FRAILTY AND SARCOPENIA

Keywords: Sarcopenia, frailty, sarc-f, sarc-c, resistance training, falls

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INTRODUCTION

Sarcopenia is a progressive loss of skeletal muscle mass, strength and function, which exacerbates with age.[1] Progressive muscle mass affects physical function, mobility, increases the chances of falls and fractures, causes frailty, and at times mortality. It significantly affects the quality of life (QOL) of the geriatric population. It is projected that India will have 20% of the world's elderly population by 2050, higher than that reported in 2011 (8.6%). Sarcopenia and its associated morbidity are of concern and are a big challenge for the health systems of a country to provide care to the elderly.[2,3] Sarcopenia has also been linked to various medical conditions like congestive heart failure, chronic respiratory diseases, chronic liver diseases, diabetes, chronic kidney disease, and malignancy. In addition to lifestyle changes, proper diet and physical activity are important in managing sarcopenia across various conditions.[4]

Myopenia signifies muscle wasting needing medical intervention. This may not be age-related, and muscle wasting, which might be related to any disease at any age. Frailty is a clinically recognised state with a propensity to falls, sarcopenia being one component of it. Frailty is defined as a clinically recognisable state of increased vulnerability resulting from ageing-associated decline in reserve and function across multiple physiological systems, such that the ability to cope with everyday or acute stressors is compromised.

SARCOPENIA

Sarcopenia is defined as muscle mass two standard deviations below the mean appendicular muscle mass of young healthy adults of a reference population (of the same sex and race) and is accompanied by a gait speed under 0.8 m/s in the 4-m walking test.[5] With ageing, there is a progressive loss of function of different organs in the body. There is also loss of muscle mass and strength, which affects muscle function. This loss of muscle mass, strength and function is called sarcopenia.

CATEGORIES OF SARCOPENIA

Primary and secondary sarcopenia: Sarcopenia can be primary, associated with ageing, or secondary, caused by disuse, malnutrition, chronic diseases, immobility, inflammation, insulin resistance, and hospitalisation.

Acute and chronic sarcopenia: Sarcopenia lasting for less than 6 months is considered an acute condition related to an acute illness, and more than 6 months is a chronic progressive condition with increased chances of mortality.

Sarcopenic obesity: Sarcopenia associated with obesity is called sarcopenic obesity. There is infiltration of fat in the muscles. Metabolic changes, including increased free fatty acids, elevated inflammatory factors, and oxidative stress, are observed. A decrease in insulin-like growth factor-1 (IGF-1) levels occurs. Physical activity and movement are decreased.6 Nearly one-fourth of patients with sarcopenia have accompanying obesity.[7]

Normal weight obesity: Excessive body fat with a normal BMI is a characteristic of normal weight obesity (NOW). An observational study showed that being in the NWO category meant a 22-fold higher risk of sarcopenia in males and a 25-fold higher risk in females.[8]

EPIDEMIOLOGY

A global study reported the prevalence of sarcopenia to be 17.5% in Indian elderly (≥ 65 years).[9] A systematic review and meta-analysis showed that sarcopenia prevalence varies with the patient population studied, such as in a community setup or in a hospital. It reported a prevalence of 11% and 9% in community-dwelling men and women, in nursing homes was 51% and 31%, and in hospitalised men and women was 23% and 24%, respectively.[10] A meta-analysis revealed a 48% prevalence of ICU-acquired sarcopenia. Critically ill patients diagnosed with sarcopenia face a 2.28-fold higher risk of mortality than patients without sarcopenia.[11] A cross-sectional study from India reported a sarcopenia prevalence to be 28% in individuals aged 35-70 years.[12]

After age 50, muscle mass decreases at an annual rate of 1–2%.[13-15] The decline in muscle strength is even higher, amounting to 1.5% per year between the ages of 50 years and 60 years and 3% per year thereafter. Thigh muscle

strength decreases 10%–15% per decade after 40 years of age and 25%–40% per decade after age 70.[16] Overall, the decline in muscle mass starts at the age of 20 years and an average loss is 0.4–0.8 kg per decade, but this does not occur at the same rate and age in both sexes.[14] It is estimated that nearly 5–13% of elderly people between 60 and 70 years are affected by sarcopenia, and the numbers increase to 11–50% by 80 years.[15,16] Gradual loss of muscle mass in women tends to occur after the 3rd decade and shows an accelerated decline after the 5th decade, possibly making them weaker at 65–69 years than men at 85–89 years. A cross-sectional study by Rolland et al showed a decline of 0.6% per year in muscle mass after menopause. Accordingly, total body potassium, a marker of lean body mass, has been shown to decrease significantly during the first 3 years of menopause.[17]

MORBIDITY AND MORTALITY

Sarcopenia represents a major cause of disability and increased health costs in older persons. It is correlated with functional decline and disability. It has also been associated with increased mortality.[18] Out of different variables, weakness has been demonstrated to be a more powerful predictor of mortality in elderly people than muscle mass.[19] The Cardiovascular Health Study reported that the likelihood of disability was 79% greater for those with "severe" sarcopenia.[20] During the 8-year follow-up, only those with severe sarcopenia were more likely to develop physical disability. Sarcopenia has also been found to predict nosocomial infections during hospitalisation.[21] The risk of falls and consequently of fractures is closely related to reduced muscle mass.

A 2.3-fold increase in the risk of falls is reported among patients in the lower third of handgrip strength compared with those in the upper third. Likewise, another large-scale study in more than 2,100 elderly subjects found that a low walking speed is an independent risk factor for falls related to sarcopenia.[14] Low grip strength in sarcopenic individuals with less than 36 kg for men and less than 23 kg for women as a cutoff point is better than the Frailty phenotype for identifying risk of mortality in older subjects.[22] Sarcopenia is associated with an increased risk of all-cause mortality in patients with cancer and those who are critically ill.

CAUSES OF SARCOPENIA

The pathophysiology of sarcopenia is multifactorial and complex. It is a syndrome-like condition seen with ageing. Important factors associated with it include ageing, inflammation, nutritional deficiencies, sedentary lifestyle, physical inactivity, and mitochondrial dysfunction at the cellular level. [23]

Primary Sarcopenia

There is decreased synthesis and turnover of muscle protein. Neuromuscular degeneration is more common in sedentary individuals. Nutritional factors, such as decreased energy and protein intake, anorexia, and malabsorption, are important causes. There are changes in hormones, including decreased growth hormone, sex steroids, insulin-like growth factor-1 (IGF-1), and myostatin, and increased insulin resistance. Chronic inflammation, as evidenced by elevated inflammatory markers such as interleukin-6 (IL-6) and C-reactive protein, is seen. Chronic inflammation and oxidative stress is more prevalent. Genetic susceptibility is also a factor.

Secondary Sarcopenia

This can occur across any age group. Patients with chronic diseases like renal diseases, malignancies, chronic obstructive pulmonary disease, diabetes mellitus, inflammations, prolonged immobilisation after surgeries, gastrointestinal diseases, chronic nutritional diseases, osteoporosis, osteoarthritis and vitamin D deficiency may suffer from sarcopenia.[17] With age, these morbidities increase. Decline in skeletal muscle mass and function is an additional co-morbid outcome. Depending on the clinical presentation and history, associated investigations may be performed, and treatment initiated. It has recently been suggested that skeletal muscle wasting directly attributable to chronic disease should be termed "myopenia", with sarcopenia referring only to muscle declines associated with ageing.[13,24]

Pharmacotherapy causing sarcopenia

Elderly people, over time, take many prescription medicines. Usage may reach 80% in community-dwelling older adults. An increase in medication use over 10 years is associated with a greater decline in knee strength in older men. Statins, furosemide, nitrates, calcium channel blockers, benzodiazepines and fibrates used for a long duration have been suggested in some studies to affect muscle strength. Further, emerging evidence suggests that gut microbiota dysbiosis contributes to sarcopenia genesis.[25]

MECHANISM OF SARCOPENIA IN MENOPAUSE

There is a higher prevalence of sarcopenia in postmenopause (7.43%) as compared to premenopause (5.50%).[26] A fall in estrogen and testosterone levels at menopause adds to muscle loss and functional impairment. These are anabolic hormones, especially testosterone. Estrogen modulates protein synthesis and mitochondrial function at the cellular level, and declining levels lead to muscle deterioration and frailty, with a high risk of falls and fractures.[27,28]

Muscle tissue expresses estrogen receptors, and estradiol (E2) stimulates muscle regeneration and satellite cell proliferation. E2 levels correlate with muscle strength and mass.[27,29] A fall in estrogens at menopause causes an increase in visceral adiposity, a decrease in bone density and a decrease in muscle mass and strength. This also leads to increased inflammatory markers and oxidative stress, further reducing muscle strength.[25-31] Fall in other hormones, such as growth hormone, dehydroepiandrosterone (DHEA), insulin, and IGF-1, post-menopause affects muscle mass and function. Estrogen and testosterone suppress inflammatory cytokines, such as TNF-α and IL-6, which exert catabolic effects on muscle. Thus, hormone replacement has always received considerable interest as a therapy for sarcopenia.[24-33]

Premature ovarian insufficiency or early menopause (< 45 years), whether surgical or spontaneous, is associated with reduced grip strength later in life, increased osteosarcopenia, functional limitation and greater multimorbidity.[29] Postmenopausal sedentary lifestyle and lack of exercise, lack of protein intake, immensely contribute to sarcopenia and loss of strength in postmenopausal women.

Sarcopenia and osteoporosis have been thought to coexist. There is evidence of a mechanistic interrelationship between muscle and bone, with sarcopenic individuals at greater risk of osteoporosis and vice versa.[34] Several studies have shown a positive association between lean mass and bone mineral density (BMD) in postmenopausal women. Female hormones essentially regulate both muscle and bone health during the post-menopause and thus play a significant role in the development of sarcopenia and osteoporosis. These may be, to some extent, prevented by hormone therapy (HT).

Vitamin D deficiency may be prevalent in older adults, particularly among those living at higher latitudes, and may play an important role in the aetiology of sarcopenia. An apparent decrease in vitamin D receptors in muscle during ageing may explain some of the age- and menopause-related decline in protein synthesis. Prolonged periods of low vitamin D levels may also favour alterations in motor function and increased bone mass loss and fracture risk. Lean mass decreases by 3 kg per decade, starting in the fourth decade. This relates to a decrease in functional capacity (muscle strength and neurological coordination), which could, in fact, favour frailty and falls and limit locomotion. [35] Refer to figure 1.

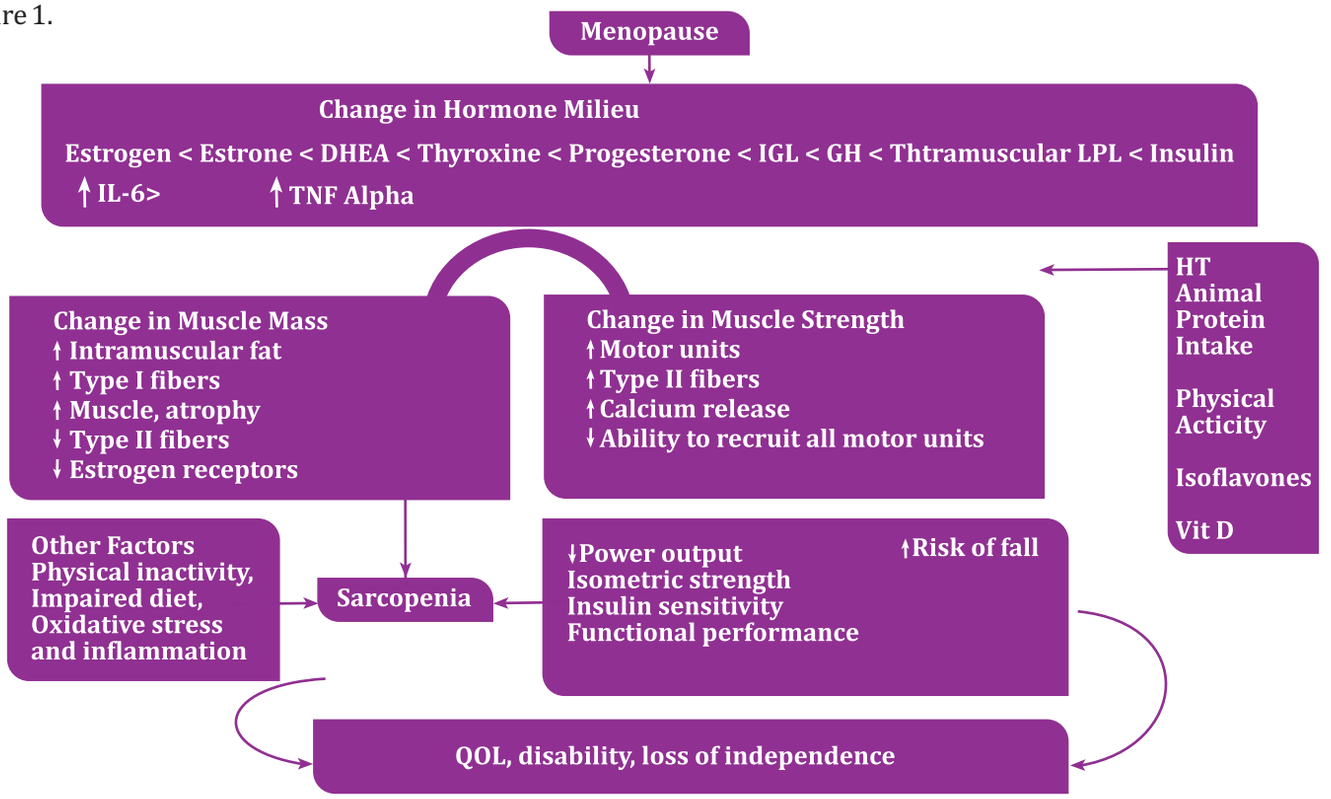


Figure 1 Menopause-related changes on muscle mass and its impacts on different characteristics that contribute to quality of life (DHEA: Dehydroepiandrosterone; GH: Growth hormone; HT: Hormone therapy; IGL: Intergeniculate le let; LPL: Lipoprotein lipase; QOL: Quality of life; TNF: Tumor necrosis factor).

SCREENING AND DIAGNOSIS OF SARCOPENIA

The diagnosis of sarcopenia involves assessing muscle mass, strength, and function. Detailed history, evaluation, and investigations to rule out concomitant chronic, non-communicable diseases such as obesity, diabetes, thyroid disorders, and osteoporosis, as well as corticosteroid intake and prolonged immobilisation, should be performed, along with assessment of nutritional deficiencies. The method for diagnosing sarcopenia is based on body composition assessment and measurement of muscle mass.

The techniques used for clinical diagnosis and research purposes can be grouped into three domains: muscle mass, muscle strength, and physical performance. For muscle mass estimation, magnetic resonance imaging (MRI) is the gold standard, accurately quantifying muscle mass and even intramuscular fat infiltration. Dual-energy X-ray absorptiometry (DXA)is commonly used to diagnose osteoporosis and can differentiate between lean body mass and fat mass. However, DXA cannot differentiate between water retention and fatty infiltration.

Clinical anthropometry, including calf circumference measurement, though simple, is confounded by many factors, such as obesity and frailty.

Biochemical markers, such as total or partial body potassium per fat-free soft tissue, are a classical method for estimating skeletal muscle; however, they are less frequently used. 24-hour creatinine excretion is also an established method that correlates with total body creatinine, which is mostly in muscle. The disadvantage of the biochemical markers is that these methods are time-consuming and require monitoring of the diet.

Measurement of handgrip strength is a validated, simple measure of muscle strength. Hand-held dynamometry is easy to perform and cost-effective. The instrument is portable, making it practical for use in a clinical setting. Several tests are available for assessing physical performance, such as the short physical performance battery (SPPB), the gait speed test, the timed get-up-and-go test, and the stair climb power test. Usual gait speed is a component of SPPB but is also used singly as a separate parameter for assessment. The timed get-up-and-go test is often used as a geriatric assessment, but it is more pertinent to dynamic balance assessment.

RECOMMENDATIONS FROM DIFFERENT SOCIETIES

Three components have been used by various organisations to define sarcopenia. These are muscle mass, muscle strength and muscle function.Populations differ, belonging to different ethnicities and regions and exhibiting distinct phenotypes. Therefore, the criteria and cut-offs differ across recommendations.

The European Working Group on Sarcopenia in Older People (EWGSOP) gave a diagnosis based on documentation of low muscle mass with either low muscle strength or low physical performance. The group also classified it into 'presarcopenia', 'sarcopenia' and 'severe sarcopenia'. If there is only low muscle mass, we define it as presarcopenia. If low muscle mass was associated with low strength or function, it was diagnosed as sarcopenia. If all three were present, it was labelled as severe sarcopenia. This was mainly for the community population.

