problems with balance may play a role in the incidence of forearm fractures in women.

70.GSM

- The prevalence of urogenital symptoms in the postmenopause in the IMS study was 15%. It presents as vaginal dryness in 32%, pruritus vulvae in 10%–17%, and dyspareunia and urinary urgency in 10%. It is due to urogenital atrophy as a result of declining estrogen levels and may also present as recurrent urinary tract infections.^[11,71] Although it effects the QOL, women in general do not complain about it; hence, suggestive questions need to be posed during history-taking
- Physical signs of vulvovaginal atrophy are variable and include reduced vulval fat, reduced vaginal rugae, and blood flow, leading to a pale appearance; a change from moderately acidic range (pH 3.5–5.0) to a neutral range (pH 6.0–8.0) in the vaginal pH; there is a shift in the vaginal maturation index
- Vaginal lubricants can be recommended for the subjective symptom improvement of dyspareunia (Grade B)
- Vaginal moisturizers can be offered for vaginal dryness and dyspareunia (Grade B)
- Local estrogen therapy (ET) is the first line of management, the only contraindication being active estrogen dependant tumors (Grade A)
- Lifestyle modification, bladder drill, and pelvic floor exercises are recommended for urinary incontinence (Grade B).

71.Sexual problems

- A woman's sexual response to her partner is significantly related to her baseline feelings for the partner, their relationship qualities, and partner's age and health
- Sexual dysfunction is multifactorial and needs to be addressed accordingly^[72]
- Vaginal atrophy with aging may lead to dyspareunia causing sexual dysfunction, which is corrected by local ET
- Acquired sexual desire disorder in some women responds to testosterone therapy. Formulations of testosterone for use in women are not available in India. Testosterone preparations meant for males should not be prescribed for women. Tibolone is

a good option since it contains androgenic activity and can be used to treat libido problems.

Central nervous system

72. Dementia

- In 2010, there are 3.7 million Indians with dementia, consisting of 2.1 million women and 1.5 million men, and the total societal costs is about 14,700 crore. While the numbers are expected to double by 2030, costs would increase three times. The prevalence of dementia is 0.6%–3.5% in rural India and 0.9%–4.8% in urban India^[73]
- The core mental functions are memory, communication and language, ability to focus and pay attention, reasoning and judgment, activities of daily living, and visual perception. Impairment of any two functions is suggestive of dementia
- Many dementias are progressive; early diagnosis allows a person to get the maximum benefit from available treatments and provides an opportunity to plan for the future
- Factors that increase the risk of dementia are family history, genetic factor apolipoprotein E, mild cognitive impairment, CVD risk factors, physical inactivity, diabetes, hypertension, dyslipidemia, smoking, obesity, autoimmune diseases, depression and stress, social engagement and diet, head trauma and traumatic brain injury, and age (Grade B)
- An objective marker is the examination of cerebrospinal fluid for amyloid-beta or tau-protein and phosphorylated tau-protein concentration. They have a sensitivity between 94% and 100% (Grade A)
- ET is not currently recommended for reducing risk of dementia developing in the postmenopausal women or retarding the progress of diagnosed Alzheimer's disease (Grade A)
- For best preservation of memory and cognition, women should be advised about the importance of good overall health, good cardiac and vascular health, exercise, maintenance of active mind, avoidance of excessive alcohol consumption, and measures to reduce risk of diabetes and hypertension. At present, MHT is not indicated for neuroprotection
- Introduction of accessible diagnostic and early-stage dementia care services, such as memory clinics, is recommended.

73. Depression

- There is a significant increased risk of new-onset depression in women during the menopausal transition compared with their premenopausal

years. In a within-woman, 8-year, longitudinal study to determine the risk factors for depressive disorders, a diagnosis of depression was 2.5 times more likely to occur in the menopausal transition compared with when a woman was premenopausal.

74. Cognitive changes

Evidence supports the relation of estrogen to cognitive function; women face problems with memory loss and difficulty in concentration at menopause transition. A definitive role of MHT for treating cognitive symptoms without VMS is lacking.

75. Sleep

- In a study conducted in the UK Asians, sleep problems were noted in 32%. A large study of over 9000 older adults aged >65 years found that 42% of participants reported difficulty in initiating and maintaining sleep.^[74] The estimate of the prevalence of sleep disorders in India, by the WHO extrapolated data from the US data, is 156,628,027 in 1,065,070,607 population
- A detailed assessment of menopausal symptoms should always include questions about sleep pattern. Sleep questionnaires or sleep diaries can be useful to assess sleep in detail (Grade B)
- Adverse lifestyle factors, social factors, and risk factors should be considered and treated accordingly (Grade C)
- If insomnia is identified, medical or psychiatric causes of insomnia should be ruled out, and if present, it should be treated accordingly. If specific neurological or breathing disorders are suspected, further investigations and referrals to specialists should be initiated (Grade B)
- Sleep hygiene measures and lifestyle modifications should be recommended as the first-line treatment. Psychological treatments, such as cognitive behavioral therapy, should also be considered (Grade B)
- If insomnia is resistant to lifestyle modifications, then hypnotics, benzodiazepines, or melatonin agonists can be used in the short term, but there is no definite or convincing evidence to suggest its efficacy. These should only be prescribed by supervision or after liaison with psychiatrists or sleep experts (Grade C)
- No recommendations can be made about the use of herbal remedies for insomnia as there is insufficient evidence. Mind-body therapies such as yoga and tai chi have some evidence but need further rigorous studies to prove its effectiveness (Grade D)

Skeletomuscular system

76. Osteoporosis: Refer Clinical Practice Guidelines on Postmenopausal Osteoporosis: An executive summary and recommendations: Indian Menopause Society.

77. Osteoarthritis

- The prevalence of osteoarthritis in India as reported from community dwellers in a small study conducted in Delhi was 47.3%, and in others, it is reported to be between 22% and 39%^[75-77]
- Age, weight, female sex, quadriceps weakness, and overloading of the knee joint are the main contributors than menopause *per se* in the incidence of osteoarthritis. Those contributing factors should be addressed on a priority basis
- Epidemiological studies of a potential role for estrogens in osteoarthritis showed two very different findings. First, estrogen deprivation at the menopause seems to be associated with increases in the frequency of knee, hip, and finger osteoarthritis and in the severity of hip osteoarthritis. Second, MHT for the menopause may decrease the incidence and progression of hip and knee osteoarthritis
- The identification of the estrogen receptors (ERs) in normal and osteoarthritic cartilage and the effects of 17-beta-estradiol on cartilage *in vivo* in animals and *in vitro* confirm that the cartilage responds to estrogens. Finally, this response is dose dependent: physiological doses (as with MHT) are protective and higher dosages are deleterious
- Once osteoarthritis sets in, there is no protection from MHT and osteoarthritis takes its own course. In such cases, osteoarthritis should be treated on its own merits
- Age, weight, female sex, quadriceps weakness, and overloading of the knee joint are the main contributors than menopause *per se* in the incidence of osteoarthritis. Those contributing factors should be addressed on a priority basis
- First two stages of osteoarthritis can be addressed by lifestyle modification, pharmacotherapy, and physical therapy (Grade A). A Cochrane review found that about 60% of the patients achieved at least 50% improvement in pain with topical nonsteroidal anti-inflammatory drugs, which was comparable to the effect obtained with oral formulations and slightly better than that observed with topical placebo.
- Third and fourth stages need surgical intervention, for which total knee replacement is the gold standard (Grade B).

78. CVD.

Prevention and management

- Lifestyle interventions (Grade A)
- Encourage optimal BP <120/80 mmHg through lifestyle approaches (Grade A)
- Pharmacotherapy if BP \geq 140/90 mmHg to avoid end-organ damage, more so in diabetes (Grade A)
- Use thiazide diuretics, unless there is an absolute contraindication
- Optimal lipid targets (Grade A) – Low-density lipoprotein (LDL) <100 mg/dL, high-density lipoprotein (HDL) >50 mg/dL, triglycerides <150 mg/dL, non-HDL cholesterol <100 mg/dL (Grade A)
- Women at high risk: Initiate statin if LDL >100 mg/dL (Grade A)
- Women at intermediate risk: Initiate statin if LDL >130 mg/dL (Grade A)
- Lifestyle approaches and pharmacotherapy to achieve near-normal glycosylated hemoglobin (HbA_{1c} <7%) in women with diabetes (Grade A)
- Aspirin in high-risk women (75–162 mg/day) (Grade A)
- Routine use of aspirin in women <65 years of age is not recommended for MI prevention (Grade C)
- MHT is not indicated solely for primary or secondary cardioprotection
- A 2015 Cochrane review of randomized controlled trial (RCT) data found that MHT initiated fewer than 10 years after menopause onset lowered coronary heart disease (CHD) in the postmenopausal women (relative risk [RR], 0.52). It also found a reduction in all-cause mortality (RR, 0.70), no increased risk of stroke, but an increased risk of VTE (RR, 1.74), similar to the findings of an earlier meta-analysis of studies in women who initiated MHT within 10 years of menopause onset or in women aged younger than 60 years (Grade A)
- Do not use antioxidant supplements for CVD prevention (Grade C)
- Do not use folic acid, with or without B6 or B12 supplements for CVD prevention (Grade C).