In its 2018 definition, EWGSOP2 mod ied EWGSOP, emphasising muscle strength as the primary parameter of sarcopenia, and diagnosis was confirmed by either low muscle mass or decreased muscle function. If all three were present, then sarcopenia was considered severe sarcopenia. Specifically, sarcopenia was labelled as probable when low muscle strength is detected. When low muscle strength, low muscle quantity/quality and low physical performance are all detected, sarcopenia is considered severe.[36]

The Asian Working Group for Sarcopenia (AWGS) 2019 gave a diagnostic algorithm tailored for the Asian population. This was in line with EWGSOP2. It introduced quick screening methods, such as calf circumference (CC), and questionnaires, such as the SARC-F and SARC-CalF, for case finding. They removed the term pre-sarcopenia because of insufficient evidence of prognostic value. The term 'possible sarcopenia' was introduced to describe low muscle strength, with or without low muscle performance, for use in community settings without access to muscle mass measurement.[37]

South Asian Working Action Group on Sarcopenia (SWAG-SARCO)[7] gave guidelines for screening, diagnosing and managing sarcopenia in the South Asian population. The group defines sarcopenia as a condition in which any two of

the following parameters are suboptimal, as assessed by clinical, biochemical and/or imaging modalities: muscle function, muscle strength and muscle mass. An algorithm-based, easy, practical, and cost-effective approach for screening and diagnosing sarcopenia was presented. It consisted of the 5 'S' pathway: Suspect, Screening, Secondary sarcopenia (including concomitant therapy), Severity (muscle strength, function, and/or mass), and Shared decision-making.

It included secondary sarcopenia (including concomitant medications) and sarcopenic obesity, biomarkers for diagnosis, and introduced the concept of osteo-arthro-muscular triad, as muscle cannot function in isolation. The recommendation has a wider scope applicable to community-dwelling, clinical and hospital practice.

The common measures for muscle mass in the European Working Group on Sarcopenia in Older People (EWGSOP) 2018 and the Asian Working Group for Sarcopenia (AWGS) 2019 included appendicular lean mass index and height squared (ALM/Ht2), with men < 7.0 kg/m2 and women < 5.4 to 5.5 kg/m2 by DXA. The EWGSOP 2018 sets handgrip strength (HGS) thresholds at < 27 kg for men and < 16 kg for women, whereas AWGS 2019 sets thresholds at < 28 kg for men and < 18 kg for women. There are regional and ethnic differences between the West and Asia arising from unique anthropometric features and cultural and lifestyle distinctions. [38]

The Global Leadership Initiative in Sarcopenia (GLIS) recently suggested that muscle mass, muscle strength, and muscle-specific strength should be considered core components of sarcopenia, while impaired physical performance should be viewed as an outcome rather than a component of the syndrome.[39]

SCREENING QUESTIONNAIRES

Sarcopenia can also be defined by simple functional questions. The SARC-F questionnaire helps screen five sarcopenia-related components: strength, assistance with walking, rising from a chair, climbing stairs, and falls. On a 0–10 scale, a score ≥ 4 is predictive of sarcopenia.

EWGSOP2 and AWGS 2019 Consensus Update on Sarcopenia Diagnosis and Treatment recommends the use of SARC-F to screen for sarcopenia.[40]

The AWGS 2019 also recommends using the SARC-CalF questionnaire for screening, which combines calf circumference with the SARC-F. A score of ≥ 11 is predictive of sarcopenia.[41]

SARC-CalF is found to be more sensitive and accurate than SARC-F in screening and diagnosing sarcopenia in community-dwelling elders and in clinical practice as well. In patients with clinical suspicion of sarcopenia, the experts recommend that SARC-F (score ≥ 4) or SARC-CalF (score ≥ 11) can be used to screen for sarcopenia.[42]

CLINICAL TOOLS TO ASSESS MUSCLE STRENGTH, FUNCTION AND MASS[43]

Muscle Mass Can Be Measured By:

Anthropometry

Calf circumference (CC), mid-arm circumference (MAC), and thigh circumference.MAC is measured with the patient flexing the biceps while the arm is raised to shoulder level and the elbow bent to 90 °. CC is measured with the patient standing with feet shoulder-width apart.[44] Measurement of the CC, though simple, is confounded by many factors, such as obesity and frailty. Subcutaneous fat can be subtracted by deducting triceps skin fold thickness from MAC to get the mid-upper arm muscle mass.[45] Clinically feasible measurements, such as mid-arm circumference (MAC) or mid-upper arm circumference (MUAC), and CC can be used instead, as they also correlate very well with SMM.

Imaging

DXA or Bioelectrical impedance analysis (BIA), with height-adjusted appendicular skeletal muscle mass (SMM) as the index. CT and MRI detect lean muscle mass quite accurately, but their cost and availability limit their use for this purpose. CT and MRI also help accurately differentiate lean body tissue from fat. Ultrasound can also be used to measure skeletal mass, but it is not particularly sensitive. However, recent studies from Japan and Turkey found that gastrocnemius thickness was more likely to predict low hand grip strength (HGS) than skeletal muscle index (SMI) or appendicular skeletal muscle index (ASMI) measured by BIA. So it may be used in low-resource settings.[46,47] The reference group was defined as young adults with muscle mass ≤2 standard deviations below the mean or < 20% of the mean.

DXA is reliable for assessing skeletal mass; it is expensive and not freely available. Despite the high cost, DXA is a useful tool for assessing multiple parameters, including fat mass, lean soft tissue mass, and bone mineral content. The assessment can be localised or involve the whole body, and helps to differentiate between sarcopenia, obesity, sarcopenic obesity, and osteoporosis. Appendicular lean mass (ALM) adjusted for BMI or height can help differentiate between physiological (primary) and pathological (secondary) sarcopenia.[48,49]

BIA helps assess and normalise total skeletal muscle mass (SMM or ASMI) with respect to height.[50] BIA is as effective as axial CT, CC, or grip strength for screening sarcopenia, especially in patients with malignancy. Although BIA is less expensive than DXA, its reliability is compromised at a BMI of ≥ 35 kg/m, and hence may not be very useful in sarcopenic obesity. Nevertheless, given its portability relative to DXA, BIA can be used for community-wide mass screening. [51]

Muscle strength

Measured by hand grip strength (HGS) and lower extremity muscle strength (LEMS) .Loss of muscle strength is also known as dynapenia. HGS is the easiest way to clinically assess upper-limb muscle strength using a handheld dynamometer (HHD).[23] Hand-held dynamometry is easy to perform and cost-effective. The instrument is portable, making it practical for use in a clinical setting. LEMS can be measured using isokinetic dynamometers or HHDs. Isokinetic dynamometers are bulky and costly.[52] Three readings are usually taken on each limb after giving some in-between resting interval; then the highest reading is recorded as HGS or LEMS. However, some clinicians prefer to use the mean of the 3 readings.[53]In settings where a dynamometer is unavailable, HGS is measured by asking the patient to lift a 1 kg weight with the elbow fully extended for at least 30 s. HGS is considered normal if the patient is able to hold the weight for at least 30 seconds in that position. [54]

Muscle function

Muscle function can be assessed by a 4-metre gait speed test, sit-to-stand (STS) test, timed STS (5TSTS), 30-second chair stand test (30CST), Short Physical Performance Battery (SPPB) and the timed up-and-go test (TUGT).

A 4-m gait speed test is a reliable way to assess muscle function and performance. Time taken by the patient to walk for a distance of 4 m (on a flat surface) is noted as the gait speed. A normal person usually takes less than 5 s to cover the distance; thereby, a gait speed of more than 0.8 m/s is considered normal. Gait speed is considered low if the patient takes longer than 5 s to walk this distance. This method also tests the patient's balance.[44]

Muscle function can also be assessed using sit-to-stand (STS) tests, which are mainly of two types: 5 times STS (5TSTS) and 30 s chair stand test (30CST).[55] Function can be measured using a chair-rise test of 5 ups in 15 seconds from a chair without hand supports.

Muscle function can also be assessed using a more comprehensive test, such as the Short Physical Performance Battery (SPPB). SPPB tests the patient's ability to stand with feet together in 3 positions: side-by-side, semi-tandem, and tandem. It also assesses the time taken to walk 8 feet and the average time taken to rise from a chair and return to a seated position (over 5 efforts).[23] The timed up-and-go test (TUGT) is another way to evaluate muscle function and performance. The patient gets up from the chair, walks for 3 metres, turns back, walks again, and sits down. A normal individual usually completes the TUGT in less than 10.2 s. [56]

BIOCHEMICAL MARKERS

Routine assessment, to be done, includes haemoglobin, total protein, lipid profile, vitamin D levels, and serum magnesium and calcium for sarcopenia. Serum testosterone and estrogen may be measured. Serum creatinine signifies muscle turnover, creatinine phosphokinase (CPK) reveals muscle damage, and C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) denote muscle inflammation. Special tests may be done as indicated to rule out causes of secondary sarcopenia.[57,58]

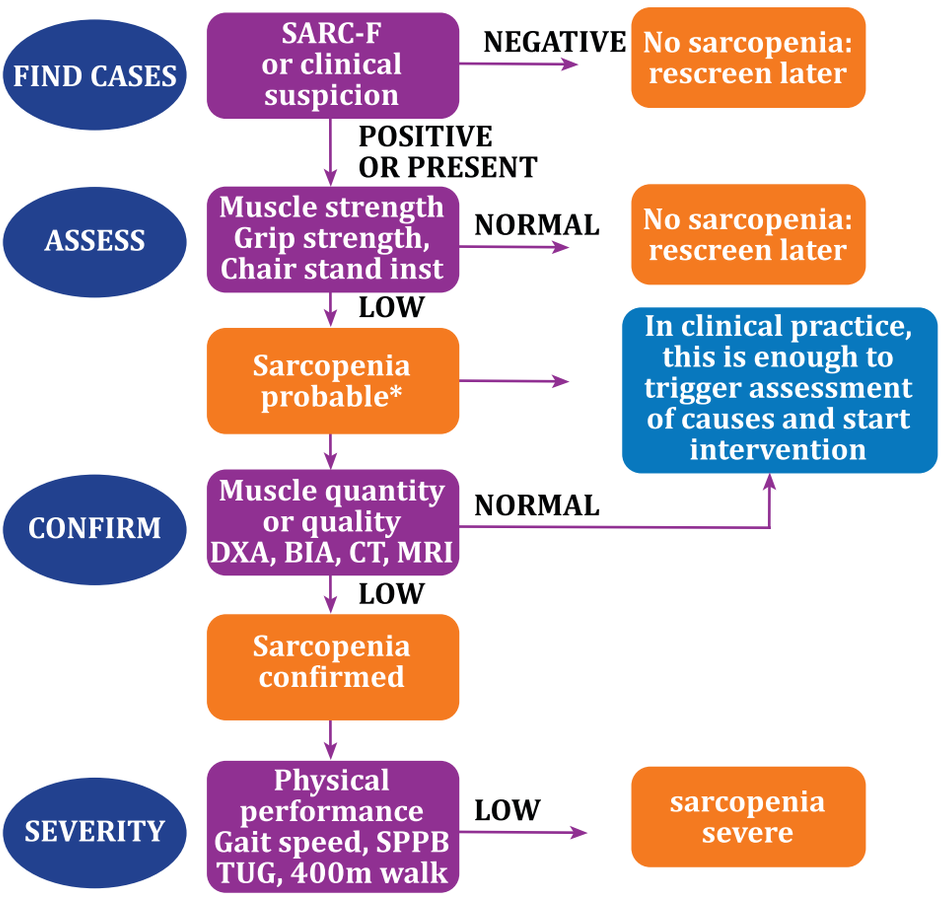
SCREENING AND DIAGNOSIS CUT-OFFS

Screening is done with clinical suspicion, calf circumference (CC), SARC-F, SARC-CalF questionnaires, or hand grip strength.Refer to flowchart 1 to screen and diagnose sarcopaenia.

The various cut-offs for the Asian population are mentioned in Table 1.

Table 1: Sarcopenia diagnostic cut-offs for the Asian population

Parameter	Men	Women	Notes
Hand grip strength (HGS)	< 27.5 kg	< 16 kg	—
Gait speed	≤ 0.8 m/s	≤ 0.8 m/s	Validated in other guidelines
Timed Up and Go Test (TUGT)	< 10.2 s	< 10.2 s	—
Calf circumference (CC)	< 34 cm	< 33 cm	Validated for South East Asians
Sarc-CalF score	≥ 11	≥ 11	Validated in South East Asians
Appendicular Skeletal Muscle Index (ASMI)	< 7.0 kg/m2	< 5.7 kg/m2	Lee's equation; Validated in SE Asians; Indians < 5.0[26]
CC (Indian studies)	—	≤ 32 cm	Threshold for identifying risk[59]



Flow chart 1: Screen and diagnose Sarcopenia: FMGSOP2 algorithm for case finding, making a diagnosis and quantifying severity in practice. The steps of the pathway are represented as Find-Access-Confirm-Severity (F-A-C-S). "Consider other reasons for low muscle strength, such as estrogen, tsstosterone, anabolic depression, stroke, balance disorders, and peripheral vascular disorders.

POTENTIAL INTERVENTIONS FOR SARCOPENIA
EXERCISE AND PHYSICAL ACTIVITY

Evidence has shown that older adults who are less physically active are more likely to have lower skeletal muscle mass and strength and are at increased risk of developing sarcopenia.[60] Women of all ages should be encouraged to exercise. Even if they suffer from chronic illness, exercise may improve symptoms or even arrest the condition. There are three types of exercise that women should be encouraged to participate in. They are endurance, resistance, and balance training.

Endurance training: improves cardiovascular status. This status depends upon cardiac output and the ability of muscles to extract oxygen. Cardiovascular endurance decreases with age at approximately 1 cubic millimetre of oxygen per kilogram of body weight per year. Maximum heart rate decreases with age at about 1 beat per year.

Muscle mass also decreases with age, even in very active individuals, but the decline is more pronounced in sedentary people. Endurance training is defined as rhythmic contraction of large muscle groups at a specific heart rate for a specific period of time, and may be either weight-bearing or non-weight-bearing. The weight-bearing type has an additional beneficial effect on bone mass but may worsen problems involving the hip, knee, or ankle. Thus, the type of endurance exercise should depend on the patient's general health and condition, as well as what she is capable of doing.

It has been shown that endurance training can improve cardiovascular conditioning by 10–30%, depending on how hard the individual exercises and the number of muscle groups involved. The American College of Sports Medicine recommends that individuals engage in 30 minutes of cumulative exercise per day, at least 3 days per week.

Weight-bearing and aerobic exercises include walking, jogging, cycling, stair climbing, cross-country skiing, aerobic dance, and treadmill walking. Non-weight-bearing exercises include swimming, rowing, and upper-body exercises.Many patients with sarcopenia may not be able to perform aerobic exercises. Low-impact exercises should be preferred over high-impact ones, especially in persons with osteoporosis.

Resistance exercises: The goal of resistance training is to improve muscle mass. Muscles are composed of two types of muscle fibres: slow-twitch and fast-twitch. Fast-twitch fibres account for rapid, powerful movements, and with age, they tend to decrease in number, whereas slow-twitch fibres remain relatively stable. Weight-lifting exercises help increase the number of fast-twitch fibres and the size of the muscle, thereby increasing muscle strength. Exercises utilising weights can be performed by individuals of all ages and conditions, and should be done, at least at the start, under the direction of a personal trainer. Specific muscle groups can be targeted based on the patient's needs, or the exercises may be generalised. Resistance exercises include weight lifting, pulling against resistance bands, or moving body parts against gravity. A Cochrane review of 121 randomised controlled trials of progressive resistance training (PRT) in older people showed that doing PRT 2–3 times per week improved physical function, gait speed, timed get-up and-go, climbing stairs and balance, and more importantly had a significant effect on muscle strength, especially in the high-intensity training groups.[61]

Thus, it is recommended to encourage resistance exercises among postmenopausal women. Posture and balance training are important for the elderly because they may reduce the risk of falls. It will also improve posture. It integrates the sensory and motor systems and helps the individual react more quickly to environmental changes.

Balance training: Balance training can be separated into static and dynamic components. Static exercises include balancing the centre of gravity or standing in the same spot. The exercises may begin on a wide base, but then are performed on progressively narrower bases, going gradually from a double-leg support to a semi-tandem, to a tandem, to a single-leg support, and finally to static support on toes. Exercises may be sit-to-stand or scapular retraction and elevation.

Dynamic balance: Dynamic balance is maintaining the balance during movements and can be made progressively more difficult by narrowing the base of support and using side steps, cross-over steps, forward or backward steps, high steps, heel-to-toe walking, and toe tapping.