79. Metabolic syndrome: Insulin resistance (IR)

The prevalence reported in India at perimenopause is 22.2%, rising to 32.2%–48% at postmenopause.^[78,79] It is 1.5–2 times more common in women than in men

80. The metabolic syndrome is also known as IR syndrome and syndrome X, and an average of 40% of the Indian women are affected

81. Clinical conditions associated with IR include T2DM, CVD, polycystic ovary syndrome (PCOS), nonalcoholic fatty liver, obstructive sleep apnea, and certain cancers. It is also a prominent feature of the

Table 3: Body mass index in kg/m² category and management

Category and intervention			
Category	WHO	Indian	Intervention
Under weight	<18.5	<18	Encourage balanced diet and exercise
Healthy	18.5-24.9	18.0-22.9	Encourage balanced diet and exercise
Overweight	25.0-29.9	23.0-24.9	Lifestyle (diet, exercise and behavior therapy)
Obese Grade I	>30.0-34.9	>25	Lifestyle, lifestyle plus drug therapy if comorbidities* exist
Obesity Grade II	35.0-39.9		Lifestyle plus drug therapy: If comorbidities* exist, bariatric surgery
Obese Grade III	≥40		Lifestyle, drug therapy, and bariatric surgery

*Comorbidities: Hypertension, diabetes, and hyperlipidemia. WHO: World Health Organization

Table 4: Obesity as defined by waist circumference

WHO	Indian	Management
>80 cm	>72 cm	Action line 1 - Avoid weight gain or lose weight
>88 cm	>80 cm	Action line 2 - Supervised weight management

WHO: World Health Organization

metabolic syndrome

82. Diagnosis of metabolic syndrome: National Cholesterol Education Program Adult Treatment Panel III (NCEP ATO III 2005 revision); abdominal obesity defined as >35 inches in females; serum triglycerides >150 mg/dL; BP >130/85 mm Hg; and fasting plasma glucose >110 mg/dL – any three out of the five criteria

83. Effect of MHT: A meta-analysis of pooled data from 107 trials concluded that MHT reduced IR, abdominal obesity, new-onset diabetes, lipids, BP, adhesion molecules, and procoagulant factors in women without diabetes and reduced fasting glucose and IR in women with diabetes. The effects were diminished by the addition of progestin (Grade A)

84. The basis of dietary recommendations is to reduce exposure to insulin both as a result of dietary stimulus and through decreased IR (Grade B). We should advocate exercise as it improves insulin sensitivity, aiming for a minimum of 30 min of moderate physical activity/exercise per day

85. Indications for the intervention by body mass index (BMI) category are shown in Table 3^[79]

86. Abdominal obesity based on the waist circumference^[79] is shown in Table 4

87. DM

- India has 63 million people with diabetes and is second largest in numbers. The prevalence rate of diabetes in the last 30 years has increased from 2.3% in urban and 1.2% in rural areas (1971) to 15%–20% in urban and 10% in rural areas (2012)
- The prevalence of diabetes in women in the age group of 15–49 years was 10.5% in the urban population and 7.5% in the rural, based on the

data from the National Family Health Survey, 2015-2016 (NFHS-4)

- The prevalence in hospital-based multicenter study by the IMS in the postmenopausal woman was 12%
 - In India, T2DM occurs a decade earlier than the Caucasians. More than 50% of the subjects are undiagnosed^[80]
 - Screening: Opportunistic screening for all women above the age of 30 years, every 3 years for younger women with risk factors (Grade C), should be done. Diabetic women should be screened for hypertension, dyslipidemia, and microalbuminuria and undergo yearly eye check
 - Laboratory test for screening: The best test is a fasting plasma glucose or nonfasting HbA_{1c}.^[81] If fasting blood glucose is normal at <100 mg/dL or HbA_{1c} <5.7%, retesting should be done at 3-year intervals. If the fasting blood glucose is 100–125 mg/dL or HbA_{1c} is 5.7%–6.4%, repeat testing should be done in 1–3-year intervals. Prediabetes should be defined if the fasting blood glucose is 100–125 mg/dL or HbA_{1c} is 5.7%–6.4%.
 - The goal in management is to maintain the HbA_{1c} around <7% and control risk factors for CVD
 - It may be indicated to evaluate the endometrium by transvaginal scan before starting MHT.
88. **Thyroid disease**
- The prevalence from hospital-based data in the postmenopausal women for hypothyroid in India is 3%–7%^[82]
 - Hypothyroidism is much more common in older than younger individuals
 - Symptoms and signs include lethargy, constipation, dry skin, alopecia, memory impairment, and depression. The individual is often obese and may have elevated cholesterol
 - The prevalence of hypothyroidism is approximately 5% in otherwise healthy individuals. Thyroid-stimulating hormone (TSH) is a good screening test.

89. Anemia

Anemia is common in the elderly people in India. The overall prevalence of anemia was 68.7%.^[83] The prevalence of iron deficiency anemia, Vitamin B₁₂ deficiency, and folate deficiency is common and should be an integral part of the management of menopause.

90. Eye

- Blindness was more likely with increasing age and decreasing socioeconomic status, in female subjects and in rural areas. The causes of blindness were easily treatable in 60.3% (cataract, 44%; refractive error, 16.3%).^[84] Preventable corneal disease, glaucoma, complications of cataract surgery, and amblyopia caused another 19% of the blindness [Table 5]^[85]
- Blindness due to primary angle-closure glaucoma is potentially avoidable if this condition is detected early and peripheral iridotomy or iridectomy is performed. This requires the detection of occludable angles, which lead to primary angle-closure glaucoma, using slit-lamp examination and gonioscopy. Blindness due to primary open-angle glaucoma is more difficult to prevent and medication in open-angle glaucoma could prevent the progression of the disease (Grade A)
- There is increased risk of dry eye in both genders with age due to decreased tear production. The incidence is more in women than in men. Menopause also contributes to the ocular surface impairment due to hormonal imbalance
- MHT after menopause, especially unopposed ET, has been implicated to cause the dry eye (Grade B).

91. Prevention of blindness

- Improvement in the quality of cataract surgery and increase in the number of surgeries on persons blind in both eyes
- Effective screening to detect the refractive error blindness and provision of spectacles
- Initiation of long-term strategies to prevent corneal and glaucoma blindness
- Effective control of diabetes and yearly eye checkup to prevent diabetic retinopathy.

Table 5: Causes of blindness

Disease	Percentage of contribution (%)
Cataract	62.6
Refractive error	19.7
Glaucoma	5.8
Corneal pathologies	0.9
Other causes	11.00

Cancers

92. A population-based study (Million Death Study Cancer Mortality in India: A Nationally Representative Survey, 2012) revealed that 1 in 22 men or women aged 30 years alive today in rural India is likely to die of cancer before 70 years of age based on the rates of actual deaths and in the absence of other disorders. In urban areas, the risks are 1 in 20 for men and 1 in 24 for women.^[86,87]

Breast cancer

93. Breast cancer in India is now the most common cancer in most cities and second most common in the rural areas. In 2012, it is estimated that approximately 145,000 new patients were diagnosed with breast cancer in India, and nearly 70,000 women died of the disease. The data from Atlas Project suggest that breast cancer in urban areas of India is three times higher than in rural parts of the country.^[88-90]
94. More younger women are getting diagnosed with breast cancer. 25 years back, 69% of the patients were above 50 years of age. At present, almost 48% of patients are below 50 years age. Breast cancers in the young are hormone positive in 48%; the rest are negative and tend to be more aggressive. Indian women are more likely to develop breast cancer at earlier ages than their Western counterparts.^[91,92]
95. In the United States, 89 women out of 100 are likely to survive for 5 years after breast cancer. In India, a rough estimate is not even 60% and present late in Stage III.^[93,94]
96. Nonmodifiable risk factors for breast cancer are age, family history, benign breast disease, BRCA (breast cancer) 1 or 2 carriers, early menarche (<12 years), late age at menopause (after age 55 years), increased breast density, and a chest irradiation between ages of 25 and 55 years
97. Modifiable risk factors are age at first child, breastfeeding, parity, obesity, physical activity, and menopausal HT.

Screening in breast cancer

98. The debate about value of screening continues. There is no organized, systematic, government-funded screening program for breast cancer in India. The screening in developing countries can be regarded as "opportunistic screening." There are no evidence-based guidelines for breast cancer screening in India at present
99. There are no validated breast screening tools in India. The 5-year NCI or IBIS breast cancer risk assessment is arrived at and classified as low, intermediate, or high. These tools are simple to implement in the population. The limitation is that they have not being

validated in the Indian population. MHT needs to be avoided in the moderate and high risk category.

100. Methods

Breast cancer screening includes three methods of early detection (Grade C).

- Breast self-examination (BSE) monthly starting in the 20s
- Clinical breast examination (CBE) every 3 years starting in the 20s till 39 and annually thereafter
- Mammography screening (annually) starting at the age of 40 years.

101. BSE

- BSE is performed by the woman herself and involves examination of the breast, skin, and axillae – based on the palpations by her hands
- The woman should examine the look and feel of her breasts as well as any signs, symptoms, or changes to the breasts
- BSE is recommended so that women understand their breasts for detecting any suspicious changes over time
- Initially, BSE should be performed very frequently and regularly so that a woman understands the physiological changes that occur during the different phases of menstrual cycle and then continue monthly around 7th or 8th day of cycle. They are encouraged to report any recent or persistent changes
- Nodular and lumpy feel of the breasts and increased pain and tenderness, which is a physiological finding before menstruation, needs to be explained to the patient
- Women can be taught to examine the breasts in any of the following ways in supine as well as standing positions.

102. CBE

- CBE and increasing awareness of breast cancer are viable alternative in view of limited healthcare resources and advanced stage of disease distribution for Indian women aged 50 years
- Early results of trial by the WHO in India (*Journal of the National Cancer Institute* [JNCI 2011]) and studies for cost-effectiveness of screening in Indian women support that CBE is an effective way and survival can be improved by up to 16% at half the cost^[93]
- For women between 50 and 70 years of age, annual CBE and selective use of mammography, once in 3 years, in high-risk groups, determined by the above-mentioned criteria have been found to be equally effective (JNCI 2011)
- CBE is performed by a clinician or other health professional and involves a systematic examination of the breast skin and tissue

- The health professional is looking for signs and symptoms or if any changes occur, including development of a lump or swelling, skin irritation or dimpling, nipple pain or retraction (turning inward), redness or scaliness of the nipple or breast skin, or a discharge other than breast milk
- CBE should include all the four quadrants of the breast and the central nipple areola complex followed by examination of the axilla and supraclavicular fossae
- Fibroadenoma, a benign condition, feels as a firm and freely mobile swelling, characteristically described as a “mouse in the breast,” whereas an irregular hard painless lump is a characteristic of malignancy
- These findings are generalized and all lumps may not classically fit into these descriptions
- Normal breasts may feel lumpy and tender before menstruation, especially if felt with the tips of the fingers; hence, the use of a flat hand is recommended.

103. Mammogram

- In India, breast cancer incidence peaks before the age of 50 years, and a recent review of the evidence in younger women (aged 39–49 years), based on eight trials conducted between 2001 and 2008, suggests that mammography screening is also beneficial in this younger age group
- An approximate 12%–15% reduction in breast cancer mortality is associated with mammography screening for women aged 40–69 years^[94]
- Imitations of mammography in developing countries are economic constraints and quality assurance. Cost-effectivity and false-positive rates are the other limitations in the use of mammography in India
- The decision to perform mammography should be determined with shared decision-making about risks and benefits and by individual patient values

104. MRI

- Currently, MRI screening in combination with mammography is targeted to high-risk patients, which includes:
 - BRCA 1 or 2 mutation carriers
 - Untested women who have a first-degree relative with a BRCA 1 or 2 mutation
 - Life time risk of breast cancer of 20%–25% or more
 - Received radiation treatment to the chest between ages of 10 and 30 years
 - Women with silicon implants.

105. Role of positron-emission tomography (PET) imaging

PET has currently a limited role in breast cancer, due to its low sensitivity, and is not recommended in most of the cases, especially in early disease. The most useful application of PET or computed tomography is monitoring the changes in 18-fludeoxyglucose uptake during chemotherapy to detect an early response to treatment.

106. Breast cancer prevention

- The risk of breast cancer may be lowered to some extent by lifestyle changes, working on modifiable risk factors, and diligent use of MHT
- The best way to protect one's self is through early detection

Prevention in high-risk population

107. Indications of risk reducing surgery, mastectomy, salpingo-oophorectomy, and chemoprevention can be discussed with experts. The decision is individualized.

Cancer cervix

108. The number of new cases of cervical cancer detected in India is 96,922 every year. Deaths due to cervical cancer in India are 60,078/year^[95]

109. Opportunistic screening coverage varied from 6.9% in Kerala to 0.006% and 0.002% in the western state of Maharashtra and southern state of Tamil Nadu, respectively^[96]

110. India contributes to over 25% of the disease burden and more than 26% of the deaths due to cervical cancer, worldwide. More than 75% of the cases presenting in the late stage of the disease render poor prospects for survival and cure. About 134,420 new case are being diagnosed every year^[97]

111. Risk factors are human papilloma virus (HPV), sexual intercourse at an early age, multiple sexual partners, sexual partners who have had multiple partners, HIV-positive status, and smoking

112. Screening tests available

- Visual inspection
- Visual inspection with acetic acid (VIA)
- Visual inspection with Lugol's iodine
- Papanicolaou (PAP) smear both conventional and liquid-based cytology
- HPV-DNA testing
- Cervicography
- Polar probe.

113. The first three are useful at community and low-resource setting

114. Cost-effectiveness studies on VIA screening also suggest that, once in a lifetime, screening at the age of 35 years involving one or two visits reduced the

lifetime risk of cancer by approximately 25%–36%. The relative risk further decreased by 40% with two rounds of screenings (at 35 and 45 years of age).^[98]

Screening at different levels of care

115. Primary care (rural/urban)

- Cytology-based screening has made little impact in developing countries due to relatively high false-negative rate and lack of organized screening program and referral pattern
- Several studies have shown the benefit of a single-visit approach in the form of “see and treat,” which involves VIA followed by cryotherapy. This unique approach is based on the principle that the screening test should provide rapid and accurate results and the treatment modality should be appropriate, adequate, and effective. VIA and cryotherapy satisfied these criteria and yielded satisfying results. A randomized trial in South India done by Sankaranarayanan *et al.*, in 2007, has shown 25% reduction in cervical cancer incidence and 35% reduction in mortality compared to control with VIA and cryotherapy.^[98] This approach is useful in primary care level to make the screening program more cost-effective. This can be carried out both by physicians and by trained nurses and midwives^[99-105]
- Colposcopy: For diagnostic confirmation with guided biopsies in screen-positive women, post any primary screening method adopted. Because of hormonal changes, many postmenopausal women will have an unsatisfactory colposcopy. Estrogen treatment (estrogen cream application intravaginally each evening for 2 weeks and stopped 1 week before repeat cytology) will cause enough ectropion of the endocervical cells to result in a satisfactory examination
- HPV testing also has been tried in a screen-and-treat approach. A few studies reported screening with HPV DNA testing followed by cryotherapy. However, it has two limitations: time and infrastructure required for the current HPV testing and a lack of consensus about appropriate follow-up for test positives and also treatment strategy. Hence, in some other studies,

Table 6: Screening at different levels of cancer cervix

Level of care	Intervention
Primary	VIA + cryotherapy/HPV + cryotherapy
Secondary	PAP±HPV cotesting
Tertiary	PAP±HPV cotesting

Pap: Papanicolaou, HPV: Human papilloma virus, VIA: Visual inspection with acetic acid

HPV DNA-positive women had VIA followed by cryotherapy if VIA was positive

- Some studies suggest that cryotherapy is protective against the future development of cervical disease among women with current HPV infection. Because of this, and due to the low morbidity of cryotherapy, the occasional treatment of screen-positive women without confirmed cervical disease is acceptable.

116. Secondary and tertiary level

PAP smear and HPV-DNA testing are being used commonly at secondary and tertiary care level.

117. Screening techniques' recommendations from different organizations may be applicable at different settings both in rural and in urban [Table 6]

118. HPV co-testing is to be performed only if the woman crosses 30 years of age as most of the HPV infection clears by then with natural immunity. If both PAP and HPV are negative, the screening interval can be increased, which again becomes cost-effective

119. Colposcopy: For diagnostic confirmation with guided biopsies in screen-positive women, post any primary screening method adopted. Because of hormonal changes, many postmenopausal women will have an unsatisfactory colposcopy. Estrogen treatment (estrogen cream application intravaginally each evening for 2 weeks and stopped 1 week before repeat cytology) will cause enough ectropion of the endocervical cells to result in a satisfactory examination

120. Screening recommendations from different organizations are presented in Table 7

121. Women with negative PAP and positive HPV testing can be either rescreened with co-testing in 1 year or with a test specific for type of HPV

122. All these screening methods may be sometimes inconclusive in the menopausal women whose transformation zone is inside the cervical canal

or due to atrophic changes. Hence, choosing the appropriate test is important.