A well-rounded exercise programme includes attention to endurance, resistance training, and balance, and can often be obtained in a health club setting. In addition to the obvious benefits of improving endurance, muscle mass, strength, and balance, many individuals with chronic illness experience improvements in their symptoms. Pain relief in arthritis sufferers has been noted, and patients with high blood pressure, chronic obstructive pulmonary disease, congestive

heart failure, pulmonary hypertension, left ventricular dysfunction, angina, and cardiac arrhythmias often experience symptomatic relief. Individualised exercise prescriptions adhering to the FITT framework (Frequency, Intensity, Time, and Type) demonstrate therapeutic efficacy in ameliorating sarcopenia-related muscle weakness and functional decline in older adults.[62]

NUTRITION

Protein intake is important for postmenopausal women, especially in the form of essential amino acids. Many older adults do not consume sufficient amounts of dietary protein, which leads to a reduction in lean-body mass and increased functional impairment.[63] The current recommended dietary allowance (RDA) of proteins is 0.8 g/kg/day. Almost 40% of people more than 70 years do not meet this RDA.[64] This is considered as the minimum to maintain the balance between protein synthesis and breakdown.

Protein and energy supplementation may increase muscle strength even in very old people in the short term, but a Cochrane review has found no definite functional benefit of nutritional supplementation.[65] Another study investigating the effect of dietary protein supplementation in combination with a 12-week resistance training period found that protein supplementation increased muscle mass but not muscle strength.[66] Medical nutrition therapy (MNT) should be designed to increase the patient's current protein intake by at least 10% to a maximum of 1 g/kg body weight/day.[67] Patients having sarcopenic obesity will need a calorie-restricted diet to lose fat. Refined sugar, non-nutritive artificial sweeteners, and high-fat diets (especially saturated fats) should be restricted in patients with sarcopenic obesity. On the other hand, patients with protein-energy malnutrition (PEM) should be prescribed energy-dense, protein-rich foods.

The elderly with sarcopenia often have vitamin D deficiency. Increasing vitamin D intake through supplements and increasing exposure to sunlight often helps improve sarcopenia. Zinc deficiency is associated with sarcopenia and frailty, and supplementation may improve taste acuity, gut nerve activity, appetite, and local gut immunity, thereby improving food intake and nutrition.[31] The most effective strategies for a clinically meaningful increase in muscle mass of sarcopenic individuals involve either progressive resistance training protocols or targeted nutritional interventions combining extra energy with adequate protein intake. Current evidence strongly supports structured resistance exercise programmes, particularly when combined with leucine-fortified essential amino acid supplementation or whey protein administration in cases of dietary protein inadequacy, as foundational therapeutic approaches for sarcopenia management.[68]

HORMONE THERAPY AND SARCOPENIA

Estrogen thrapy: The effect of hormone therapy (HT) in women is controversial in relation to muscle function and mass. HT may attenuate the loss of muscle mass which occurs in the perimenopausal period. Estrogen replacement therapy has only modest effects on muscle composition, and these effects may not translate into improved physical functioning.

Menopause hormone therapy (MHT) combined with resistance training may have a role in improving lower extremity function; however, more evidence is needed.[69]

Loss of lean mass during the ageing process is mostly related to reduced physical activity, rather than to age or ovarian function decline. Several studies have demonstrated the importance of exercise in maintaining strength and muscle mass. MHT is considered a potential strategy for protecting muscle strength and power, although contradictory results have also been reported.[70-74] Bea and colleagues demonstrated that treatment with conjugated equine estrogens alone or in combination with medroxyprogesterone acetate reduced lean mass loss at year 3 in comparison to the control group. In addition, compliant patients who took at least 80% of their treatment medications across any of the HT groups had fewer falls during this period. Despite all this, the authors indicated that the reduced number of falls could not be attributed to changes in body lean mass. The beneficial effect of HT on lean mass loss, however, was lost after 6 years of treatment, and no differences between the groups were observed.

Hence, the effect was found to be transient and time-limited. It is speculated that if HT had been given to younger women (and for a shorter time since the onset of menopause), the beneficial effects of HT would have lasted up to the 6th year. Prior studies support this observation from the Women's Health Initiative (WHI) trial, demonstrating that in young postmenopausal women who received HT for 1 year, lean mass was preserved or even increased. Exercise enhances estrogen receptor transcriptional activity in skeletal muscle, and the response is greater when HT is used. In the older population, HT has been demonstrated to produce greater risks than benefits.[75]

Isoflavone supplements, which are important in preventing disease, are found in soybeans, legumes and soybean products, and they are structurally similar to the human hormone estradiol. Aubertin-Leheudre et al. studied the effects of 70 mg/day of soy isoflavone supplementation for 24 weeks on muscle mass in obese-sarcopenic postmenopausal women and recorded a significant increase in lean mass and muscle mass.[76] The potential mechanism underlying isoflavone supplementation is that it may attenuate elevated levels of pro-inflammatory markers that contribute to muscle protein breakdown. Those promising results lead us to conclude that this alternative strategy, combined with strength training, might be beneficial for postmenopausal women. However, more research is needed. A systematic review studying the relationship between menopausal hormone replacement therapy and sarcopenia concluded that there was no consistent evidence of benefit. The quality of studies was poor with high bias and methodological flaws, and many were small and used older HRT regimens and an outdated definition of sarcopenia.[77]

Tibolone: It has been shown to increase muscle strength. Unlike HRT, tibolone also increases lean body mass and significantly reduces total body fat. Tibolone increased both maximal hand grip strength, representing upper body strength, and maximal quadriceps strength, representing lower body strength.[78]

Dehydroepiandrosterone: The impact of DHEA supplementation on muscle mass is not yet clear in postmenopausal women. One study demonstrated positive effects of a 12-month course of percutaneous DHEA administration on muscle mass in 15 postmenopausal women.[38] However, many studies demonstrated negative results of the administration of DHEA alone. Yet, there is evidence of a beneficial effect of weight-lifting exercise combined with DHEA supplementation on increasing muscle mass and strength.[79]

OTHER POTENTIAL INTERVENTIONS

Growth hormone: Studies have shown an increase in muscle mass but no improvement in muscle strength, whereas others have shown an increase in both muscle mass and strength after GH supplementation. The failure of exogenous GH to mimic the pulsatile pattern of normal GH secretion has been blamed for the negative results. It was hypothesised that the combination of GH replacement and exercise training may have a synergistic effect on muscle function in older people. However, the results were disappointing, and GH supplementation did not augment the improvements in skeletal muscle observed with exercise alone.

Vitamin D: It is known that vitamin D plays an important role in bone and muscle metabolism. Low levels of vitamin D have been associated with increased sarcopenia. A myopathy has been reported in severe vitamin D deficiency.[80] The evidence for the benefit of vitamin D supplementation on physical performance is controversial. Some studies have shown improvements in muscle strength with intermittent dosing, and others have shown small gains in lower-extremity strength and reduced body sway with daily dosing. This improvement has been hypothesised as the mechanism behind a 23–53% reduction in falls among older nursing or residential home residents given vitamin D, in addition to a reduction in fractures. Conversely, other studies have found no benefits on physical function or falls risk. It is recommended that 25-hydroxy vitamin D levels < 40 nmol/L require supplementation, and 75 nmol/L is the level for optimal bone and muscle health. The recommended daily intake of vitamin D is between 400 IU per day and 600 IU per day, which may be inadequate to raise serum vitamin D levels to a desirable level 70 nmol/L.[81] Studies have shown that to achieve optimal levels of 75–100 nmol/L of 25-hydroxy vitamin D, doses of 700-1,000 IU are needed.[81]

EXPERIMENTAL DRUGS

Creatine: It plays an important role in protein and cellular metabolism. It has been hypothesised that creatine increases the expression of myogenic transcription factors, such as myogenin and myogenic regulatory factor-4, thereby increasing muscle mass and strength.[81] Several studies of creatine supplementation have shown increased muscle strength and power in younger men and women, but few studies have looked at the effect of creatine supplementation in older people.

Myostatin: Myostatin is a natural inhibitor of growth factors. It was initially discovered when mutations of the myostatin gene were found to correlate with exaggerated muscle hypertrophy.[81]

Angiotensin-converting enzyme inhibitors: It has now been suggested that angiotensin-converting enzyme (ACE) inhibitors may have a beneficial effect on skeletal muscle. ACE inhibitors may exert their beneficial effects on skeletal muscle through several mechanisms. ACE inhibitors may improve muscle function by enhancing endothelial function, metabolic function, anti-inflammatory effects, and angiogenesis, thereby improving skeletal muscle blood flow. ACE

inhibitors can increase mitochondrial numbers and insulin-like growth factor 1 (IGF-1) levels, thereby.[81]

Peroxisome proliferator-activated receptor delta agonist: The peroxisome proliferator-activated receptor delta (PPAR-δ) agonist GW1516 significantly increases exercise capacity when combined with exercise.[82] Ursolic acid: A water-insoluble pentacyclic triterpenoid, ursolic acid is the major waxy component in apple peels.[82] It is also found in many other edible plants. Interestingly, it exerts beneficial effects in animal models of diabetes and hyperlipidaemia-related sarcopenia.

Eicosapentaenoic acid (EPA) is a 20-carbon omega (n)-3 polyunsaturated fatty acid with anti-inflammatory properties, which is synthesised from ingested alpha-linolenic acid or is consumed in fish and fish oil such as cod liver, sardine, and salmon oil.[82] It may help improve muscle function.

Cyclophilin inhibitor (Debio-025) Ca2+ overload is known to cause cellular necrosis by directly inducing the opening of the mitochondrial permeability.[82] These two molecules are presently under research.

Other agents: Testosterone, synthetic steroids, selective androgen receptor modulators, anti-myostatins agents, beta-adrenergic agonists, acetylcholine esterase inhibitors, anti-inflammatory therapy and stem cell therapy are under various phases of clinical trials.[82]

FRAILTY

Frailty refers to the decline in physiological reserve capacity resulting from the deterioration of multiple physiological systems (brain, endocrine system, immune system, and skeletal muscle), leading to increased vulnerability and decreased stress tolerance. Women have a higher prevalence of frailty than men, although the epidemiological factors underlying this phenomenon are not fully understood. Menopause and menopause-related characteristics may be among the contributing factors.

Longitudinal studies have identified several negative outcomes associated with frailty, which can have a significant impact on individuals and society as a whole. These include falls, worsening mobility, disability, hospitalisation and increased risk of mortality. Overall prevalence of frailty in older people ranges from 7 to 24% and increases with age.[83]

The prevalence of frailty among postmenopausal women ranged from 5.9% to 57.3%. Existing studies suggest that menopause is associated with frailty. Early menopause, hysterectomy, low-free testosterone levels, and high C-reactive protein levels may increase the likelihood of frailty among postmenopausal women. Changes in hormone and inflammatory cytokine levels may mediate frailty among postmenopausal women. More research is needed to address this.

DEFINITION

Frailty can be described as a state of physiological vulnerability with diminished capacity to resolve a stressor event, as a consequence of disordered systems and decreased physiological reserve capacity.[84]

Frailty is not only associated with a decline in physiological reserves in multiple systems, but there is also a vulnerability to stressors. The biomedical view considers it as a part of a comorbid/debilitating condition; while other views add it as a dependency on others for activities of daily living (ADL) as an integral component of frailty. Buchner and Wagner perceive frailty as "losses of physiologic reserve that increase the risk of disability" and that it precedes disability and dependence on others for ADL. Frailty is considered to progress ultimately and spiral to disability, dependence, institutionalisation, hospitalisation, and mortality.

Frailty is a multifactorial complex condition with a dynamic trajectory with a possibility of reversibility to a prefrail and independent state. However, frail individuals can rapidly deteriorate to disability and dependence.

Fried et al. have standardised the definition as 3 or more of the following 5 criteria: unintentional weight loss, self-reported exhaustion, weakness (grip strength), slow motor performance (walking speed), and low physical activity. Those having 1 or 2 of the 5 characteristics are considered "pre-frail." Although the frailty syndrome remains ill-defined, this "5 criteria phenotype" is currently the most used in clinical practice and research. However, this widely applied d ition lacks the psychosocial dimension of frailty.[85]

PATHOPHYSIOLOGY

Frailty syndrome involves the declining function of several systems and their physiological reserves. The syndrome is

multifactorial. Decline in anabolic hormones, growth hormone (GH) and insulin-like growth factor-1, immune deficiency, and an increase in proinflammatory markers, interleukin (IL)-6 and IL-15, are indicative of underlying chronic inflammation. The triad of adiposity, sarcopenia, and insulin resistance (cardiometabolic risk factors), and the depletion of visceral proteins (transthyretin, retinol-binding protein, and albumin) are among the implicated causative factors of the prefrail and frail status of elderly individuals. Many of these changes result from DNA damage in the aged, leading to mutations. A growing body of evidence strongly implicates mitochondria in the initial onset and progression of functional decline.[85]

DETERMINANTS

The various determinants are biological (ageing), clinical (non-communicable diseases), psychological (poor cognition and mood disorder), sociocultural (empty nest), and socioeconomic. Factors identified like sarcopenia, poor nutrition, physical inactivity and inflammatory state could be determinants for initiating frailty, while osteoporosis and poor balance are high risks for fall and fracture, which could exacerbate frailty.

MEASURES AND ASSESSMENT

Mainly, there are two definitions: one by Fried et al. , which includes 3 out of 5 phenotypic features that identify frailty. The Fried's frailty phenotype tool includes five items: unintentional weight loss (4.5 kg or more over the past year), exhaustion (self-reported), low physical activity, weakness (low grip strength), and walking speed. Individuals with two deficits are considered prefrail, and those with three or more deficits are classified as frail.[85]

The other approach considers frailty as a state rather than a syndrome. Frailty index (FI) suggested in such an approach recognises the number of deficits (> 30) that progressively accumulate with advancing frailty and makes the prognosis feasible about the outcome, including mortality. Variants to be recorded in FI include medical, functional, environmental, and social aspects.

Clinical Frailty scale is yet another measurement tool with a 9-point ordinal scale ranging from point 1 (fit) to 9 (terminally ill with an expected survival of less than 6 months).

These three assessment tools of frailty are validated with pros and cons; one by Fried et al. is easy to use in clinical setting, while the FI, although precise in measurements and reproducible across nations and disease states, is too cumbersome to use in clinical settings. There is a need to develop frailty assessment scale for Indian women.[85]

RECOMMENDATIONS FOR ASSESSMENT AND MEASUREMENT

For clinical assessment, we can use a scale that is based on the 5 phenotypic features. And for research and qualitative measurement, we could use either FI or the 9-point clinical frailty scale.

Indications for assessment

People who have experienced weight loss (≥ 5%) during unintentional dieting within the last 1 year are recommended to screen for frailty.[82,85]

All adults more than 65 years of age.

Older people when seen perioperatively for elective surgery.

PREVENTION AND MANAGEMENT

Screening for frailty should be done in the elderly. A 4-metre gait speed test or timed up-and-go test, along with the SARC-F questionnaire, may be used to assess frailty. Those found to be positive should have a complete geriatric assessment by trained professionals.

Polypharmacy is a major contributor to frailty pathogenesis. Reducing inappropriate medications could reduce the incidence of frailty in older people.[86]

THERAPEUTIC LIFESTYLE MODIFICATION

Nutrition and exercise: These are key components for preventing and managing this condition. To date, physical exercise is the only intervention consistently demonstrated to attenuate functional decline among older adults. Multi-component physical exercise, including resistance, power, aerobic, flexibility and balance exercises, may be the best

strategy to improve the physical condition of frail older patients. For older people who are sedentary, they can start with a single exercise, and then consider other forms of exercise after they gradually adapt. Flexibility training includes dynamic and slow-motion stretching and static stretching and is best recommended after aerobic exercise and resistance training. Balance training includes backward walking, lateral walking, heel walking, toe walking, sitting-to-standing, standing on both feet, straight walking, step exercises, and standing on one leg.

Nutrition

Nutritional assessment should include evaluation of changes in body composition, such as BIA. Frail older people experiencing unexpected weight loss or malnutrition should consider protein/caloric supplementation.[87] It is recommended that frail older people should consume 1.2–1.5 g/kg/day of protein, and each meal should provide 20–40 g of protein to stimulate muscle protein synthesis. Vitamin D is only recommended for frail older people with vitamin D deficiency. Drug therapy, such as hormone therapy, is not recommended for frailty. Management of postmenopausal women with balance impairment should incorporate a multifactorial fall prevention approach combining individualised exercise therapy, medication review, vision correction, and footwear optimisation consistent with global evidence-based recommendations.[88,89]

Pharmaceutical

Drug management for osteoporosis, vitamin D supplementation in deficient women is needed. High protein diet is important. Menopausal hormone therapy for older individuals is not recommended and may do more them.

Frailty and technology

The physical environment around the patient can be improved through assistive technologies that enable the patient to independently and safely carry out ADLs and reduce functional decline. Patient's home environment can be made safe by adding cameras, in-home and wearable sensors, and connected devices that automate home environment. ADLs can be made easy and safe through use of walking aids such as walking sticks and frames or external orthoses, grab rails, wearable sensors, using western toilets and toilet chairs. The rooms should be well lighted and have minimal furniture.[90] Cognitive training interventions typically involve computerised "games" aimed at progressively training specific cognitive skills such as working memory and attention using a series of challenging tasks should be done.