- High-risk (oncogenic) HPV DNA testing could be adopted for appropriate triage management of postmenopausal women with unequivocal cytology results
- HPV DNA testing is indicated in postcolposcopy management of women of any age with initial cytological result of atypical glandular cells (or atypical squamous cells cannot exclude-high-grade squamous intraepithelial lesion in initial workup does not identify a high-grade lesion)
- If a low-cost and rapid HPV is available, this may be used as primary screening test every 5 years up to the age of 65 years. With HPV testing as the primary screening method, PAP or VIA testing can be used to triage to evaluate those with HPV-positive test results to plan for appropriate treatment options
- Above recommendation holds true for women seeking opportunistic services in apex and secondary care levels in public and private sector health facilities where good-quality PAP cytology services and molecular testing for HPV-DNA are available
- In the absence of organized cervix cancer screening for the vast women population in rural and urban areas, once in a lifetime, screening by co-testing by combined use of cervical cytology and high-risk HPV-DNA testing would be appropriate [Table 7].

Primary prevention

123. Women should be educated early on to think of cervical cancer as an extension of a sexually transmitted disease

124. Behavioral changes to reduce the risk of cervical cancer include limiting the number of sexual

Table 7: Screening recommendations from different organizations

Age (years)	USPSTF	ACS/ASCCP
30-65	Co-testing with PAP + HPV every 5 years (preferred) PAP alone every 3 years (acceptable) (Grade A)	Same as USPSTF Recommendations
>65	Screening not recommended in women who have had adequate prior screening and or not high risk for cervical cancer (Grade D)	Adequate prior negative screening no history of high-grade CIN in the last 20 years, no screening should not be resumed even a woman reports having a new sexual partner
Posthysterectomy, artificial menopause	No screening if hysterectomy with removal of the cervix is performed for benign lesions and no history of high-grade CIN (Grade D)	No screening if hysterectomy is performed with no history of high-grade CIN
HPV vaccinated	Screening as per the age	Screening as per age

USPSTF: United States Preventive Services Task Force, ACS: American Cancer Society, ASCCP: American Society for Colposcopic and Cervical Pathology, CIN: Cervical intraepithelial neoplasia, PAP: Papinocolau, HPV: Human papilloma virus

partners, delaying initial age of sexual intercourse, and avoiding sexually transmitted disease. The association of cigarette smoking with cervical cancer should also be emphasized

125. An HPV vaccine needs to be promoted, especially in the age group of 9 years to the age of first sexual debut. Data from a large placebo-controlled trial showed that the vaccine reduced the incidence of both HPV-16 infection and HPV-16-related cervical intraepithelial neoplasia.^[106]

Endometrial cancer

126. Indian incidence of EC is 4.3/100,000 as per the Delhi population-based cancer registry. EC commonly occurs in the postmenopausal women^[107]
127. Overall morbidity and mortality of EC are low because most patients present at an early stage because of abnormal bleeding or PMB
128. Risk factors
- Factors that increase the risk of EC are those associated with increase in endogenous ET or HT with estrogens
 - A strong modifiable risk factor is increasing obesity; the relative risk of EC with obesity is 3 in women 9.5–22 kg overweight and 10 in women more than 22 kg overweight
 - Women taking tamoxifen for more than 2 years have a 2.3-fold to 7.5-fold relative risk of EC^[108]
 - Adenomatous hyperplasia and EH are the common precursors of endometrial carcinoma
 - Unopposed ET in women with an intact uterus increases the risk of EC 2–10-fold, and the risk increases with the duration of use
 - The lifetime risk of EC for women with hereditary nonpolyposis colorectal cancer (HNPCC) and for women who are at high risk for HNPCC is as high as 60%^[109]
 - Cyclic or continuous progestin given along with estrogens reduces the risk of EC.
129. There is no evidence that screening by USG or endometrial biopsy reduces mortality from EC. Most cases of EC (85%) are diagnosed at low stage because of symptoms, and the survival rates are high^[110]
130. There is no indication that screening for EC is warranted for women who have no identified risk factors^[111]
131. It is recommended that, at the time of menopause, women at average risk should be informed about the risks and symptoms of EC and strongly encouraged to report any unexpected bleeding or spotting
132. For those with increased risk and special situations, such as on MHT (tibolone sequential MHT), genetic

risk, and tamoxifen therapy, they should have a follow-up and complete diagnostic evaluation as needed. Regular screening for high-risk group for EC has not been fully evaluated

133. Women diagnosed with EC should have the benefit of multidisciplinary team approach.

Endometrial hyperplasia

134. Definition: EH is a pathological condition that most often results from persistent, prolonged exposure of unopposed estrogenic (endogenous production or exogenous administration of estrogens) stimulation of the endometrium. It is known to be precursor of EC
135. There are two methods of classifying EH:
- The 2014 WHO EH classification system has only two categories – hyperplasia without atypia (nonneoplastic) and atypical hyperplasia (endometrial intraepithelial neoplasm [EIN])^[112]
 - The EIN classification system defines two classes of endometrial changes: benign and intraepithelial neoplasia^[113]
136. EH is a histologic diagnosis made based upon the results of evaluation of an endometrial biopsy, endometrial curettage sample, or hysterectomy specimen
137. Clinical significance: EH is of clinical significance because it is often a precursor lesion to Type I endometrioid adenocarcinoma of the endometrium. Endometrial stripe thickness and age were the strongest predictors of concurrent endometrial cancer at time of hysterectomy for EIN. An endometrial stripe of ≥ 2 cm was associated with 4.0 times the odds of concurrent EC (95% confidence interval, 1.5–10.0), controlling for age
138. Management
- All management strategies should also be accompanied by the removal of the extrinsic or intrinsic source of unopposed estrogen since excess exposure to estrogen is a main etiology of endometrial neoplasia
 - Conservative management: if the risk of an occult cancer or progression to cancer is low and the inciting factor that resulted in endometrial proliferation has been eliminated (e.g., patient with anovulation, now corrected, who had developed simple hyperplasia without atypia) and requires vigilant follow-up with two negative biopsies 6 months apart^[114]
 - Benign EH: (1) Conservative with use of continuous progestones and follow-up (2) Surgical—total hysterectomy (TH) when associated with high-risk factors, postmenopause
 - EIN: TH with bilateral salpingo-oophorectomy

(BSOP) for EIN provides definitive assessment of a possible concurrent carcinoma and effectively treats premalignant lesions in a postmenopausal woman. In premenopausal women, decision regarding BSOP needs to be individualized. Supracervical hysterectomy, morcellation, and endometrial ablation are unacceptable for the treatment of EIN.^[115]

Cancer ovary

139. The general or lifetime risk of ovarian cancer is 1.4%
140. The most common sign of ovarian cancer is enlargement of the abdomen caused by the accumulation of fluid or a large ovarian mass
141. However, many women have bloating or weight gain in the abdominal area, making this sign nonspecific
142. In women aged over 40 years, digestive disturbances that persist and cannot be explained by any other cause indicate the need for a thorough evaluation for ovarian cancer, including a carefully performed pelvic examination and ultrasound (US)
143. Risk factors
 - A first-degree relative with ovarian cancer (mother, sister, or daughter)
 - Personal history of breast cancer <40 years or age
 - Personal history of breast cancer <50 years or age and one or more close relative with breast or ovary cancer at any age; two or more close relative with breast cancer <50 years of age or ovarian cancer at any age.
144. Screening
 - No screening guidelines are available for mass screening for ovarian cancer. Recommendation for screening is dependent on the risk status of women^[116]
 - A heightened awareness of the symptoms of early ovarian cancers on the parts of the patients and practitioners may help reduce the delay in diagnosis and hopefully result in an improvement in the outcome of some progress
 - For general population, annual pelvic examination, PAP smear, and transvaginal sonography are recommended as a part of postmenopausal surveillance
145. Primary prevention: Limited data are available on the efficacy of prophylactic oophorectomy in decreasing the risk of ovarian cancer in mutation carriers. Still, it is recommended that prophylactic surgery be considered in BRCA mutation carriers who have completed childbearing.

Vulvar cancer

146. Epidemiology: Cancer of the vulva is a rare disease that accounts for approximately 5% of

gynecological cancers. The median age of onset is approximately 65–70 years for invasive cancer and approximately 45–50 years for carcinoma *in situ*

147. Risk factors for vulvar cancer including HPV, previous genital warts, greater number of sexual partners, current smoking, abnormal PAP smear, diabetes, obesity, chronic vulvar pruritus, and poor personal hygiene have also been suggested as contributing to risk
148. Protected intercourse, monogamy, and adequate hygiene of the external genitalia protect against vulvar cancer
149. Prevention and detection: The prevention of vulvar cancer rests in the avoidance of risk factors and application of protective factors as summarized above. Annual examinations should be performed to check for vulvar cancer. High-risk patients should be examined every 6 months. White lesions and chronic ulcerative lesions should be biopsied for evaluation.