FALLS AND FRACTURES

Frailty related falls and fractures have been reported with odds ratio of 1.38 to 2.4 for recurrent falls, 1.40 and 1.7 for hip fracture in old women. Planning of individualised exercise programme, for preventing vertebral fractures and strengthening for fall prevention, takes into consideration patients cardiovascular condition, muscular strength, flexibility, core stability, and bone's biochemical competence. The programme addresses balance and strengthening to prevent falls and fractures. Women's healthcare programmes that provide comprehensive care can make a significant contribution by educating women to take care of their musculoskeletal health through lifelong commitment to proper nutrition, exercise, and understanding of fall prevention.[88,90] Social factors, proper footwear, elder-friendly homes, proper ophthalmic assessment, balance training, and group education are key to optimising the health of the elderly.

ADVANCES

Gut Microbiota and Sarcopenia: Emerging evidence has elucidated the critical role of gut microbiota dysbiosis in the pathogenesis of sarcopenia via the gut-muscle axis.[91]

Stem Cell Therapy: Mesenchymal stem cell (MSC) therapy offers a promising approach for treating substantial diseases due to their self-renewal and differentiation potential into various somatic cells.[92]

SYNOPSIS

- Sarcopenia and frailty are diseases associated with increasing age, with presentations more prevalent in postmenopausal females.
- Clinical suspicion, along with SARC-F and SARC-CALF or CC, or HGS screening, should be done in older people.

- Nutrition, with emphasis on adequate protein and calorie intake, combined with resistance training, is the most important intervention to treat and prevent sarcopenia and frailty.
- Vitamin D supplementation is important when there is a deficiency.
- Hormone therapy is not recommended for the prevention or treatment of sarcopenia.
- Advances in technology should be used to enable smart homes, wearables, and social connectivity to prevent falls and support communication for the elderly.

RESEARCH AGENDA

Improvement in SARC-CALF score after a structured resistance exercise and protein supplementation schedule.

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OSTEOARTHRITIS

Keywords: Estrogen, osteoarthritis, management

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INTRODUCTION

Low back pain (LBP) and osteoarthritis (OA) are two of the most common, disabling, and costly health conditions.[1] OA, the most common form of arthritis, is characterised by progressive cartilage degradation and low-grade joint inflammation, and represents one of the leading causes of chronic pain, functional limitation, and disability. While multiple factors contribute to OA development, age and sex are primary risk factors, particularly affecting postmenopausal women. The decline in physical activity among those living with OA contributes to both physical limitations and diminished mental health.[2,3] The most common sites of OA are the hand, knee, and hip. Specifically, OA of the knee or hip (weight-bearing OA) is more common in postmenopausal women and is more strongly associated with cardio vascular disease (CVD) risk than hand OA.[4] Intervertebral disc (IVD) degeneration and facet joint OA (FJOA) are two major contributors to LBP.[5] FJOA is a consequence of spinal degeneration and is considered a primary cause of LBP. FJOA is a whole-joint failure disease that results from injury to one or more components of the spinal motion segment.[6] Women with severe menopausal symptoms are more likely to experience chronic back pain and OA.[7]

Gynaecologists are often the first clinicians to encounter women during the menopausal transition. Awareness of rheumatic disease manifestations enables timely referral, coordinated care, and informed counselling on hormone therapy (HT), bone health, sexual function, and long-term disease risk.

EPIDEMIOLOGY

India is facing a rapidly escalating burden of OA. In a nationwide chronic disease awareness campaign, it has been projected that over 60 million Indians are affected by arthritis, positioning India among countries with the highest OA burden globally.[8] A contemporary systematic review and meta-analysis of community and clinic based studies reported that approximately one in three elderly Indians has knee OA, with higher prevalence in women and a trend towards a greater burden in urban and metropolitan populations.[9] Urban rural variation is substantial. A large multicentric Indian community survey found that the prevalence of primary knee OA was 33.2% in metropolitan cities, 19.3% in small cities, 18.3% in towns, and 29.2% in villages, highlighting both urbanisation-related risk and a persistent rural disease burden.[10]

RISK FACTORS AND MECHANISM

Non-modifiable risk factors include age, gender, and genetic predisposition. Modifiable risk factors include obesity, malalignment due to congenital causes, traumatic malunions, inflammatory arthropathies, overuse, and cartilage damage due to infections.[11] OA is characterised by cartilage deterioration, alterations in the subchondral bone, and the development of osteophytes, resulting in pain and physical disability. The mechanism of OA pain is complex and involves tissue damage, cell senescence and apoptosis, nerve sensitisation, biomechanical factors, and psychological factors.

Effect of Aging

Normal articular cartilage is characterised by a relatively stable chondrocyte population, a high extracellular matrix-to-cell ratio, avascularity, and a remarkable ability to tolerate repetitive mechanical loading in weight-bearing joints. With advancing age, chondrocytes undergo phenotypic and metabolic alterations, including the accumulation of lipofuscin pigments and advanced glycation end-products (AGEs), which impair matrix synthesis, reduce collagen elasticity, and increase cartilage stiffness.[12] Chondrocyte responsiveness to major growth factors, such as insulin-like growth factor-1 and transforming growth factor-β (TGF-β), also decreases with age.[13] OA was once considered a normal ageing process; however, physiological ageing should be distinguished from OA. Normal ageing is characterised by synovial atrophy, mild cartilage thinning, and osteopenia. In contrast, OA exhibits distinct pathological features, including focal cartilage erosion, subchondral bone sclerosis, osteophyte formation, and low-

grade synovial inflammation.[14,15] Changes seen in OA are believed to be caused by either excessive stress on once-normal joint tissues or by everyday stresses acting on tissues altered by systemic (obesity, metabolic syndrome, menopause) or local (malalignment, muscle weakness, meniscal damage) risk factors. OA results from an inadequate repair response to these stresses. In early OA, chondrocytes show increased proliferation and metabolic activity in an attempt to restore matrix integrity; however, this reparative response is inefficient and progressively overwhelmed.[16] Repetitive mechanical loading disrupts the collagen–proteoglycan network, leading to matrix edema, fibrillation, and eventual chondrocyte apoptosis and necrosis.[16] A reduced chondrocyte population decreases the tissue's capacity to maintain matrix proteoglycan concentration, increasing tissue vulnerability to injury. Pathological changes due to OA are seen in all the articular and periarticular tissues. OA is now recognised as a whole-joint disease, involving articular cartilage, subchondral bone, synovium, menisci, ligaments, and periarticular muscles.[17]

Importantly, pathological processes begin years before clinical symptoms manifest. Additionally, elements of the local joint environment, such as joint-protective muscle activity, muscle strength relative to body weight, proprioception, varus-valgus laxity and meniscal condition, may become impaired and contribute to disease progression.

Effect of Sex

The age-related increase in the incidence and prevalence of knee, hand, and hip OA is consistently greater in women than in men. Early clinical observations by Cecil and Archer described an “arthritis of the menopause,” characterised by the rapid onset of hand and knee OA around the cessation of menses. Subsequent epidemiological studies have confirmed that before the age of 50 years, OA prevalence is similar in both sexes, whereas after menopause, women exhibit significantly higher incidence, prevalence, symptom burden, and structural progression of OA, suggesting a modifying role of estrogen deficiency in disease pathogenesis.[18–20] Large population-based cohorts show that radiographic generalised OA is nearly three times more prevalent in women aged 45–64 years than in men of the same age, and that hip and knee OA are more often symptomatic and progressive in postmenopausal women.[21] Moreover, the lifetime risk of developing symptomatic knee OA is approximately 40% higher and that of hip OA approximately 10% higher in women than in men.[22,23] Women aged 50–60 years are also more than three times more likely to develop hand OA than men in the same age group.[20] More than half of women with knee OA report symptom onset during the perimenopausal period or within five years of natural or surgical menopause, further supporting a temporal association between estrogen decline and OA manifestation.[24] Meta-analytic evidence confirms that women experience more severe knee OA than men, with sex differences in severity most pronounced after menopause.[11,19]

Biological Effects of Estrogen Deficiency

Declining estrogen levels after menopause lead to cartilage thinning, increased matrix brittleness, reduced collagen synthesis, and diminished synovial fluid quantity and quality. Estrogen deficiency is associated with increased chondrocyte apoptosis, impaired subchondral bone remodelling, and a shift towards a pro-inflammatory joint microenvironment characterised by chronic low-grade synovitis, thereby amplifying pain and stiffness.[24] Concurrent sarcopenia and loss of periarticular muscle strength further compromise joint stability, increasing fall risk and accelerating OA progression. Animal and translational studies demonstrate that estrogen modulates cartilage metabolism and subchondral bone turnover, and ovariectomised models show accelerated OA-like degeneration that is attenuated by estrogen replacement.[25]

Osteoarthritis And Hormone Therapy

Experimental models consistently demonstrate a chondroprotective role for estrogen. In animal studies, ovariectomised rodents develop accelerated cartilage degeneration, whereas estrogen supplementation delays OA onset and reduces the severity of cartilage lesions, confirming estrogen’s regulatory role in cartilage and subchondral bone remodelling.[26] Chondrocytes express estrogen receptor-α and -β, providing direct biological plausibility for estrogen-mediated modulation of matrix synthesis, inflammatory signalling, and chondrocyte survival.[27]

Human Observational Evidence

Population-based and longitudinal cohort studies of menopausal HT report heterogeneous but predominantly protective associations, particularly for hip and knee OA. The Chingford Study, United Kingdom ,found an inverse association between current HT use and radiographic knee OA, suggesting a protective effect.[28] The Framingham cohort reported that current estrogen therapy was associated with a modest, non-significant reduction in the radiographic progression of knee OA.[29] Oliveria et al. observed reduced OA development among estrogen users.[30]

Narrative and systematic reviews further support a lower prevalence and slower progression of hip and knee OA among estrogen users, an increase in the knee cartilage volume, with a possible reduction in arthroplasty rates, especially for hip OA among women receiving estrogen-only therapy.[31],[32] In the Women's Health Initiative (WHI) randomised trial, postmenopausal women receiving HT reported significantly lower prevalence and severity of joint pain compared with those receiving placebo, calcium, or vitamin D supplementation.[33] Long-term follow-up of the WHI cohort of women aged 50–79 years without prior joint replacement demonstrated that menopause hormone therapy (MHT) may influence structural joint outcomes, with the reduction in arthroplasty risk being largely confined to unopposed estrogen and appearing more pronounced for hip than for knee OA. Further age-stratified and menopause-transition subgroup analyses would be valuable to determine whether women treated in early menopause derive greater joint protection, consistent with a possible "window of opportunity" effect for HT.[34] Pang et al. emphasise that estrogen has potential disease-modifying and analgesic properties, but human studies of HT remain inconsistent. They highlight a critical window hypothesis, suggesting that timing, formulation and dosage of estrogen may determine analgesic and structural benefit, but caution against routine HT use solely for pain or OA prevention.[1]

In contrast, a Korean study from the National Insurance Database cohort found that MHT was associated with an increased risk of OA, with consistent findings across tibolone, Estrogen–Progestogen Therapy (EPT), and Estrogen Therapy (ET), particularly affecting joints other than the hip.[35] Another cross-sectional study conducted in Korea examined the relationship between spinal OA prevalence and the use of HT, postmenopausal women undergoing HT therapy treatment had a lower prevalence of spinal OA. Moreover, women who had received treatment for more than 1 year were at an even lower risk than those who had received treatment for less time.[36] A German study found no difference in the effect of HT on OA progression.[37] The first meta-analysis on MHT and OA reported an increased risk of OA with HT use, unlike the WHI results.[38] The meta-analysis included observational cohort studies and was not case-controlled.

Although estrogen demonstrates cartilage-protective effects in experimental studies and is associated with a lower radiographic OA prevalence in observational studies, there is currently insufficient evidence to recommend HT solely for OA prevention or treatment. However, early identification and management of OA and cardiometabolic risk during the menopausal transition may reduce long-term morbidity in ageing women.

Limitations of Current Evidence

Despite biological plausibility and favourable observational signals, randomised controlled trials are lacking, and results remain inconsistent. A 2025 mechanistic review emphasises that ovariectomy models incompletely simulate menopause-associated OA and calls for improved ageing-relevant OA models to better define estrogen's disease-modifying role.[25,39]

Presentation And Investigations

OA manifests in a variety of ways, including joint pain, stiffness, and restricted range of motion.[40] Despite the slow progression of this disease, it can eventually cause joint failure and disability. The most common symptoms of knee OA are pain with activity and/or functional limitations, such as difficulty getting up from a chair, climbing stairs, and walking. Additional symptoms may include morning knee stiffness lasting more than 30 minutes, knee swelling, and a sensation of the knee buckling or giving way. Symptoms of knee OA typically begin gradually and may include brief, intermittent flares of knee pain. Knee OA is typically diagnosed based on a patient's medical history and physical examination. Common signs include a cracking or popping sound with knee movement, knee joint enlargement, and a limited range of motion.

CLINICAL FEATURES

OA is usually diagnosed based on clinical features, age, symptoms, the location and number of joints involved, and radiographic findings. Secondary causes of OA include prior joint trauma, congenital or developmental abnormalities, other bone and joint diseases (such as rheumatoid arthritis and calcium deposition disorders), and other systemic diseases (such as diabetes mellitus and thyroid disease), as well as idiopathic cases. OA may be local (confined to one joint) or generalised (commonly defined as affecting the hands and at least one major weight-bearing joint). Localised OA most commonly occurs in the hands (proximal), and radiography is limited in capturing pain-related elements of the disease. The pain typically worsens after activity and is relieved by rest. In advanced disease, pain may come on with progressively less activity and ultimately may occur at rest. Since cartilage is not innervated, cartilage damage is not a direct cause of pain. Osteophytes occurring on the distal and proximal interphalangeal joints of the hand are

referred to as Heberden's and Bouchard's nodes, respectively. As the osteophytes grow, they may cause erythema of the overlying skin and significant pain. These bony growths can lead to loss of motion, manifested as locking or contractures of joints, like in the fingers and knees. The most common symptoms of knee OA are pain with activity and/or functional limitations, such as difficulty getting up from a chair, climbing stairs, and walking. Additional symptoms may include morning knee stiffness lasting more than 30 minutes, knee swelling, and a sensation of the knee buckling or giving way. Symptoms of knee OA typically begin gradually and may include brief, intermittent flares of knee pain. The likelihood of a poor functional outcome was increased by greater varus-valgus laxity, age, body mass index (BMI), muscle weakness, knee pain intensity, and greater proprioceptive inaccuracy.

MANAGEMENT

The primary aim is to prevent pain and disability, improve quality of life, and provide pain relief. Treatment is varied and includes both non-pharmacological and pharmacological modalities. Management should be tailored to each patient and take into account the individual's functional status, occupational needs, coexisting medical problems, disease severity, and joint deformity. Depending on the stage and general condition, it can be addressed by lifestyle modification, pharmacotherapy, and physical therapy. Standard surgical intervention, total joint replacement, is the final choice.

Nonpharmacological Therapy: The major nonpharmacological modalities used to treat OA include patient education, weight loss, Physical therapy (PT), Pulsed Ultrasound (LIPUS), transcutaneous electrical nerve stimulation (TENS), orthoses, and quadriceps strengthening exercises.

PT, as a non-pharmacological measure, does not produce hormone-related side effects and is useful for the prevention and relief of pain in perimenopausal women with KOA. PT mainly involves aerobic exercises, resistance training, and mind–body exercises.[40,41] LIPUS and TENS are often used as adjunctive treatments.[42]

Orthoses: Orthotic devices, including knee braces, splints, hand orthoses, and shoe insoles, reduce pain and improve joint function in knee, hand, and wrist OA. Lateral wedge and variable-stiffness insoles can reduce medial knee loading and pain in medial compartment OA, particularly in varus alignment. Exercise therapy improves gait mechanics, lexibility, muscle strength and joint stability and is foundational to OA management.[43]

Pharmacological Intervention: Paracetamol should not be used as routine first-line monotherapy for OA. It may be used as short-term rescue analgesia or when non-steroidal anti-inflammatory drugs (NSAIDs)s are contraindicated.[44] NSAIDs provide superior pain relief compared with paracetamol but carry gastrointestinal, renal and cardiovascular risks. COX-2 selective inhibitors such as celecoxib have a lower GI bleeding risk but similar CV risk to non-selective NSAIDs. Long-term use requires risk stratification and monitoring.[45] Adverse effects of NSAIDs include allergic reactions, gastrointestinal bleeding with or without abdominal pain, central nervous system impairment in the elderly, impairment of liver, kidney, or bone marrow function, and bleeding secondary to impairment of platelet aggregation. Topical NSAIDs are strongly recommended for knee and hand OA because they have comparable analgesic efficacy to oral NSAIDs with markedly reduced systemic adverse effects.[45]

A Cochrane review found that about 60 per cent of patients achieved at least 50 per cent improvement in pain with topical NSAIDs, comparable to the effect with oral formulations and slightly better than that with topical placebo. The risk of gastrointestinal, renal, and cardiovascular toxicity is much lower with topical NSAIDs as compared with their oral formulation due to the reduced systemic absorption (5- to 17-fold lower for topical diclofenac compared with oral).[46]

Nutraceuticals: Glucosamine sulfate and chondroitin sulfate show inconsistent benefit; current guidelines do not recommend their routine use.[47]

Topical Capsaicin: provides modest pain relief in knee and hand OA and may be used as an adjunct therapy.[48]

Intra-articular Injections: Corticosteroids provide short-term pain relief (up to 4–6 weeks). Repeat injections may be used cautiously (≤3/year)[49] Hyaluronic acid may benefit selected patients but has variable efficacy and is not universally recommended.[50] Neither modality alters disease progression. Platelet-Rich Plasma (PRP) may be offered as an adjunct for symptomatic relief in early knee OA (Grade B). Still, it should not be promoted as a cartilage-regenerating or disease-modifying therapy.[51]

Surgical Intervention: Procedures offered include joint arthroscopy, debridement, lavage, and fusion, as well as osteotomy. However, the indications and effectiveness of these interventions remain unclear. In those with significant

disability due to OA and advanced radiographic disease, joint replacement should be considered, as it commonly has a dramatic effect on quality of life.[52] Preoperative optimisation of anaemia, malnutrition, vitamin D deficiency, obesity, and sarcopenia, combined with targeted strength training, can substantially improve physical fitness within 12 weeks and is associated with significantly better postoperative outcomes.[53]

SYNOPSIS

- OA is the most common form of arthritis, affecting the knee or hip, and is a leading cause of disability.
- In India, OA of the knee is four times more common than OA of the hip.
- Management includes both pharmacological and nonpharmacological modalities, which are treatment options and include weight loss, physical and occupational therapy, over-the-counter NSAIDs, prescription drugs and surgery.

RESEARCH AGENDA

Effect of menopause on knee OA.

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Section 5

MENOPAUSE AND OTHER SYSTEMS

OCULAR HEALTH

Keywords: Eye, ageing, menopause, ocular diseases, ocular health

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INTRODUCTION

The worldwide prevalence of moderate to severe visual impairment and blindness is estimated at 285 million, with nearly 65% of visually impaired individuals and 82% of all blind people being aged 50 years and older.[1] Meta-analyses have demonstrated that women account for approximately two-thirds of the global burden of blindness in both developed and developing countries.[2]

Menopause represents a pivotal transition in a woman's life, marked by the cessation of ovarian hormone production, primarily estrogen and progesterone. This hormonal decline results in widespread systemic changes affecting the cardiovascular, skeletal, genitourinary, and ocular systems. The eye is a hormonally responsive organ. Estrogen receptors (ER-α and ER-β) are widely expressed in ocular tissues, including the cornea, conjunctiva, lacrimal and meibomian glands, ciliary body, lens, retina, and optic nerve.[3] Consequently, depletion of circulating estrogens during the peri- and postmenopausal periods leads to measurable alterations in intraocular pressure, ocular surface integrity, tear film stability, and retrobulbar blood Flow.[4] Among the lesser-known yet clinically signIFicant consequences of menopause are ocular manifestations such as dry eye disease, glaucoma, diabetic retinopathy, and age-related macular degeneration.[3,4] Women are also disproportionately affected by uncorrected refractive errors, including myopia, hyperopia, astigmatism, and presbyopia.[1]

This chapter examines the role of hormonal changes during menopause in the pathogenesis and progression of major ocular disorders, including dry eye disease, glaucoma, diabetic retinopathy, and age-related macular degeneration.

INTRAOCULAR PRESSURE (IOP) AND AQUEOUS DYNAMICS

Menopause has been consistently associated with a modest but clinically meaningful elevation in intraocular pressure (IOP), a critical risk factor for primary open-angle glaucoma (POAG). Epidemiological studies demonstrate that postmenopausal women have higher mean IOP values than age-matched premenopausal women, with reported increases typically ranging from 1 to 3 mm Hg, a shift that may significantly influence glaucoma susceptibility in predisposed eyes.[5] The underlying mechanism appears closely related to alterations in aqueous humour dynamics, particularly reduced aqueous outflow facility through the trabecular meshwork. Experimental ovariectomy models simulating the postmenopausal state show a direct reduction in aqueous outflow, supporting a causal role for estrogen deficiency.[6,7] ERs are expressed in trabecular meshwork and Schlemm's canal tissues, and estrogen has been shown to modulate extracellular matrix turnover and nitric oxide–mediated relaxation, thereby reducing outflow resistance.[8] Clinical studies further corroborate this mechanism, demonstrating that estrogen therapy is associated with improved outflow facility and reductions in IOP of approximately 0.5–3 mm Hg.[9] Collectively, these findings provide a biologically plausible explanation for menopause-related IOP elevation and highlight estrogen decline as a contributory factor in glaucoma risk among postmenopausal women.

OCULAR COMPLIANCE AND BIOMECHANICS

Beyond intraocular pressure alone, menopause is associated with important alterations in ocular biomechanics, particularly ocular compliance and tissue stiffness. Ocular compliance, defined as the change in ocular volume per unit change in IOP, reflects the viscoelastic properties of the corneoscleral shell. Although chronological ageing is generally associated with increased scleral stiffness, experimental ovariectomy (OVX) models simulating menopause demonstrate increased ocular compliance, indicating reduced corneoscleral stiffness attributable to estrogen deficiency.[7] Estrogen is known to regulate extracellular matrix remodelling and collagen cross-linking in ocular connective tissues, and its loss appears to shift the biomechanical behaviour of the globe toward greater deformability.[7] Clinically, increased ocular compliance may permit greater strain and deformation of the optic nerve head (ONH) in response to IOP-related stress, potentially amplifying susceptibility to glaucomatous axonal injury even when IOP remains within statistically normal limits.[10] These biomechanical changes provide a pressure-independent mechanism through which menopause may contribute to glaucoma risk.

DRY EYE DISEASE, MENOPAUSE, AND MENOPAUSE HORMONE THERAPY

Dry eye disease (DED) is a chronic, multifactorial disorder of the ocular surface characterised by tear film instability, hyperosmolarity, inflammation, and neurosensory abnormalities, leading to ocular discomfort and visual disturbance. It affects women nearly twice as often as men after the age of 50 years, and epidemiological studies demonstrate that women are diagnosed approximately six years earlier than men, emphasising the strong influence of sex hormones and ageing on disease onset.[11,12] Women report greater symptom severity, increased treatment utilisation, and a more pronounced adverse impact on quality of life, making dry eye a major cause of morbidity during the menopausal transition.[13]

DED is broadly classified into aqueous-deficient dry eye (ADDE) and evaporative dry eye (EDE). ADDE results from impaired lacrimal gland secretion and is commonly associated with autoimmune diseases such as Sjogren's syndrome and systemic medications, whereas EDE arises from excessive tear evaporation, most frequently due to Meibomian gland dysfunction (MGD).[14]

In postmenopausal women, evaporative dry eye predominates, reflecting hormonally mediated alterations in lipid secretion from the Meibomian glands. Sex steroid hormones play a central role in maintaining ocular surface homeostasis. Androgens exert a protective effect by stimulating lipid synthesis and secretion from the Meibomian glands and enhancing lacrimal gland function, thereby stabilising the tear film.[15] In contrast, estrogen and progesterone appear to have inhibitory or modulatory effects on Meibomian gland lipid production. The high prevalence of dry eye in postmenopausal women is therefore thought to reflect relative androgen deficiency rather than absolute estrogen deficiency.[15] Women with premature ovarian insufficiency demonstrate increased ocular surface damage and dry eye symptoms independent of tear production, further supporting a hormonal mechanism.[16]

Diagnosis relies on symptom assessment combined with objective tests such as tear break- up time (TBUT), Schirmer testing (types I and II), and evaluation of Meibomian gland structure and function.[17]

Management includes tear supplementation, lubricating ointments, topical anti-inflammatory agents such as cyclosporine or lifitegrast, treatment of MGD, dietary omega-3 fatty acid supplementation, and, when appropriate, reassessment of systemic hormonal therapy in collaboration with gynaecologists or endocrinologists.[18]

The effect of menopause hormone therapy (MHT) on the ocular surface is heterogeneous and highly dependent on the hormonal formulation and its androgenic balance.The role of MHT in dry eye disease remains complex and somewhat controversial. Observational studies have shown that estrogen-only MHT is associated with an increased risk of dry eye symptoms, whereas combined estrogen–progesterone therapy appears to confer a lower risk, suggesting differential effects of hormone formulations on the ocular surface.[19] Conversely, some smaller clinical studies have demonstrated improved tear stability and symptom relief with MHT, particularly when therapy restores hormonal balance rather than inducing estrogen dominance.[4] These conflicting findings highlight the heterogeneity in MHT type, dose, duration, and route of administration, as well as individual susceptibility. Sex hormones also influence lacrimal gland physiology. Androgens enhance aqueous tear secretion and immunoglobulin A (IgA) production, contributing to ocular surface immunity, while the effects of estrogen and progesterone on lacrimal function remain inconsistent across studies.[20] Taken together, endogenous hormonal decline during menopause and exogenous hormonal modulation with MHT may both influence the onset and severity of dry eye disease, underscoring the need for individualised assessment in postmenopausal women. Tibolone, a synthetic steroid with combined estrogenic, progestogenic, and androgenic activity, has been shown to significantly improve both Schirmer's test values and tear film break-up time (TFBUT) after six months of therapy, with statistically robust improvements ($p < 0.001$), suggesting a clinically meaningful enhancement of both aqueous and lipid tear components.[21,22]

In contrast, studies evaluating conventional combined MHT regimens, particularly estradiol combined with medroxyprogesterone acetate, have failed to demonstrate significant improvements in tear function tests or conjunctival cytology scores, indicating limited benefit for ocular surface physiology.[9] Short-term estrogen-based MHT has, however, been reported to increase both tear quantity and quality within two months of treatment in broader clinical cohorts ($p < 0.001$), suggesting that estrogen supplementation may partially reverse age-related and menopause-associated desiccating stress, although these effects appear to be formulation- and duration-dependent.[23] Collectively, these findings indicate that MHT-related ocular benefits are not uniform and are strongly influenced by the regimen's androgenic properties, with androgen-active compounds such as tibolone showing more consistent improvements in tear film parameters.

SJOGREN'S SYNDROME

Sjoren's syndrome should be suspected in those with severe, persistent, or treatment-refractory symptoms. Autoimmune lymphocytic destruction of the lacrimal glands leads to marked aqueous tear deficiency, low Schirmer's test values, and significant ocular surface damage. Menopause-related immune and hormonal changes may unmask or worsen Sjoren's syndrome, necessitating systemic evaluation as management differs from age-related or evaporative dry eye disease.[24]

GLAUCOMA, MENOPAUSE, AND MENOPAUSAL HORMONE THERAPY

Glaucoma is a progressive neurodegenerative optic neuropathy characterised by retinal ganglion cell loss, thinning of the retinal nerve fibre layer, and characteristic optic disc changes, leading to irreversible visual field loss and potential blindness. Although elevated intraocular pressure (IOP) is the most significant modifiable risk factor, glaucoma can occur with normal IOP, and pressure elevation is not required for diagnosis. Currently, no curative therapy exists; however, disease progression can be delayed or prevented by lowering IOP through pharmacological treatment, laser procedures, or surgery.[25]

Globally, glaucoma is the leading cause of irreversible blindness, affecting more than 60.5 million individuals worldwide.[26] In India, the estimated prevalence is approximately 11.2 million cases, a figure projected to increase with population ageing.[27] The two principal forms of glaucoma, open-angle glaucoma (OAG) and angle-closure glaucoma (ACG), are distinguished by anterior chamber anatomy. ACG accounts for approximately 26% of glaucoma worldwide and is disproportionately prevalent among women and Asian populations.[28] In India, the prevalence of ACG in individuals over 40 years ranges from 1.26% to 1.5%.[28,29]

The increased susceptibility of women to ACG is attributed to anatomical and age-related factors, including shorter axial length, thicker crystalline lenses, cataract formation, and a shallower anterior chamber, all of which predispose to impaired aqueous humour outflow.[30] Emerging evidence suggests that sex hormones, particularly estrogen, play an important modulatory role in glaucoma pathophysiology. Epidemiological studies indicate that longer lifetime estrogen exposure, reflected by early menarche and late menopause, is associated with a reduced risk of open-angle glaucoma.[31,32] The Rotterdam Study demonstrated a higher prevalence of glaucoma among women with early menopause, supporting a protective role for estrogen.[33] Experimental and clinical studies suggest that estrogen may lower IOP by enhancing trabecular meshwork flexibility through collagen remodelling, increasing nitric oxide (NO) production, reducing episcleral venous pressure, and modulating aqueous humour production.[9] Consistent with these mechanisms, IOP has been observed to decrease during pregnancy and increase after menopause.[34,35]

MHT has therefore been investigated for its potential ocular benefits. Some observational studies report lower IOP and reduced prevalence of retinal nerve fibre layer defects among postmenopausal women receiving estrogen therapy, although results regarding IOP reduction remain inconsistent across studies.[36,37] The heterogeneity likely reflects differences in hormone formulations, therapy duration, and individual susceptibility. Nevertheless, estrogen's demonstrated neuroprotective effects, including antioxidant activity, improved ocular blood flow, and direct protection of retinal ganglion cells, suggest a potential role in slowing glaucomatous neurodegeneration independent of IOP.[38] Progesterone may further influence glaucoma risk through its antagonistic action on glucocorticoid receptors. Endogenous glucocorticoids, such as cortisol, increase IOP by reducing trabecular meshwork permeability. Progesterone competes with glucocorticoids for binding to the glucocorticoid receptor in trabecular meshwork cells, potentially enhancing aqueous humour outflow and mitigating steroid-induced IOP elevation.[39,40] In contrast, elevated testosterone levels have been associated with increased IOP.[41] Testosterone suppresses endothelial nitric oxide synthase (eNOS) activity in the trabecular meshwork, reducing nitric oxide production. This results in increased trabecular stiffness, impaired aqueous outflow through Schlemm's canal, and subsequent elevation of IOP.[42]

Management of glaucoma in postmenopausal women follows standard principles and includes topical medications, laser procedures such as peripheral iridotomy and argon or selective laser trabeculoplasty, and surgical interventions such as trabeculectomy, glaucoma drainage devices, and minimally invasive glaucoma surgery (MIGS).[25] Given the influence of hormonal changes on ocular physiology, menopause represents an important modifier of glaucoma risk, progression, and treatment response, warranting further investigation into personalised, sex-specific management strategies.