Stomach cancer

150. According to the GLOBOCAN 2018 data, in women aged 30–69 years, the fourth most common fatal cancer was stomach (14.1%). Stomach cancer rates were higher in rural than in urban areas of India due to increased prevalence of chronic *Helicobacter pylori* infection. Treating for *H. pylori* may prevent stomach cancer
151. Million Death Study Cancer Mortality in India: A Nationally Representative Survey 2012: This may include stomach and primary liver cancer. The prevalence of hepatitis B virus (HBV) in India was <1.9% in 72,000 pregnant women aged 15–49 years who were tested in 2002
152. Nearly, 37% of all female cancer deaths were from infection-related cervical, stomach, and liver cancers and 18.3% were from tobacco-related cancers. This underscores the importance of vaccination and control of infection. Vaccination against HBV would reduce future liver cancer deaths and cirrhosis. Use of tobacco in pan and beedi should be strongly discouraged.

Hyperandrogenism at menopause

153. Postmenopause is a state of relative androgen excess in relation to estrogen; the postmenopausal ovary remains hormonally active, secreting significant amounts of androgens and relatively fewer estrogens years after menopause
154. There is no consensus regarding specific clinical and hormonal indices and/or imaging modalities required for diagnostic certainty^[117]

155. Hyperandrogenism in the postmenopausal women can be generally categorized as functional/nontumorous or tumorous
156. The causes of functional hyperandrogenism, such as PCOS and nonclassic congenital adrenal hyperplasia, are clinically manifested before menopause
157. Androgen-secreting neoplasm should be suspected in cases of clitoromegaly (clitoral size >1.5 cm × 2.5 cm) and other signs of virilization even if symptom progression is not rapid. Very high serum testosterone (>150–200 ng/dL) and/or DHEAS (>6000 ng/mL) levels are indicative of an androgen-secreting tumor of the ovarian and adrenal origin, respectively
158. The long-term sequelae of nontumorous hyperandrogenism in the postmenopausal women in respect to cardiovascular morbidity and mortality are not known.^[117]

Polycystic ovary syndrome at menopause

159. Increased androgen secretion by the ovarian theca cells is a primary defect in PCOS and may persist as hyperandrogenism in a subset of the population
160. Androgen excess favors the development of abdominal adiposity, IR, and compensatory hyperinsulinism, and this further increases androgens, leading to a vicious circle that predisposes these women to metabolic dysfunction and cardiovascular risk^[118]
161. Menopausal transition does not seem to be associated with worsening of cardiometabolic profile in PCOS patients. This may be related to the improvement in phenotypic features of PCOS with aging. The phenotype of PCOS plays an important role in determining the cardiometabolic risk in patients with the syndrome^[119]
162. Population-based, longitudinal studies examining cardiometabolic morbidity and mortality in women with PCOS are lacking
163. Identifying clinical and biochemical characteristics of PCOS in the postmenopausal period may provide a reliable method for following women to help define the true cardiovascular morbidity and mortality
164. As a part of menopause workup, vigilance is needed in women with hyperandrogenism and PCOS or a history of PCOS as this forms an additional risk factor for cancers. Persistent thickened endometrium and/or risk factors including prolonged amenorrhea, abnormal vaginal bleeding, or excess weight need to be investigated^[117]
165. Therapeutic strategies currently in use for PCOS, including lifestyle modification, oral contraceptives (OCs), antiandrogens, and insulin sensitizers, are used throughout the lifespan such that these women enter menopause with a healthy metabolic profile.

Endometriosis and menopause

166. Endometriosis in the postmenopausal women is a rare condition
167. Postmenopausal endometriosis may have a greater tendency to spread and involve extragonadal organs and structures that may develop into constrictive and/or obstructive lesions^[120]
168. Surgical treatment is the first-line therapy to exclude malignancy case of postmenopausal endometriosis, but drug treatment may be an option in case of pain recurrence after surgery^[121]
169. In a Cochrane review, authors concluded that MHT may increase the risk of endometriosis symptoms and disease recurrence after surgically induced menopause. The current data are, however, insufficient to justify not administering HRT for symptomatic women after surgically induced menopause^[122]
170. The evidence is currently insufficient to support any conclusions about the optimal MHT regimen for women with endometriosis. Few data suggest a higher malignancy risk with estrogen-only MHT compared with combined MHT^[121]
171. Postmenopausal women should be conscientiously evaluated before initiating MHT. Patients with endometriosis receiving MHT should be monitored regularly for pain recurrence.

Fibroid and menopause

- Fibroids are benign tumors that probably arise from a somatic myometrial stem cell. They have ERs and progesterone receptors (PRs). After menopause, fibroids generally shrink, and some may become calcified due to the loss of estrogen
- Malignant transformation into sarcoma is possible but exceedingly rare (around 1/2000)^[123]
- At menopause transition, depending on the patient's symptoms and age, fibroids can be managed expectantly, medically, radiologically, or surgically
- MHT use in the menopausal women with asymptomatic fibroid demonstrates variable effects on the volume and size of uterine fibroids
- Some combination estrogen and progestin therapy may increase in size of preexisting myomas and increase in frequency of new myoma formation, especially with higher doses of MPA (5 mg/day). Use the lowest possible dose of progestin with estrogen
- The use of tibolone for menopausal symptoms is generally associated with fewer episodes of irregular spotting and no significant changes in volume or size

- of myoma compared with estrogen, progestin therapy
- Raloxifene appears to be relatively safe for menopausal women at risk of osteoporosis or breast cancer, who present with asymptomatic fibroids
- If on MHT, periodic follow-ups with an ultrasound every 3 months for appearance of symptoms and growth of myoma are advisable in the initial year.

SECTION III

ABNORMAL MENOPAUSE

Premature ovarian insufficiency

- 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. At the age of 48–49 years, 55.8% of the women are amenorrheic. It is probably an overestimate for the study that did not differentiate between natural, surgical, or secondary causes
- 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
- Conventionally, the diagnosis of overt POI is more likely if there is amenorrhea of 3–4 months and serum FSH levels >40 IU/mL (that is the menopause range) repeated a month apart accompanied by low estradiol levels. The ESHRE 2015 guidelines recommend these diagnostic criteria for POI: (1) the presence of menstrual disturbance such as oligomenorrhea or amenorrhea for at least 4 months and (2) an elevated FSH level >25 IU/L on two occasions at least 4 weeks apart (Grade C)
- Appropriate counseling, 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.^[124,125] OCs may be used.^[126] However, emerging evidence suggests that physiological dose of HT is superior to hormone contraceptives. 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
- 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
- Women with untreated premature menopause are

at increased risk of developing osteoporosis, CVD, dementia, cognitive decline, and Parkinson's and all-cause mortality^[127-129]

- Women receiving chemotherapy or radiotherapy (pelvis) should be cautioned about iatrogenic premature menopause
- Premenopausal hysterectomy alone may cause early menopause^[130,131]

Iatrogenic menopause

- The exact prevalence of surgical menopause is not known but varies from rural to urban areas and across states
- A significant number of hysterectomies along with bilateral oophorectomies are performed at a young age. This trend of unwarranted hysterectomies and surgical castration for fear of cancer by the professional and the women should be discouraged
- The physicians should have appropriate knowledge to recognize menopausal symptoms and whenever in doubt should get the tests done (FSH >40 IU/mL, E2 <20 pg/mL)
- Women who need oophorectomy before menopause should be counseled about the risk of surgical menopause
- Routine MHT is not recommended for surgical menopause in a postmenopausal woman as the primary prevention for chronic conditions
- MHT should be considered in women aged <50 years who have undergone surgical menopause
- Results of the WHI studies in older women do not apply to women with early menopause, and observational evidence suggests benefit with the use of HT taken up to the average age of menopause
- Younger women may require higher doses for symptom relief or protection against bone loss
- HT may have a beneficial effect on BP when compared with a combined OC
- HT has bone protection effect. Combined OCs may protect bone depending on the estrogen status of the woman.^[125,126]

SECTION IV

CLINICAL EVALUATION

General considerations

- Clinical examination includes a holistic approach to health, rather than simply looking for the features of menopause in isolation; this leads to diagnose the latent and overt noncommunicable diseases NCD.^[132-135] The age-related factors, lifestyle, and socioeconomic status need to be evaluated the woman and plan the management strategies
- A detailed history, followed by general and physical

examination, and assessment and categorization for risk of disease is done based on history and by using validated tools described below which are simple and can be easily incorporated in practice. These help in individualizing and plan long-term management for the midlife woman [Refer Appendix 1]