OCULAR BLOOD FLOW AND HAEMODYNAMICS

Alterations in ocular blood flow and haemodynamics have been documented in postmenopausal women, with several studies reporting elevated vascular resistance and reduced perfusion in retrobulbar vessels. Specifically, the resistivity index (RI), a surrogate marker of downstream vascular resistance, is significantly increased in the central retinal artery (CRA), temporal posterior ciliary artery (TPCA), and nasal posterior ciliary artery (NPCA) in postmenopausal women, concomitant with reductions in peak systolic velocity (PSV) in these vessels, indicating diminished blood flow.[43] Importantly, these haemodynamic impairments appear at least partially reversible with estrogen therapy after two months of treatment. RI decreased significantly in the CRA, nasal short posterior ciliary artery (NSPCA), and temporal short posterior ciliary artery (TSPCA), and PSV changes in the CRA and TSPCA also suggested improved flow efficiency.[43]

These vascular effects are clinically relevant, given the role of ocular blood flow in the pathophysiology of optic neuropathies such as glaucoma and age-related macular degeneration.[44] However, conflicting evidence exists; for example, a Doppler ultrasonography study comparing women on MHT with controls found no significant differences in flow velocities, resistivity indices, or pulsatility indices in the ophthalmic artery (OA), CRA, or posterior ciliary artery (PCA).[45,46] Such discrepancies may stem from methodological heterogeneity, including differences in MHT formulation and duration, small cohort sizes, and variability in imaging techniques and operator expertise. Nonetheless, the preponderance of evidence supports a beneficial effect of estrogen on ocular perfusion.[47]

PRIMARY VASCULAR DYSREGULATION SYNDROME

Vascular dysregulation refers to an inappropriate regulation of blood flow that fails to adequately meet the tissue's metabolic demands. Primary vascular dysregulation (PVD), formerly termed vasospastic syndrome, is distinguished from secondary vascular dysregulation (SVD) by the absence of an identifiable underlying systemic or local cause. PVD shows a marked female predominance, with a substantially higher prevalence in women than in men, suggesting a hormonal influence on vascular regulation.[48]

Patients with PVD characteristically present with a constellation of systemic and ocular features, including cold extremities, low systemic blood pressure, reduced thirst perception, altered drug sensitivity, increased pain sensitivity, prolonged sleep onset latency, signs of oxidative stress, and a low body mass index. Triggering factors such as cold exposure, emotional or mechanical stress, and fasting can precipitate or exacerbate symptoms.[49] The eye is one of the organs most frequently involved. Ocular manifestations include increased retinal vessel stiffness and irregularity, impaired neurovascular coupling, and reduced autoregulatory capacity. Retinal venous pressure is often elevated, even in the absence of elevated intraocular pressure. These microvascular abnormalities contribute to unstable ocular perfusion and increased susceptibility of the optic nerve head to ischaemic stress.[49]

PVD has been strongly associated with several ocular disorders, most notably normal- tension glaucoma, where vascular factors are considered central to disease pathogenesis.[50] Other reported associations include optic nerve syndrome, central serous chorioretinopathy, Susac syndrome, retinal artery and vein occlusions, and non-atherosclerotic anterior ischaemic optic neuropathy. A higher prevalence of optic disc haemorrhages has also been consistently observed in affected individuals.[51] The syndrome typically manifests at or shortly after puberty and tends to attenuate with advancing age. In women, symptoms often diminish or may disappear after menopause.[51] However, recurrence or worsening of symptoms has been reported in postmenopausal women receiving estrogen replacement therapy, suggesting a modulatory role of estrogen on vascular tone, endothelial function, and autoregulatory mechanisms. This observation supports the hypothesis that estrogen influences susceptibility to vascular dysregulation rather than exerting a uniformly protective vascular effect.[52]

Recent evidence further implicates endothelial dysfunction, mitochondrial instability, and oxidative stress as central mechanisms linking PVD to optic nerve vulnerability, particularly in glaucoma patients with normal intraocular pressure.[53]

AGE-RELATED MACULAR DEGENERATION

Age-related macular degeneration (AMD) is broadly classified into two clinical forms: dry (atrophic or non-neovascular) AMD, which accounts for approximately 80–85% of cases, and wet (neovascular) AMD, which comprises the remaining cases but is responsible for the majority of severe vision loss.[54,55] The dry form is characterised by progressive dysfunction and atrophy of the retinal pigment epithelium (RPE) and overlying photoreceptors, whereas

the wet form is defined by the development of pathological choroidal neovascularisation extending into the subretinal or sub-RPE space, leading to exudation, haemorrhage, and eventual fibrovascular scarring in the macula. Although less prevalent, wet AMD accounts for most cases of legal blindness associated with the disease.[55]

Globally, AMD represents a major public health burden. It was estimated that approximately 196 million people were affected by AMD in 2020, with projections suggesting an increase to nearly 288–300 million by 2040, largely driven by population aging. AMD accounts for approximately 8–9% of global blindness, making it one of the leading causes of irreversible visual impairment worldwide.[56] A large global meta-analysis demonstrated significant ethnic variation in AMD prevalence, with nearly 50% lower prevalence of early and any AMD in Asian populations compared with European white populations (early AMD: 6.8% vs 11.2%; any AMD: 7.4% vs 12.3%).[57]

Advancing age is the most important risk factor for AMD in both sexes. Women, on average, have a longer life expectancy than men, which may partly explain the higher crude prevalence of AMD observed in females in population-based studies.[58,59] However, recent large meta-analyses and pooled data analyses have reported no consistent sex-specific difference in AMD prevalence after adjusting for age, suggesting that longevity rather than biological sex per se may account for observed differences.[60] Established risk factors for AMD include genetic susceptibility, white ethnicity, cigarette smoking, poor dietary antioxidant intake, obesity, hyperopia, and lens opacities. Smoking remains the strongest modifiable risk factor, conferring a dose-dependent increase in AMD risk. Other proposed risk factors, such as cardiovascular disease, sunlight exposure, iris colour, and alcohol consumption, have shown inconsistent associations across studies.[61,62]

The role of estrogen exposure, whether endogenous or exogenous, in AMD risk remains controversial. Several epidemiological studies have suggested that early menarche, late menopause, longer reproductive lifespan, and prolonged lactation are associated with a reduced risk of AMD, as reported in the Blue Mountains Eye Study and other cohorts.[63] Some observational studies have also suggested protective effects of oral contraceptive use and MHT. However, these findings have not been consistently replicated, and other population-based studies and meta-analyses have failed to demonstrate a significant association between estrogen exposure or HRT use and AMD risk. As a result, no definitive protective or harmful role of estrogen can currently be established.[64]

Biologically, estrogen acts via ERα and ERβ, with ERα identified in the human retina and RPE. The RPE plays a central role in AMD pathogenesis by regulating photoreceptor maintenance, extracellular matrix turnover, and inflammation. Estrogen regulated genes influence oxidative stress responses, angiogenesis, and extracellular matrix remodelling, suggesting that fluctuations in estrogen levels, particularly after menopause, may alter RPE resilience and susceptibility to degeneration.[65] AMD pathogenesis involves a complex interplay of oxidative stress, chronic low-grade inflammation, complement activation, and pathological angiogenesis.[66] Estrogen possesses antioxidant and anti-inflammatory properties, and its withdrawal after menopause has been hypothesised to exacerbate oxidative damage within the retina and RPE.[65,67]

Several studies have demonstrated a significant association between AMD and cataract, supporting the existence of shared pathogenic mechanisms related to oxidative stress and ageing.[68] Interest has also focused on dehydroepiandrosterone sulphate (DHEAS), an adrenal steroid and precursor of estrogen and testosterone. An inverse relationship between serum DHEAS levels and AMD severity was reported in earlier studies, suggesting a potential protective role.[69] However, more recent investigations have failed to demonstrate a significant association between circulating DHEAS levels and neovascular AMD, indicating that its role, if any, remains uncertain.[70]

DIABETIC RETINOPATHY

Diabetic retinopathy accounts for approximately 1% of all visual impairment worldwide. Although it contributes less significantly, there is an apparent increasing trend in prevalence due to rising diabetes rates and longer life expectancy. It is also the leading cause of preventable blindness among working-age individuals, with a significant economic impact on society.[71] About 22.3% of all diabetic patients, regardless of type, develop diabetic retinopathy, making it one of the most common complications of diabetes.[71]

Among men, diabetic retinopathy prevalence increased with increasing testosterone levels but decreased with increased prolactin levels. Among women, high follicle-stimulating hormone (FSH) and luteinising hormone (LH) levels were linked with increased diabetic retinopathy prevalence. No associations were found in premenopausal women, but postmenopausal women with high prolactin levels had increased diabetic retinopathy prevalence.[72]

Diabetic retinopathy is a microvascular disorder of diabetes, which may be classified as either non-proliferative or proliferative. The latter is a more severe condition in which abnormal blood vessels develop in the retina, leading to leakage, vitreous haemorrhage, and, eventually, fibrotic strands extending from the retina into the vitreous, with a risk of retinal detachment. In addition, diabetes may also result in macular oedema.

The menopausal transition is characterised by declining estrogen levels, increased insulin resistance, central adiposity, and greater glycaemic variability, all of which can accelerate retinal microvascular damage and contribute to the onset or progression of DR.[73,74] Recent reviews found that in the majority, there was an insignificant gender difference regarding diabetic retinopathy, while some reported a higher predisposition for males.[75,76] In addition, a recent Japanese study has reported that women with type 2 diabetes mellitus have a higher predisposition for advanced diabetic retinopathy at baseline and that the female sex is an independent risk factor for the progression of diabetic retinopathy.[77] Estrogens exert protective effects on the retinal vasculature through modulation of nitric oxide synthesis, inhibition of leukocyte adhesion, reduction of oxidative stress, and stabilisation of the blood–retinal barrier.[78]

Experimental studies have demonstrated that estrogen deficiency exacerbates retinal capillary degeneration and pericyte loss, while estrogen supplementation attenuates retinal inflammation and vascular leakage in diabetic models. These findings suggest that menopause-related hypoestrogenism may increase susceptibility to DR progression.[79] Clinical evidence regarding MHT and DR remains limited but suggestive of potential benefit. Observational studies indicate that postmenopausal women using MHT may have a lower prevalence or slower progression of DR compared with non-users, possibly due to improved glycaemic control, enhanced insulin sensitivity, and favourable vascular effects.[80] Estrogens can exert differential effects depending on the stage of retinopathy: during the initial stages, estradiol-induced endothelial cell proliferation has a beneficial effect, protecting the retina by promoting repair, whereas during the proliferative stage, the same effect exacerbates the disease.[81] However, the impact of MHT appears to depend on factors such as duration of therapy, formulation (estrogen-only versus combined estrogen–progestin), and baseline metabolic risk. Large randomised trials specifically evaluating DR outcomes in MHT users are lacking, and current evidence does not support the use of MHT solely for the prevention or treatment of diabetic retinopathy.[82,83]

Overall, menopause may represent a period of increased vulnerability to diabetic retinal microvascular damage, while estrogen replacement may confer indirect retinal protection through systemic metabolic and vascular effects. Further prospective, mechanistic studies are needed to clarify MHT's role in modifying DR risk and to identify patient subgroups that may benefit most.

CATARACT

Cataract is the leading cause of blindness worldwide in both sexes, with advancing age being the strongest risk factor. Population-based studies from India have demonstrated a high prevalence of unoperated cataract among individuals aged ≥60 years, estimated at approximately 58% in North India and 53% in South India. The prevalence of cataract increases with age and is consistently higher in women than in men, with women having nearly 1.5–2 times higher odds of cataract; this excess risk is not fully explained by differences in access to cataract surgery.[84]

The pathogenesis of cataract is multifactorial and includes genetic predisposition, oxidative stress, metabolic abnormalities, ultraviolet radiation exposure, and ageing-related biochemical changes in the lens. Experimental and epidemiological studies suggest that estrogen may protect against cataractogenesis through its antioxidant, anti-inflammatory, and anti-apoptotic properties. Consequently, estrogen withdrawal during menopause has been hypothesised to increase susceptibility to age-related cataract.[30,85] Recent large cohort studies and meta-analyses have reported an association between menopausal status and increased risk of nuclear and cortical cataracts, particularly in women with earlier age at menopause.[30] Greater lifetime exposure to endogenous estrogen, reflected by early menarche and late menopause, has been associated with a reduced risk of cataract in several observational studies.[86]

The effect of exogenous hormones remains inconclusive. Some studies suggest a modest protective association of oral contraceptive use or MHT, particularly for nuclear cataract, whereas others have demonstrated no benefit or a small increase in risk depending on hormone formulation, duration of use, and timing relative to menopause.[87,88] Overall, current evidence does not support a consistent association between total reproductive span and cataractogenesis, and hormone therapy is not recommended solely for cataract prevention.[89]

REFRACTIVE ERRORS AND MENOPAUSE

Menopause is associated with subtle but clinically relevant changes in refractive status, reflecting the influence of sex hormones on multiple ocular structures. Population-based studies in older women demonstrate an age-related shift toward hyperopia, with a higher prevalence in females, suggesting that postmenopausal hormonal changes may contribute to refractive alterations beyond chronological ageing alone.[90]

ERs have been identified in the cornea, lens, ciliary body, and retina, and estrogen is known to regulate corneal thickness, curvature, and lens metabolism; therefore, declining estrogen levels after menopause may alter the refractive index of the lens and reduce accommodative capacity, leading to relative hyperopia and earlier manifestation of presbyopia.[91] In addition, postmenopausal women exhibit an increased prevalence of against-the-rule astigmatism, which is thought to result from age- and hormone-related changes in corneal biomechanics and eyelid tension.[91]

MHT appears to exert variable effects on refraction: some studies suggest stabilisation or mild myopic shifts, while others report no significant refractive change, indicating that the impact of exogenous hormones depends on formulation, dose, and duration of therapy.[92] Overall, refractive changes around the menopausal transition are multifactorial and should be interpreted in the context of hormonal status, ocular surface health, and coexisting age-related lenticular changes.

GENERAL RISK FACTORS FOR OCULAR DISEASES IN WOMEN

- Lack of awareness and underutilisation of regular ophthalmic checkups after 40 years of age.
- Early menopause, including surgically induced menopause at a younger age.
- Childhood malnutrition leads to long-term ocular susceptibility.
- Hormonal imbalance affecting ocular surface, lens, and retinal health.
- Inappropriate or prolonged use of drugs can cause ocular adverse effects.
- Hormonal changes after menopause increase the risk of ocular diseases.
- Environmental exposures such as smoke, pollution, dry air, and prolonged screen use.
- Medical disorders such as diabetes mellitus and hypertension increase the risk of retinopathy, cataract, glaucoma, and vascular ocular diseases.[93]

PREVENTION OF OCULAR PROBLEMS AT MENOPAUSE

Lifestyle factors such as unhealthy diet, physical inactivity, smoking, and excessive alcohol consumption adversely affect ocular health. Smoking is a well-established risk factor for cataract and AMD and should be strongly discouraged.[94] Women should be encouraged to preserve eye health through a balanced diet rich in antioxidants, including vitamins A, C, and E, omega-3 fatty acids, and zinc, which have been shown to support retinal and ocular surface health.[95] Limiting alcohol intake is particularly beneficial in women with dry eye disease, and protection from excessive ultraviolet exposure may reduce the risk of cataract and AMD.Estrogen is believed to protect ocular tissues, possibly through vasodilatory, antioxidant, and neuroprotective mechanisms.[4] Observational studies suggest that hormone therapy in postmenopausal women may reduce the risk of AMD and glaucoma; however, findings are inconsistent.[37] MHT should be individualised and guided by systemic indications rather than solely by ocular benefit.[96]

SYNOPSIS

- Women have higher rates of visual impairment and blindness, particularly after age 50.
- Menopause-related hormonal withdrawal is a major contributor to this sex disparity. Estrogen,
- progesterone, and androgens are expressed in the cornea, retina, lacrimal glands, and meibomian glands.
- Hormonal balance regulates tear production, intraocular pressure (IOP), extracellular matrix remodelling, ocular blood flow, and retinal neuroprotection. Occurs about twice as often in women as in men.

- Hormonal imbalance disrupts lacrimal and meibomian gland function. Women with premature ovarian insufficiency may develop dry eye independent of tear volume. More prevalent in women than men.
- Estrogen withdrawal increases oxidative stress in the lens, raising cataract risk. Longer reproductive lifespan (early menarche, late menopause) may have a protective effect.
- Angle-closure glaucoma is more common in women due to anatomical factors and menopausal age-related risk.
- Estrogen may lower IOP by improving trabecular meshwork function and provides retinal ganglion cell neuroprotection. Early menopause is associated with increased glaucoma prevalence.
- The female predominance of AMD partly reflects longer life expectancy and menopause-related hormonal changes. Early menopause increases AMD risk; longer reproductive lifespan may be protective.
- Estrogen regulates retinal pigment epithelium (RPE) genes involved in extracellular matrix turnover and inflammation.
- Evidence for sex differences in DR is mixed. Postmenopausal hormonal changes (elevated FSH, LH, prolactin) may worsen disease severity.
- Menopause represents a critical window for the onset or acceleration of ocular disease.
- Awareness of hormone-related mechanisms supports earlier screening in midlife women.
- Multidisciplinary care involving ophthalmology and endocrinology may improve prevention and outcomes

RESEARCH AGENDA

Correlate ocular biological age with age at menopause, reproductive lifespan, and circulating sex hormone profiles.

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SKIN AND HAIR

Keywords: Effects of menopause, vulva, vagina, photoaging, melasma, management, alopecia, hirsutism, cosmetics.

21

INTRODUCTION

The skin is the body's largest organ and serves as a physical barrier against mechanical, microbial, and environmental insults. Sweat, sebaceous secretions, and oils derived from epidermal cellular debris form a natural emulsion that helps maintain skin softness and moisture.[1] The skin is composed of two main layers, the outer epidermis and the underlying dermis. The epidermis is continuously renewed by cells originating from the dermis. The dermis contains sweat glands, hair follicles, blood vessels, and a substantial amount of fibrous connective tissue, predominantly collagen.[2] Collagen is a major structural component of skin and bone and is responsible for the skin's strength, resilience, and thickness. It is produced by fibroblasts, which possess estrogen receptors. Estrogen stimulates collagen synthesis by fibroblasts and promotes biochemical changes that increase dermal water content, thereby contributing to skin firmness and elasticity.[3] The stratum corneum, comprising the outermost few microns of the skin surface, contains the principal defence mechanisms responsible for pH regulation, anti-inflammatory action, mechanical protection, selective permeability, hydration, and thermal regulation. Natural moisturising factors within the stratum corneum include free amino acids, lactic acid, urea, and salts. In addition, intracellular lipids form multilamellar structures that trap water and prevent excessive trans epidermal water loss.[4] Skin surface pH is typically maintained between 4 and 6, whereas the body's internal environment remains near neutral. This acidic surface environment, known as the acid mantle, plays a crucial role in protecting the skin against microbial invasion and maintaining barrier integrity.[5] Normal vaginal pH in reproductive-age women ranges from 3.8 to 4.2 and is maintained primarily by lactobacilli, which produce lactic acid and other antimicrobial substances such as hydrogen peroxide, lactacin, and acidophilin. Estrogen-dependent glycogen deposition in the vaginal epithelium supports the growth of lactobacilli. Together, the vaginal mucosa and skin, through their keratinised epithelium and acid mantle, form a stable protective ecosystem.[6]

AGE, MENOPAUSE AND SKIN

As with other organ systems, ageing and menopause significantly affect the skin, the body's largest organ. Skin ageing results from the interaction of intrinsic factors (genetic and chronological ageing) and extrinsic factors such as ultraviolet (UV) exposure, poor nutrition, smoking, and alcohol consumption.[7] Many age-related cutaneous changes are not due solely to senescence but are influenced by concomitant degenerative processes, among which estrogen deficiency during the climacteric period plays a major role.[3] Estrogen influences nearly every organ system, including the skin. Estrogen and androgen receptors are present in dermal fibroblasts, the epidermis, hair follicles, sebaceous glands, blood vessels, and sweat ducts. Estrogen receptors are unevenly distributed across the body, with higher densities in the genital region, face, and lower limbs, making these areas particularly susceptible to reduced circulating estrogen levels. This distribution explains why certain skin conditions are more prevalent in peri- and postmenopausal women.[8] In these regions, estrogen receptors are predominantly localised in the epidermis, sebaceous units, hair follicles, and sweat ducts and may influence corneocyte size and epidermal turnover. Estrogen receptors are relatively sparse in the dermis and sweat glands. A high estrogen receptor–to–androgen receptor ratio is observed in the vagina, whereas the reverse is seen in the vulva. Both estrogen and progesterone receptor expression in the skin decline progressively after the climacteric.[9] During the first 4–5 years after menopause, up to 30% of skin collagen may be lost, with an average decline of approximately 2.1% per year thereafter.[10,11]

EFFECT OF ESTROGEN DEFICIENCY ON VARIOUS LAYERS OF SKIN

Epidermis And Epidermal Structure

Skin thickness decreases progressively with increasing menopausal age. Brincat et al. demonstrated that mean skin thickness declines from approximately 0.88 mm at the onset of menopause to about 0.69 mm after 10 years, independent of chronological aging. Importantly, this reduction in skin thickness and collagen content showed a strong correlation with the duration of estrogen deficiency rather than with chronological age, indicating that hypoestrogenism is a key determinant of postmenopausal skin changes.[10,11]

Dermis

Estrogen plays a crucial role in maintaining dermal thickness and structural integrity by preventing dermal atrophy and preserving collagen and elastic fibres. Hair follicles and sebaceous glands are sex-steroid–responsive target structures that express estrogen and androgen receptors.[3,8] With menopause, declining estrogen levels and a relative increase in androgenic influence lead to flattening of epidermal ridges and dermal papillae, along with a progressive reduction in scalp and body hair follicle density.[8] Hormonal imbalance during menopause alters hair growth patterns, resulting in scalp hair thinning and darkening and thickening of fine facial hair, reflecting increased androgen sensitivity.[12] Sebaceous gland activity decreases with estrogen deficiency, and glands become less responsive to physiological stimuli, contributing to reduced sebum production.[3,13] Additionally, diminished sweat and sebaceous gland activity, combined with epidermal thinning, results in dry, fragile, and easily traumatised skin, often associated with pruritus.[13] Recent observational and interventional studies indicate that women receiving menopausal hormone therapy (MHT) have significantly better skin hydration and elasticity, with a lower prevalence of dry, wrinkled skin compared to non-users. Estrogen has been shown to enhance collagen synthesis and elastic fibre content, thereby helping to delay or partially reverse wrinkle formation.[9,14]

Hormone Therapy And The Dermal Microvasculature

The dermal microvasculature comprising arterioles, capillaries, and venules differs from that of other organs because of the unique structural organisation and thickness of skin blood vessels. Estrogens play an important regulatory role in cutaneous vascularisation and microvascular tone in women.[8] Menopausal flushing reflects episodic vasodilation, most prominently affecting the face, neck, chest, palms, and soles, and represents an active neurovascular process influenced by estrogen deficiency and dermal connective tissue remodeling.[8] Flush prevalence during the early climacteric phase is primarily due to estrogen depletion, which impairs the regulation of peripheral microvascular tone. Several studies suggest that these vasomotor symptoms partially diminish with MHT. In addition, maximal inducible vasodilation has been reported to be lower in climacteric women receiving hormone therapy compared with untreated postmenopausal women, indicating improved vascular stability.[15] Estrogen also influences skin pigmentation, as melanocytes express estrogen receptors and respond to estrogen by modulating melanin synthesis. Additionally, estrogen enhances blood flow through small dermal vessels and supports vascular proliferation. There is substantial evidence that estrogen exerts anti-inflammatory and immunomodulatory effects, partly resembling glucocorticoid activity, thereby contributing to improved barrier function and reduced inflammatory responses in the skin.[3,16]

Overall, menopause is consistently associated with declining collagen content, reduced elasticity, and decreased skin thickness, changes that are closely linked to estrogen deficiency rather than chronological ageing alone. Hormone therapy may mitigate some of these alterations, although its effects vary depending on duration, formulation, and timing of initiation.

Estrogen Therapy

The effects of hormone therapy on the skin have long attracted clinical and scientific interest; however, evidence regarding its efficacy remains heterogeneous. Current data suggest that short-term hormone therapy does not result in substantial structural improvement of the skin, particularly with respect to collagen content and thickness. The greatest protective effect against skin ageing appears to occur when hormone therapy is initiated during the perimenopausal or early postmenopausal period, supporting the concept of a “window of opportunity” for estrogen action on the skin.[3,8] While estrogen therapy has been shown to improve skin hydration, elasticity, and collagen content, its impact varies depending on treatment duration, formulation, route of administration, and timing of initiation. At present, the role of phytoestrogens and the clinical relevance of environmental endocrine disruptors in managing climacteric skin changes remain unproven, with insufficient high-quality evidence to support their routine use in menopausal women.

Scope For Hormone Therapy Use

There is a limited but growing scope for the use of topical or systemic hormonal therapies in dermatology, particularly for selected hypoestrogenic states. However, hormone therapy is not recommended solely as an anti-ageing intervention, and its use must be guided by systemic indications and individualised risk–benefit assessment.[3,9] In contrast, topical retinoids have robust evidence supporting their role in skin ageing. Retinoids stimulate collagen

synthesis, normalise keratinocyte differentiation, and improve elastic fibre organisation, leading to clinically measurable reductions in fine wrinkles and improvement in skin texture. As such, retinoids remain the first-line, evidence-based therapy for photoaging, irrespective of menopausal status.[17,18]

Beneficial Effects Of Hormone Therapy On The Skin

MHT exerts several beneficial effects on the skin through estrogen receptor–mediated actions on keratinocytes, fibroblasts, endothelial cells, and extracellular matrix components. At the epidermal level, estrogen therapy has been shown to reduce epidermal atrophy, enhance the water-holding capacity of the stratum corneum, and improve epidermal barrier function, resulting in better hydration and reduced transepidermal water loss.[3,8,9] Within the dermis, estrogen therapy is associated with increased dermal thickness, enhanced hyaluronic acid turnover, and a consequent rise in dermal water content. Estrogen stimulates fibroblast activity, leading to increased type III collagen synthesis, improved collagen organisation, and morphological restoration of elastic fibres. These changes contribute to improved dermal resilience, with increased numbers, thickness, and vertical orientation of collagen and elastic fibres.[9,11,16] The overall cutaneous effects of estrogen therapy include a measurable increase in skin thickness (approximately 7–15%), reduced skin slackness, and decreased mechanical extensibility, thereby improving skin firmness. Estrogen has also been shown to enhance DNA repair capacity and mitigate skin dryness and fine wrinkling, particularly when therapy is initiated during the perimenopausal or early postmenopausal period.[11,14,16] Despite these benefits, hormone therapy may be associated with cutaneous adverse effects, primarily related to estrogen receptor activation. Hypersensitivity reactions, including irritation or contact dermatitis, may occur with transdermal preparations due to sensitivity to patch adhesives. Pigmentary changes, particularly melasma, have been reported with systemic estrogen use. Uncommon cutaneous adverse effects include acanthosis nigricans, erythema multiforme, photosensitivity reactions, pompholyx, spider telangiectasia, stomatitis, and urticaria, although these are infrequent and generally reversible upon discontinuation of therapy.[14,19,20]

COMMON SKIN CONDITIONS IN POSTMENOPAUSAL WOMEN

Table 2: Common skin conditions seen in perimenopausal and postmenopausal women

Atrophic vulvovaginitis	• Thinning (atrophy) of vaginal skin including the entrance to the vagina (vestibule). • The vulva is less affected (it has fewer estrogen receptors than the vagina) • Symptoms include itchiness, tenderness, a burning sensation dyspareunia, painful urination
Skin changes	• Skin becomes thin and dry (xerosis) • Easy bruising • Glow decreases, nails become brittle • Hyperpigmentation
Vaginitis	• There are several causes • There may be a profuse discharge is present
Vulvar lichen sclerosus (VLS)	• Chronic, atrophic skin disease that affects mainly the anogenital area • May be asymptomatic in some patients • Signs and symptoms include: • Itching and irritation • White, thinned, wrinkled skin • Recurrent fissures of posterior Fourchette (vaginal tears) • Painful intercourse • Labial fusion • Possible association with autoimmune disorders

Vulvodynia	• Chronic vulvar burning, irritation, stinging and rawness (rather than itch) • May also involve the thighs • Cause is not known (thought to be neurological)
Hirsutism	• Facial hirsutism is very common in postmenopausal women not on hormone therapy
Alopecia	• Approximately one-third of postmenopausal women on the frontal area
Menopausal flushing	• Occurs in 70–85% of women throughout the perimenopausal stage • Reddening of the face, neck and upper chest that lasts 3–5 minutes and subsides quickly • May be associated with sweating, palpitations, anxiety and sleep problems
Keratoderma climactericum	• Thickening of skin on the palms and soles • Occurs more commonly in obese postmenopausal women • May be itchy and painful cracking and splitting may occur

ATROPHIC OR SENILE VULVOVAGINITIS

Atrophic or senile vulvovaginitis is a common condition in peri- and postmenopausal women resulting from estrogen deficiency, leading to thinning of the vaginal epithelium, reduced glycogen content, and loss of lactobacilli. These changes increase vaginal pH, disrupt the normal vaginal microbiota, and increase susceptibility to irritation and infection. Clinically, it presents with vaginal dryness, burning, itching, dyspareunia, postcoital bleeding, and recurrent urinary symptoms. The vulvovaginal tissues appear pale, dry and fragile, with loss of elasticity and rugal folds. Estrogen therapy, particularly local vaginal estrogen, effectively restores epithelial thickness, lowers vaginal pH, improves symptoms, and re-establishes a healthy vaginal ecosystem.[21,22]

VAGINITIS

Vaginitis results from disruption of the acid mantle and epithelial barrier of the vaginal mucosa and adjacent perineal skin, predisposing to inflammation and infection. Metabolic conditions such as diabetes mellitus increase susceptibility to infectious vulvovaginitis, including candidiasis, diabetic vulvitis, and secondary bacterial or fungal infections, such as tinea cruris, due to altered local immunity and higher surface pH.[23]

Irritant and allergic (atopic) dermatitis are common non-infective causes and are frequently triggered by sanitary pads, medicated douches, depilatory agents, vaginal creams and spermicides, excessive use of alkaline soaps, and prolonged moisture exposure.[24,25] In addition, psychological stress has been shown to impair epidermal barrier function through neuroendocrine mechanisms, particularly increased glucocorticoid release, leading to immune dysregulation and exacerbation of inflammatory dermatoses involving the vulvovaginal region.[26,27]

VULVAR LICHEN SCLEROSUS (VLS)

VLS is a chronic, inflammatory dermatosis of the vulva that predominantly affects postmenopausal women. The aetiology is multifactorial, with strong evidence supporting an autoimmune basis, genetic susceptibility, and contributory effects of hypoestrogenism, explaining its higher prevalence after menopause.[28,29] Refractory or treatment-resistant disease should raise suspicion of vulvar intraepithelial neoplasia or vulvar squamous cell carcinoma, as VLS carries a malignancy risk of approximately 3–5%.[30] Symptoms: Patients may be asymptomatic or present with progressive symptoms, the most common being intense vulvar pruritus. Fissuring, excoriations, and scarring may result in dysuria, dyspareunia, pain during defecation, and rectal bleeding, particularly in advanced disease.[31]

Examination: VLS classically presents with porcelain-white, shiny, atrophic plaques with a “cigarette-paper” or crinkled appearance in a figure-of-eight distribution involving the vulva and perianal region. The vagina is typically spared. Long-standing disease may lead to loss of labia minora, clitoral phimosis, introital narrowing, and architectural distortion. Bullae or erosions suggest severe inflammation, secondary infection, or coexisting neoplasia.[31,32]

Treatment: Topical ultrapotent corticosteroids, particularly clobetasol propionate 0.05%, remain the gold standard. Current evidence supports daily application for 4–12 weeks, followed by long-term maintenance therapy (1–2 times weekly), which is effective and safe in preventing relapses and reducing malignant transformation.[33,34] Topical calcineurin inhibitors (pimecrolimus or tacrolimus) are recommended as second-line therapy for steroid-intolerant or refractory cases.[35] Adjunctive nonpharmacologic measures, including avoidance of irritants, gentle skin care, emollients, and patient education, significantly improve symptom control and quality of life.[36] Surgery and Follow-up: Surgery is reserved for biopsy-proven malignancy or severe scarring causing functional impairment. Regular follow-up is essential initially at 1–3 months, then annually once stable, to assess treatment response, adherence, and early detection of neoplastic change.[37]

VULVODYNIA

Vulvodynia is a chronic vulvar pain disorder characterised by vulvar discomfort or burning pain lasting ≥ 3 months, in the absence of identifiable visible or neurologic pathology. It may be localised (most commonly vestibulodynia, previously termed vulvar vestibulitis) or generalised, and may be provoked, spontaneous, or mixed.[38] Vulvodynia represents a heterogeneous constellation of disorders and remains under-recognised, despite its substantial negative impact on sexual function, psychological well-being, and overall quality of life.[39] Reported prevalence varies widely, ranging from 1% to 16% in population-based studies, with some surveys reporting lifetime prevalence of 20% or more, reflecting differences in diagnostic criteria and study design.[40,41] The aetiology is multifactorial and incompletely understood, with proposed mechanisms including genetic susceptibility, immune and inflammatory dysregulation, prior vulvovaginal infections, neuropathic pain mechanisms, pelvic floor muscle dysfunction, and central pain sensitisation. Associations with urinary oxalates and hormonal factors have been suggested but remain unproven.[38] Clinically, patients report burning, stinging, irritation, or rawness, often without objective findings on examination, making the diagnosis primarily clinical and one of exclusion.[42]

History: A detailed pain history is essential and should include duration, nature, location, timing, and aggravating or relieving factors. Standardised tools such as the McGill Pain Questionnaire help characterise pain quality and severity and monitor treatment response.[43]

Clinical Examination: Examination often reveals severe tenderness in the absence of visible pathology. The cotton swab (Q-tip) test is central to diagnosis, with gentle pressure applied to the vestibule at the 2, 4, 6, and 10 o'clock positions, and pain graded as mild, moderate, or severe to localise and map pain and aid follow-up.[38] Speculum and bimanual examinations are performed to exclude vaginal or pelvic pathology and are often normal.[42]

Investigations: Investigations are directed at excluding secondary causes and may include pelvic ultrasonography and, rarely, vulvar biopsy when dermatoses, neoplasia, or inflammatory disease is suspected. Routine imaging is otherwise not required.[38,42]

General Vulvar Care

Conservative measures form the foundation of management and include the use of cotton underwear, avoiding occlusive clothing, cleansing with water or non-irritant washes, avoiding douches and irritants, and ensuring adequate lubrication during intercourse. Emollients such as petroleum jelly or vegetable oils help restore barrier function, while cool gel packs may provide symptomatic relief during pain flares.[44]