174. Menopause-related symptoms may be documented using the menopause rating scale [Refer Appendix 2]
175. Breast: A woman may be categorized of her risk for developing invasive breast cancer by Gail Model, the limitation being that it has not being validated in India (<https://www.cancer.gov/bcrisktool>) [Refer Appendix 3]
176. CVD: 10-year probability risk of MI/stroke – based on the WHO SEAR, WHO/ISH Risk Prediction Charts for India – uses the SEAR D. They are simple to use by the paramedics and the clinician (https://www.who.int/ncds/management/WHO_ISH_Risk_Prediction_) [Refer Appendix 4]
177. Skeletal health: Risk assessment for osteoporosis may be done by OSTA/SCORE/FRAX (<http://www.shef.ac.uk/FRAX>) [Refer Appendix 5]
178. Muscle health is assessed by the SARC-F, a 5-item questionnaire [Refer Appendix 6]
Results for risk assessment for diseases are documented in Table 8
179. Examination can be broadly divided into three main categories: general physical including BMI and waist circumference, breast examination, and pelvic examination
180. Recommended laboratory tests include complete blood picture, urine test routine, fasting glucose level/Hb1Ac, lipid profile, serum TSH, stool for occult blood, PAP smear, vaginal pH, TVS, mammogram, or US
181. Investigations given in Table 9 should be chosen judiciously depending on the women's history and examination
182. Dental and eye checkup should also be done.

Table 8: Comprehensive chart for grading the health status of an individual based on tools for invasive breast cancer, CVD and Skeletomuscular health

Tool	5/10-Year risk score	Lifetime risk score	Status
Invasive breast Cancer Gail			
WHO/ISH			
OSTA/SCORE/FRAX			
SARC-F			
WHO: World Health Organization, FRAX: Fracture Risk Assessment Tool			

SECTION V

MANAGEMENT OPTIONS

183. Classifying a woman into the following categories:
It is helpful in planning management (adapted and modified from Morris Notelovitz)
The information obtained from the MRS scale and health status obtained from the risk screening results aids in classifying the women into two major groups.
Group 1-Women with no menopausal symptoms (VMS)
Group 2-Women with menopausal symptoms
In practise, charting out an individualised management plan becomes simple.
Group 1-Women with no VMS
 - Healthy, no VMS - institute preventive care
 - Healthy with risk factors for disease, no VMS —institute preventive health care
 - Women with latent disease, no VMS- institute preventive health care, treat the disease
 - Women with comorbidities, no VMS-institute preventive health care, treat the disease
 Group 2-Women with menopausal symptoms
 - Healthy with VMS - institute preventive health care, treat with MHT
 - Healthy with risk factors for disease, with VMS -institute preventive health care, risk-benefit analysis before therapeutic intervention
 - Women with latent diseases, with VMS —institute preventive health care, risk benefit analysis before therapeutic intervention
 - Women with comorbidities, with VMS - institute preventive health care, treat the disease, risk-benefit analysis before therapeutic intervention. [Refer Appendix 7]

Counseling

184. Today, the art of medical counseling and translating the statistics in simple language is an important part of the consultation
185. The objectives of counseling include addressing women's questions and concerns, providing patient's education, and enhancing the patient's confidence in decision-making. If a therapy is chosen, the patient and clinician should agree on the goals, risks, and benefits, whether they are short term (menopause symptom relief), long term (primary or secondary prevention of diseases associated with aging), or both^[136-138]
186. Classification of frequency of drug reactions according to the WHO and the Council for International Organisations of Medical Sciences is presented in Table 10.^[139] This tool is effective in counseling the woman on the risks of MHT.

Table 9: Tests performed solely on indication

Test	Indication
FSH	Premature ovarian insufficiency, women on contraceptive pills, women who had hysterectomy, doubt as to the cause of secondary amenorrhea or hot flushes, women on patches to rule out accumulation, fertility
Estradiol	Premature ovarian insufficiency, women on contraceptive pills, women who had hysterectomy, doubt as to the cause of secondary amenorrhea or hot flushes
Tests to assess increased risk of thrombosis	Where there is relevant past or family history, women with previous history of unexplained thromboembolic episodes antithrombin III, Tissue factor pathway inhibitor activity, protein C and protein S are to be estimated. Lupus anticoagulant, anticardiolipin antibodies should also be assessed
Endometrial biopsy	Postmenopausal bleeding, recent irregular bleeding, previous use of unopposed estrogen in the presence of uterus
Bone mass measurement	For specific indication (Refer Flowchart 2)
LFT	When relevant as with suspected liver disease or recent history of liver disease
Urodynamic study	To diagnose and differentiate on the severity and type of Incontinence before planning surgery
ECG, 2D Echo	CVD assessment
Vaginal pH, VMI	Vaginal atrophy
25, OH Vitamin D	Rule out secondary causes of osteoporosis

FSH: Follicle-stimulating hormone, LFT Liver function tests, ECG: Electrocardiogram, 2D Echo: Two-dimensional echocardiography, CVD: Cardiovascular disease, VMI: Vaginal saturation index

Dietary prescription

187. The National Institute of Nutrition plan for an adult sedentary woman is a good strategy for healthy living [Table 11].^[140]

Exercise prescription

188. Physical exercise helps maintain a healthy weight, improves bone density, coordination and balance, muscle strength and joint mobility, lipid profiles, genitourinary problems, relieves depression, and induces sleep
189. Social interactions, either in an exercise program or otherwise, help the postmenopausal women to improve mood, relieve depression, and relieve anxieties
190. Euphoria created with activity promotes QOL.

Immunization prescription

191. Hepatitis B vaccination is indicated for all unvaccinated adults at risk for HBV infection and all adults seeking protection from HBV infection including postexposure prophylaxis. Prevacination screening in general population has not been found to be cost-effective in India (Grade B)^[141]
192. The Expert Group of Association of Physicians of India recommends vaccination of the entire community at risk during an outbreak situation (Grade B)^[141]
193. Two doses of varicella vaccine are strongly recommended in adults at increased risk for exposure of varicella (Grade B).^[142]

Pharmacotherapy**Complementary and alternative therapies**

194. Nonhormonal prescription agents may relieve VMS but have their own side effects. These can

Table 10: Council for International Organisations of Medical Sciences definitions are as follows which can be easily communicated to the lay person

Term	<i>n</i>	Colloquial
Very common	1/1 to 1/10	A person in family
Common	1/10 to 1/100	A person in street
Uncommon	1/100 to 1/1000	A person in village
Rare	1/1000 to 1/10000	A person in a small town
Very rare	Less than 1/10000	A person in a large town

Table 11: Nutrition plan for an adult sedentary women

Food source	g/day
Cereals and millets	270
Pulses (vegetarian)	60
Nonvegetarian	30
Vegetables	300
Fruits	100
Dairy products	0.3
Fats and oils	20
Sugar	20
Salt	5
Water	8-10 glasses

be considered when MHT is contraindicated or not desired (Grade A). Complementary and alternative treatments should be advised with caution as the data are still insufficient, especially in moderate-to-severe VMS.

195. These are not as effective as MHT and include drugs used as antidepressants and anticonvulsants, i.e., the selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors. For women with insomnia as the predominant symptom, choose gabapentin, and for women with predominance of mood disorders, prefer

fluoxetine and paroxetine.^[143] In breast cancer patients, fluoxetine and paroxetine should not be used as they inhibit the effect of tamoxifen.^[144] In women with dyslipidemia, fluoxetine and citalopram exert the most favorable effect on the lipid profile

196. Awareness should be created regarding the phytoestrogens and lycopene-rich foods in the Indian diet^[145,146] (Grade C)
197. It is recommended to validate the effects of locally used herbs in the Indian context, according to the modern medicine, and prescribe them rationally using clinical research tools and well-designed and documented RCTs. While prescribing or recommending herbs, it would be essential to fully inform the women that very little human data are available on the usefulness of these formulations and side effects of the herbs have not been studied. It is important to read labels to determine isoflavone content and to warn them that in India, there are no regulations to ensure the content or quality of such products (Grade C).^[147]

Indian data are sparse on the use of MHT; hence, this section is based on the guidelines developed by various societies.^[8,147-151]

Menopausal Hormone Therapy

Terminology

198. MHT covers therapies including estrogens, progestogens, combined therapies, androgens, and tibolone
Terminology used in MHT: ET-estrogen therapy: EPT-estrogen/progesterone therapy: AT-androgen therapy: SERMs-selective estrogen receptor modulators (raloxifene and bazedoxifene): Gonadomimetics-tibolone, which contains estrogen, progestogen, and androgen activity
199. Three indications for postmenopausal HT, which have constantly withstood the test of time, derived from the results of various clinical trials are the beneficial effects of estrogens on symptom relief, urogenital atrophy, and bone. Hormone therapy is indicated in POI and early menopause
200. Contraindications for MHT: Active endometrial and gynecological hormone-dependent cancers, active breast cancer, high risk for breast cancer, severe active liver disease with impaired/abnormal liver function, venous thrombosis, established CVD and at severe increased risk of CVD, known or suspected pregnancy, and undiagnosed and abnormal vaginal bleeding.

Patient characteristics that may be favorable for estrogen/androgen combination

201. Surgical menopause with continued VMS despite estrogen replacement, decreased well-being despite estrogen replacement, and acquired sexual desire dysfunction.

Indications for hormone therapy

Vasomotor symptoms

202. The most effective treatment for VMS is MHT at menopause transition (Grade A). Progestones or low-dose OCPs may be used at menopause transition phase for relief of symptoms.

Genitourinary syndrome of menopause

203. Vaginal ET is most effective in the treatment of urogenital atrophy. Low-dose vaginal preparations are as effective as systemic therapy. Some women on oral ET may require additional local therapy
204. 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 (Grade A)
205. Recurrent attacks of atrophic vaginitis require the use of the smallest effective dose over a period of time. After control of acute symptoms, the dose of local estrogen can be tapered for long-term maintenance therapy. Treatment may be continued indefinitely although safety data from studies do not go beyond 1 year (Grade C)
206. Limited data are available on the use of vaginal ET in women with breast cancer and EC. Lifestyle management and nonhormonal treatments would be the first option, but, in resistant cases, joint consultation with the oncologist and counseling of the woman is done before prescribing vaginal estrogen. The preferred therapy may be low dose with low-potency agent like estriol
207. Recurrent urinary tract in this age after ruling out other causes may benefit from the local application of ET (Grade A)
208. Progesterone supplement for endometrial protection is not needed along with the use of vaginal estrogen (Grade C)
209. Endometrial surveillance is not necessary in low-risk asymptomatic woman. Unscheduled bleeding should be investigated by transvaginal US and endometrial biopsy (Grade A)
210. Low-dose vaginal estrogen formulations reported no incidence of increase in CHD, stroke, and VTE. There are no contraindications for use in nonestrogen-dependent cancers (Grade A).

Osteoporosis

211. 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 postmenopause in symptomatic women unless there is a contraindication. 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. It reduces the risk of spine, hip, and other osteoporotic fractures by 33%–40% (Grade A).
212. 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 (Grade B)
213. POI: HT should be offered to women with POI and early menopause (and it can be recommended until the age of natural menopause) (Grade B)
214. Depression: Estrogen may be prescribed to enhance mood in women with depressive symptoms after ruling out other causes. The effect appears to be greater for perimenopausal symptomatic women than for postmenopausal women (Grade A).

Hormone therapy use in disease

215. In women with hypertriglyceridemia (>400 mg/dL), obesity, history of deep vein thrombosis, and tobacco users, nonoral route should be preferred (Grade B).
For women at moderate risk of CVD, observational data suggest transdermal rather than oral estrogen, with micronized progesterone or dydrogesterone for those with a uterus. Non-HTs are advised for symptomatic women who are at high risk (>10% 10-year risk) for CVD.
216. MHT has a favorable effect on glucose metabolism, both in women with and without T2DM, while it may delay the onset of T2DM
217. MHT in women with T2DM should be administered according to their risk of CVD. In women with T2DM and low CVD risk, oral estrogens may be preferred, while transdermal 17 β -estradiol is preferred for women with T2DM and coexistent CVD risk factors, such as obesity. Progestogen with neutral effects on glucose metabolism should be used, such as progesterone and dydrogesterone
218. Women who have low to moderate of breast cancer may be prescribed MHT according to their need after a detailed history, examination, and counseling. They should be provided information about breast cancer risk with MHT as per evidence

219. Women at moderate risk of breast cancer, a benefit risk analysis and the choice of MHT should be discussed
220. In women with high risk and breast cancer survivors, it is recommended to use non MHT
221. HT does not appear to influence the clinical pattern of benign breast disease in a postmenopausal woman (Grade C).

Preexisting cancers and menopausal hormone therapy (Grade C)

222. MHT is neutral – Low-grade, early-stage EC type I, cervical adenocarcinoma, epithelial ovarian cancer, germ cell tumors, hematological malignancies, local cutaneous malignant melanoma, colorectal cancer, hepatocellular cancer BRCA 1/2 mutation carriers without cancer, most types of ovarian cancer, squamous cell carcinomas of cervix, vaginal and vulvar squamous cell carcinoma, prolactinoma, kidney cancer, pancreatic cancer, and thyroid cancer
223. MHT is relatively contraindicated – Leiomyosarcoma, EC type II, advanced metastatic malignant melanoma, lung cancer, gastric cancer, and bladder cancer
224. MHT is contraindicated – Breast cancer, endometrial stromal sarcoma, uterine carcinosarcoma, ovarian cancer (estrogen-dependent granulosa cell, low-grade serous, and Sertoli–Leydig, endometrioid types of ovarian tumors), adenocarcinoma of the cervix meningioma, glioma, and hormone receptor-positive gastric and bladder cancer
225. Low-dose, local vaginal ET may be an option for the treatment of vaginal dryness related to hormone deficiency after certain types of cancers, even if systemic MHT is not recommended.

Precautions

226. Progesterone in adequate dose and duration should be supplemented along with oral estrogens in women with uterus (Grade A)
227. Estrogen alone is given in hysterectomized women (Grade A)
228. Progesterone supplement for endometrial protection is not needed along with the use of vaginal estrogen (Grade C)
229. Investigations are needed, if bleeding starts at the start of progesterone therapy in cyclical regimens, or there is a change in the duration or intensity of blood flow which is not normal for that woman. Investigations are needed, if bleeding is heavy or continuous and continues after 6–12 months of use with continuous combined regimens, and in women with a high risk for uterine cancer
230. Pre-MHT workup and annual follow-up are essential when prescribing MHT. A full gynecological

assessment is mandatory before starting MHT and at regular intervals thereafter. SBE is advised monthly. Mammogram or the breast US, where available, should be carried out 1–3 yearly if the initial mammogram is normal (Grade C)

231. The dose and duration of use of MHT should be individualized, and a risk–benefit assessment is carried out annually. Follow-up after 1 month, 3 months, 6 months and then annually (Grade C)

232. **Regimens**

- Continuous-cyclic regimen, estrogen is used every day, with progesterone added cyclically for 10–14 days during each month. Progestogen is started on day 1 or day 15 each month. This regimen is suitable for women at perimenopause
- Uterine bleeding occurs in about 80% of women when progestogen is withdrawn, although bleeding can begin 1–2 days earlier, depending on the type and dose of progestogen used
- In the continuous-combined EPT regimen, fixed doses of estrogen and progesterone are administered every day. It is the treatment of choice at postmenopause
- Approximately 40% incidence of irregular spotting or bleeding in the first 6 months
- Estrogen alone is prescribed in hysterectomized woman. Progesterone is added along with estrogens in hysterectomized woman in cases of endometriosis, endometrial ablation, and supracervical hysterectomy.

233. **Routes**

- Estrogen: Oral, transdermal, and vaginal
- Progestogen: Oral, vaginal, and intrauterine levonorgestrel system.

234. **Duration of use**

235. POI: HT can be prescribed up to the natural age of menopause; further continuation of therapy is a shared decision between the woman and the physician according to the indication and the need (Grade C)

236. Natural menopause: Safety data on EPT with

CEE + MPA use are 3–5 years, and with ET, safety data are 7 years of treatment with 20 years follow-up. Role of extended use of HT is a shared decision between the woman and the physician and may be considered in cases of recurrence of symptoms after stopping therapy, in case of management of osteoporosis when other therapies are contraindicated (Grade A)

237. Stopping MHT may be abrupt or the dose and duration may be tapered off gradually (Grade C).

Potency and nonoral routes

238. Minimum effective dose is the principle to be followed while prescribing MHT. The potency needed by the woman may change over time. After starting standard-dose therapy, dose can be lowered and maintained accordingly. Low-dose and ultralow-dose therapies are effective in relieving symptoms and maintaining bone mass

239. Transdermal estrogen has a neutral effect on triglycerides, CRP, and sex hormone-binding globulin and is preferable for use in women with hypertriglyceridemia, obesity, glucose intolerance, high risk of deep vein thrombosis, and tobacco users.

CONCLUSIONS ON THE RISKS AND BENEFITS OF SYSTEMIC AND LOCAL HORMONE THERAPY-BASED ON AVAILABLE EVIDENCE

240. MHT may be given to women below the age of 60 years or within 10 years of menopause, and the risks are rare.

Risks of systemic therapy

241. The risks of MHT may be explained to the woman in terms defined by CIOMS. Refer Table 12.

Coronary heart disease

242. Systemic therapy is not to be used for primary or secondary prevention of CHD. At any age, avoid MHT in women at high risk of CVD or in established CVD

Table 12: Based on the Women's Health Initiative, number of excess events on hormone therapy versus placebo per 10,000 women per year of hormone therapy

Disease	Estrogen	WHO/CIOMS definition of risk	Estrogen + progesterone	WHO/CIOMS definition of risk
Venous thromboembolism	4	Rare	11	Rare
Stroke	1	Rare	4	Rare
Breast cancer			5	Rare
Cardiovascular disease			5	Rare

Use between the age group of 50–59 years. CIOMS: Council for International Organisations of Medical Sciences, WHO: World Health Organization

243. ET may be cardioprotective, if started around the time of menopause “window of opportunity” in a healthy woman. It reduces the risk of diabetes and has positive effects on the lipid profile and metabolic syndrome
244. Less than 60 years old, recently menopausal and without evidence of CVD, at mild-to-moderate risk of CVD, the initiation of MHT does not cause early harm and may reduce morbidity and mortality from CHD. At moderate-risk women, if indicated, transdermal MHT is preferable
245. MHT beyond the age of 60 years should be decided as a part of the overall risk–benefit analysis.
254. Losing weight and keeping it off were associated with lower breast cancer risk for women aged 50 years and over in The Nurses’ Health Study (1980–2014; $n = 73,196$) and The Health Professionals Follow-Up Study (1986–2014; $n = 38,366$)
255. The effect of MHT on breast cancer risk may depend on the type of MHT, dose, duration of use, regimen, route of administration, prior exposure, and individual characteristics
256. Avoid MHT in women with severe risk for breast cancer and in breast cancer survivors.

Venous thromboembolism

246. The risk of VTE is increased by smoking, increasing age, obesity, and oral MHT. VTE risk is as high as 29/10,000 woman-years during pregnancy and 300–400/10,000 woman-years in the postpartum period
247. HT increases VTE risk by twofold (Grade A). Transdermal ET and the natural progesterones may not have an effect. Population screening for thrombophilia is not indicated before MHT use.

Stroke

248. Unlike CHD, the timing hypothesis does not appear to apply to the risk of stroke, most likely because the risk of stroke is probably due to thrombotic rather than atherosclerotic mechanisms. Hence, literature is suggestive of an increased risk of stroke with oral MHT, there is a dose-dependent relationship, and the event rate is extremely low, especially in younger women
249. Standard-dose oral MHT increased stroke risk by about one-third in generally healthy postmenopausal women (Grade B)
250. The risk increases with estrogen dose, age, and BMI and is greater during the first years of therapy. The absolute risk is 1.5 more cases/10,000 women per year at the age of 50–54 years, 2.2 at the age of 59 years, 2.8 at the age of 60–64 years
251. Low-dose ET, transdermal route may not increase the risk of stroke (Grade C).

MHT and breast cancer

252. MHT may not initiate breast cancer and may have promotional effect on hormone receptor breast cancer in susceptible women. Tumors in MHT used women are usually ER-positive and lobular type (Level C)
253. The increased risk for breast cancer attributable to MHT is less than 1 per 1000 women per year of use in the age group of 50–59 years. This increased risk is similar or lower than those associated with common lifestyle factors, such as reduced physical activity, obesity, and alcohol consumption

Estrogen alone

257. In the WHI trial, prior randomized use of CEE alone compared with placebo, among women who had a previous hysterectomy, was significantly associated with lower breast cancer incidence and lower breast cancer mortality^[151]
258. For women who are BRCA positive and have undergone risk reducing BSOP, observational data suggest that the use of systemic HT to the median age of menopause aimed to decrease health risks associated with premature loss of estrogen does not increase breast cancer risk. Decisions are on an individual basis.

Estrogen plus progesterone

259. In the WHI trial, prior randomized use of CEE plus MPA, compared with placebo, among women who had an intact uterus, was significantly associated with a higher breast cancer incidence but no significant difference in breast cancer mortality^[151]
260. Emerging data from two independent studies report that progesterone (micronized progesterone/dydrogesterone) with estrogen may not increase the risk if given for less than 5 years (Level C)
261. The risk returns to approximately that of nonusers within 3 years of cessation (Level B).

Gallbladder

262. Risk of gallstones, cholecystitis, and cholecystectomy is increased with oral estrogen-alone and combination MHT
263. Observational studies report lower risk with transdermal MHT than with oral and with oral estradiol compared with CEE, but neither observation is confirmed in RCTs.

Benefits of systemic therapy

The absolute benefits of MHT are given in Table 13.

Other possible benefits

- MHT significantly reduces the diagnosis of new-onset T2DM

Table 13: Based on WHI: number of less events on ET and EPT versus placebo per 10,000 women per year of HT use between the age group of 50 years and 59 years

Disease	Number of less events with ET
Heart Disease	12
Breast Cancer	8
Disease	Number of less events with E / EPT
Overall Mortality	10
Fractures	5
Colorectal cancer	6

- MHT may help reduce the abdominal adipose tissue and the weight gains that are often associated with the menopause transition and thus help in reducing the emergence of new onset of metabolic syndrome
- Estrogens may have a protective effect on osteoarthritis (Grade B)
- Estrogen benefits verbal memory over the short period when initiated soon after surgical menopause (Grade B)
- MHT reduces the neovascular macular lesions (Grade C)
- MHT use has shown to reduce colorectal cancers
- MHT in the early menopausal period improves QOL by its effects on VSMs and urogenital symptoms and improvement on sleep and mood.

Benefits and risks of local therapy

- Local therapy is indicated when the woman suffers only from urogenital atrophy
- Vaginal ET is most effective in the treatment of urogenital atrophy. Low-dose vaginal preparations are as effective as systemic therapy. Some women on oral ET may require additional local therapy
- Low-dose vaginal estrogen formulations reported no incidence of increase in CHD, stroke, and VTE. There are no contraindications for use in nonhormone-dependent cancers.

Androgens

264. Available data are of low quality and conflicting regarding the risk of breast cancer relating to use of androgens (Grade D)
265. Androgen replacement for use in women is not available in India.

Raloxifene

266. It decreases the risk of development of breast cancer. The indication for use is postmenopausal osteoporosis especially in women at high risk for breast cancer given in a dose of 60mg/day
267. Tissue selective estrogen complex: Newer formulations of combination therapy of estrogen and selective ER modulators are soon to be available.

Tibolone

268. Tibolone is a selective tissue estrogenic activity regulator. It is a synthetic steroid compound, which has estrogenic, progestogenic, and androgenic properties. It has an estrogenic effect on bone, inhibiting bone resorption by reducing osteoclastic activity
269. Tibolone is effective in treating VMS and improves urogenital atrophy (Grade A)
270. It improves mood and libido (Grade B)
271. It is prescribed in a single daily dose of 2.5 mg orally. A lower dose of 1.25 mg has been found to be equally effective for most indications, including osteoporosis. It should be prescribed 1 year after amenorrhea (Grade A).

Use of oral contraceptives during the menopausal transition

272. A low-dose estrogen OC is an option, unless contraindicated for perimenopausal (40–50 years) women who seek relief of menopausal symptoms, also desire contraception, and may need control of bleeding when it is heavy. A continuous 3-monthly regimen may be beneficial to control VMS.

SECTION VI

ECONOMICS OF MENOPAUSE MANAGEMENT

273. Indian healthcare system is one of the most privatized systems where government spends much less and individual has to pay for health insurance^[152]
274. Insurance may be described as a social device to reduce or eliminate the risk of life and property. Under the plan of insurance, many people associate themselves by sharing risk, attached to individual insurance plan that covers only healthcare costs and is called health insurance
275. It is indeed very important to enroll in any of the good health insurance schemes for a secure future. Healthcare insurance provides a cushion against medical emergencies. Most companies stop enrolment after 65–70 years of age. Menopause management has significant direct and indirect costs
276. Direct costs include physician's visits, specialist's visit, and traditional pharmacotherapy or alternative and complementary medicine modality
277. Indirect costs include laboratory testing, management of adverse events, loss of productivity at home and at work, and treatment of associated medical disorders
278. Various groups of molecules are available for prevention and treatment of osteopenia and

osteoporosis. Cost of therapy varies according to the indication whether they are prescribed for prevention or treatment of osteopenia or osteoporosis

279. Menopause is a critical window of opportunity for preventing and reducing risk for CVD and maintaining skeletomuscular and urogenital health. The importance of lifestyle counseling for smoking cessation, diet modification, and physical activity in the menopausal women has to be emphasized. Adopting a healthy lifestyle is cost effective.
280. Establishing menopause clinics at primary and specialized centers would help in implementing the concept of critical window of opportunity at menopause.^[153]

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