Medical and Non-pharmacological Management: First-line pharmacologic therapy includes topical 5% lidocaine, applied nightly or before intercourse, which has demonstrated benefit in reducing provoked pain.[45] Neuropathic pain modulators, including tricyclic antidepressants (such as amitriptyline) and gabapentinoids, are commonly used for generalised or refractory pain. Topical estrogen may be beneficial in hypoestrogenic women, particularly postmenopause, while evidence for soy isoflavones and vitamin D preparations remains limited and inconclusive.[46] Adjunctive therapies such as pelvic floor physical therapy, biofeedback, and cognitive behavioural therapy have strong evidence for improving pain and sexual function and are recommended as part of a multimodal approach.[47] Intralesional injections are reserved for selected refractory cases. Surgical intervention, such as vestibulectomy is considered only for severe, localised provoked vestibulodynia unresponsive to conservative and medical therapies.[48]

MENOPAUSAL FLUSHING. Refer to chapter 9

XEROSIS, PRURITUS, AND DERMATITIS IN MENOPAUSE

 Xerosis (dry skin) and pruritus are among the most common dermatologic complaints during the menopausal

transition. Observational studies show that eczema-like eruptions and dermatitis are frequently reported in peri- and postmenopausal women. Declining estrogen levels impair epidermal barrier function by reducing ceramide synthesis, increasing transepidermal water loss (TEWL), and decreasing natural moisturising factors. These alterations lead to skin dryness, heightened sensitivity, and susceptibility to inflammatory dermatoses.[3,49] Management of xerosis, pruritus, and dermatitis during menopause centres on improving epidermal barrier dysfunction secondary to estrogen deficiency. Regular application of fragrance-free emollients containing ceramides, humectants, and occlusives reduces TEWL and relieves dryness and pruritus.[8,50] Avoidance of harsh soaps, hot baths, and environmental irritants is essential to prevent further barrier disruption.[3] Short courses of mild topical corticosteroids are effective for eczema-like inflammatory dermatoses, while antipruritic agents and non-sedating antihistamines may provide symptomatic relief.[50] Although MHT has been shown to improve skin hydration and barrier function, it is not recommended solely for dermatologic symptoms and should be individualised based on overall risk–benefit assessment.[50]

MENOPAUSE-ASSOCIATED ACNE

Acne in menopausal women typically affects the lower face, jawline, and chin, presenting as open/closed comedones, papules, pustules, and occasionally nodules. Pathophysiology is primarily related to a relative increase in androgen activity due to estrogen decline, unopposed adrenal and ovarian androgens, altered sebum composition, and localised inflammation.[51] Several factors that have been postulated to trigger or aggravate adult acne also play a role in menopausal acne, such as cosmetics, dietary factors, obesity, smoking, UV radiation, drugs, sleep deprivation and stress.[52] The approach to laboratory investigations depends on the clinical examination and associated features. If the patient has associated signs of hyperandrogenism such as hirsutism and female pattern hair loss, then a hormonal evaluation is warranted.[51] Several studies on humans have demonstrated that weight loss, exercise, adequate sleep, stress reduction, smoking cessation, a healthy diet with a low glycemic load, and avoiding milk can all help reduce acne.[53] Treatment is a challenge in clinical practice as most anti-acne products are designed for adolescent oily skin, with fewer products for sensitive mature skin in this age group. Prolonged topical therapy with judicious use of systemic therapy is the treatment of choice as acne tends to be more resistant, deep-seated and prolonged in this subset.[51] The use of a topical antibiotic as monotherapy should be avoided, and combination therapy with benzoyl peroxide, topical retinoids, azelaic acid, or salicylic acid is recommended as first-line treatment, based on the patient's skin type and tolerability, including an oral agent if necessary.[51] Spironolactone is the treatment of choice for patients requiring systemic antiandrogen therapy.[54] Procedural treatment can play a bigger role, as it can also help treat acne scars and concomitant skin ageing.[51]

KERATODERMA CLIMACTERICUM

Keratoderma climactericum, also known as climacteric keratoderma, Haxthausen's disease, or acquired palmoplantar keratoderma, is a rare disorder characterised by progressive hyperkeratosis of the palms and soles, typically beginning around menopause. The condition predominantly affects postmenopausal women and is thought to be related to estrogen deficiency, although the exact pathogenesis remains unclear.[55] Lesions usually develop initially at plantar pressure points, leading to painful fissures and difficulty in walking, while palmar involvement is often mild or discrete. Evaluation should include exclusion of secondary causes such as contact dermatitis, fungal infections, nutritional deficiencies (including vitamin A), and endocrine disorders, particularly hypothyroidism, which is a well recognised association with acquired palmoplantar keratoderma and should be suspected when systemic symptoms coexist.[56,57] Management is largely symptomatic, with topical keratolytics (salicylic acid, urea, lactic acid) and topical corticosteroids forming the mainstay of treatment. Emollients and avoidance of mechanical stress are essential adjuncts. In refractory cases, topical or systemic retinoids may be considered under specialist supervision.[20,58]

COSMOCEUTICALS

The term cosmeceuticals, introduced by Albert M. Kligman in the 1980s, refers to topical products that bridge cosmetics and pharmaceuticals by providing aesthetic benefits along with biologically active ingredients that influence skin function (Kligman, 1984). Cosmeceuticals are commonly categorised as anti-ageing agents, sunscreens, moisturisers, antioxidants, depigmenting agents, scar-reducing products, hair care actives, and condition-specfiic formulations such as those for acne or rosacea.[59]

MELASMA IN MENOPAUSE

Melasma is an acquired hyperpigmentation disorder of the face, presenting as sharply demarcated, brown patches, most commonly in a centrofacial pattern, though malar or mandibular distributions may occur. While melasma is more frequent in women of reproductive age, it can also occur or persist in postmenopausal women, particularly those with higher Fitzpatrick skin phototypes (III–V).[60] In menopause, estrogen deficiency contributes to skin thinning, impaired barrier function, and increased susceptibility to pigmentary disorders, potentially exacerbating melasma.[61] Management in menopausal women emphasises strict photoprotection, as UVB, UVA, and visible light remain potent triggers. Broad-spectrum sunscreens with physical blockers (titanium dioxide, zinc oxide, iron oxides) are preferred, especially in skin of color.[62] Topical depigmenting agents, notably triple-combination therapy (hydroquinone, tretinoin, corticosteroid), remain first-line, while adjuncts like chemical peels, retinoids, and light-based therapies may provide additional benefit. Oral tranexamic acid is emerging as a systemic option for refractory cases, although careful monitoring is required.[60-63] Evening/night routines focus on tissue repair using retinoids or depigmenting agents, whereas morning care prioritises antioxidants, photoprotection, and moisturisation. Long-term maintenance therapy is essential to prevent recurrence, which is common in menopausal women due to chronic pigmentary instability.[61,62]

PHOTOAGING IN MENOPAUSE (RHYTIDS AND DYSCHROMIA)

Menopause accelerates intrinsic and extrinsic skin ageing due to estrogen deficiency, which reduces collagen synthesis, elastic fibre integrity, dermal water content, and epidermal turnover. Clinically, postmenopausal women experience thinning skin, increased wrinkling (rhytids), dryness, and uneven pigmentation (dyschromia), which are further exacerbated by cumulative UV and visible light exposure.[3,49] Estrogen depletion also compromises antioxidant defences, making menopausal skin more susceptible to photodamage.[64] Cosmeceuticals play a central role in managing photoaging in menopause. Topical antioxidants (vitamin C, E, ferulic acid), peptides, and retinoids improve collagen synthesis, epidermal turnover, and pigmentation, reducing visible rhytids and dyschromia.[65] Chemical peels and superficial resurfacing techniques enhance keratinocyte turnover, improving skin texture and pigment distribution.[66] Laser and light-based therapies are effective adjuncts. Non-ablative fractional lasers, intensed pulsed light (IPL), and radiofrequency devices stimulate neocollagenesis with minimal downtime, whereas ablative CO_2 and Erbium-doped Yttrium-Aluminum Garnet (Er:YAG) lasers remodel deeper dermal structures but require longer recovery times.[67] Combining cosmeceuticals with energy-based devices optimises outcomes, particularly in postmenopausal skin, where intrinsic collagen deficits amplify photoaging.[68] Treatment principles for menopausal women emphasise rigorous photoprotection, morning antioxidant and sunscreen application, and evening repair strategies using retinoids and depigmenting agents. Maintenance therapy is essential to prevent recurrence of dyschromia and progression of rhytids.

HAIR CHANGES IN MENOPAUSE

Many women experience changes in hair patterns during midlife, including scalp hair thinning and, paradoxically, increased facial hair growth. Although these changes often coincide with the perimenopausal and postmenopausal period, they are generally multifactorial, involving genetic predisposition, hormonal shifts, and ageing processes rather than menopause alone.[69,70] A key hormonal influence is the relative increase in the androgen to estrogen ratio that occurs with declining ovarian estrogen production, potentially enhancing androgen effects at hair follicles that are genetically predisposed to sensitivity.[70,71] Estrogen and androgen receptors are expressed in the dermis, epidermis, hair follicles, sebaceous glands, and cutaneous vasculature. Estrogen receptors decline with age and during the climacteric, contributing to altered hair follicle biology.[70] In contrast, androgen receptor signalling remains relatively constant, and relative androgen dominance may promote follicular miniaturisation in susceptible areas.

ANDROGENETIC ALOPECIA

Female pattern hair loss (FPHL), also termed androgenic alopecia, is the most common form of hair thinning in women. It is characterised by diffuse thinning over the crown and frontal scalp with preservation of the frontal hairline. FPHL is genetically influenced and often associated with altered androgen metabolism within hair follicles, although serum androgen levels are normal in most affected women.[72] Onset may occur before menopause, but progression may accelerate with age and relative estrogen deficiency. In the absence of rapid onset or virilizing features (acne, hirsutism, menstrual irregularities), routine hormonal evaluation is not generally indicated in women

with typical FPHL. Postmenopausal women with signs of hyperandrogenism or abrupt hair loss merit endocrine assessment to exclude disorders such as androgen-producing tumours, polycystic ovary syndrome (PCOS), or thyroid dysfunction.[71] Other causes of hair loss, including iron deficiency, hypothyroidism, systemic illnesses, stress, and certain medications (such as cytotoxic agents, betablockers, retinoids),should also be considered and addressed appropriately.[73] General measures include optimised nutrition, correction of deficiencies (iron, vitamin D/B12), adequate sleep, and stress management, which are important supportive strategies but have limited direct impact on androgenic alopecia progression.[73] The only FDA-approved topical treatment for FPHL is minoxidil, available in 2% and 5% formulations; it increases hair density and slows progression but requires continuous use, as benefits diminish after discontinuation. Most clinical evidence for minoxidil comes from studies in premenopausal women; data specifically in postmenopausal populations are limited but suggest similar benefit.[74] Hormonal treatments such as estrogen therapy have not demonstrated consistent benefit for hair loss and are not recommended solely for FPHL. If hormonal therapy is indicated for systemic menopausal symptoms, choosing a progestogen with minimal androgenic activity is prudent to avoid potential exacerbation of hair thinning.[70] Anti-androgens (such as spironolactone, finasteride) may be considered in selected postmenopausal women with documented hyperandrogenism but require careful monitoring.[75] Hair transplantation can be offered to women with stable hair loss who do not respond to medical therapies.[71]

HIRSUTISM AND MENOPAUSE

Hirsutism, defined as excessive terminal hair growth in androgen sensitive areas (face, chest, back), affects 5–15% of women and is increasingly recognised in the perimenopausal and postmenopausal period.[76,77] During menopause, estrogen levels decline, while relative androgen levels may remain stable, resulting in a higher androgen-to-estrogen ratio, which can unmask or exacerbate hirsutism in genetically predisposed women.[78] Common causes include idiopathic hirsutism, polycystic ovary syndrome (PCOS) persisting from earlier life, and rarely adrenal or ovarian tumours or late-onset congenital adrenal hyperplasia.[77] Postmenopausal hirsutism typically presents with gradual facial hair growth (chin, upper lip, jawline) and occasional trunk involvement. Rapid onset or severe virilisation warrants endocrine evaluation to exclude androgen-secreting tumors.[79] Lifestyle measures such as weight management, exercise, and stress reduction can modestly reduce androgenic effects. Pharmacologic therapy includes combined oral contraceptives (COCs), which are generally not used in postmenopause but may be relevant in perimenopause; they suppress ovarian androgen production. Antiandrogens (such as, spironolactone 100–200 mg/day, finasteride 2.5–5 mg/day) are effective for facial hair reduction and are often used with caution in older women due to potential side effects.[80,81] Topical eflornithine 13.9% cream can slow facial hair growth; efficacy is maintained only with continued use.[82] Laser and light-based therapies (long-pulsed Nd: YAG, diode, Alexandrite lasers) are highly effective for long-term hair reduction, especially in women with darker hair and lighter skin.[83] Mechanical methods (shaving, plucking, waxing) are adjunctive but carry risks of folliculitis, scarring, or irritation and are primarily temporary solutions. Treatment is often long-term, combination-based, and individualised due to the hormonal changes and slower hair follicle turnover associated with ageing.

AUTOIMMUNE SKIN DISEASES: Refer to chapter 26.

HOLISTIC APPROACH TO SKIN IN MENOPAUSE

Menopause is associated with a decline in estrogen and other hormones that play essential roles in maintaining skin structure, hydration, elasticity, and repair. Because the skin reflects the body's overallef endocrine and metabolic state, hormonal fluctuations can visibly alter its appearance and function. A holistic approach combining medical, cosmetic, nutritional, and lifestyle strategies helps women maintain skin health, density, luminosity, and confidence as they age.

SYNOPSIS

- Menopause-related estrogen deficiency leads to characteristic physiological and pathological changes in skin, hair, and nails due to the presence of estrogen receptors in these tissues.
- Reduced estrogen levels cause epidermal and dermal thinning, with accelerated loss of collagen, elastin, and extracellular matrix components.
- Impairment of the epidermal barrier function increases TEWL, leading to dryness, sensitivity, and susceptibility to irritation.

- Xerosis, often associated with pruritus, is the most common cutaneous complaint during and3 after the menopausal transition.
- Altered immune and inflammatory responses predispose to eczematous dermatitis and may exacerbate pre-existing inflammatory dermatoses.
- Dermal atrophy and vascular fragility contribute to flushing, easy bruising, and senile purpura in postmenopausal women.
- Pigmentary disorders such as melasma, lentigines, and post-inflammatory hyperpigmentation may persist or worsen in menopause.
- Menopause alters the hair growth cycle by shortening the anagen phase, leading to diffuse hair thinning and increased shedding.
- Estrogen–androgen imbalance contributes to female pattern hair loss and relative androgenic effects such as facial hair growth.
- Reduced sebaceous gland activity leads to a dry scalp, brittle hair, and increased hair shaft fragility.
- Clinical guidelines recommend early recognition, patient education, lifestyle and skincare measures, targeted dermatologic therapy, and individualised consideration of MHT when benefits outweigh risks.

RESEARCH AGENDA

To generate evidence for integrative, multidisciplinary care models in menopausal skin health.

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ORAL HEALTH

Keywords: Hormones, gingiva, tobacco chewing, tooth loss, osteonecrosis.

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INTRODUCTION

Menopause is a physiological transition marked by hormonal changes that affect multiple body systems, including the orofacial complex. The presence of estrogen receptors in the oral mucosa makes the oral cavity particularly sensitive to hormonal fluctuations.[1] Although women generally maintain better oral hygiene than men, hormonal changes in later life increase their susceptibility to oral health problems.[2] Studies show that oral discomfort is significantly more prevalent in postmenopausal women than in premenopausal women. For example, the prevalence of periodontitis increases from 23% in women aged 30–54 years to 44% in dentate women aged 55–90 years.[3] Oral discomfort has also been associated with psychological symptoms during menopause, indicating that both biological and psychosocial factors contribute to the oral health burden in this population. This chapter highlights the impact of menopause on oral health and related oral manifestations during this life stage.

IMPACT OF SEX HORMONES ON ORAL HEALTH

Hormonal changes have a significant impact on the oral cavity throughout a woman's life. While the changes observed during menopause are mainly due to declining estrogen levels, age-related physiological changes in oral tissues may also contribute.[4] Research has consistently shown that fluctuations in female sex hormones, particularly estrogen and progesterone, can modify the response of gingival and periodontal tissues. During puberty, pregnancy, and in women using oral contraceptives, gingival manifestations are often more pronounced than in unaffected controls. Similarly, cyclic hormonal variations during the menstrual cycle are known to affect periodontal health.[5] A study by Norderyd et al. found that women aged 50 to 64 who took extra estrogen had less oral bleeding than women of the same age who were not taking estrogen.[6]

Gum health is strongly influenced by fluctuations in progesterone and estrogen levels, as evidenced by the fact that many women experience increased gingival inflammation and discomfort around the time of menstruation.[7] Estrogen can also affect how gum tissues respond to lipopolysaccharides and maintain bone density by altering the production of inflammatory proteins.[7] The persistent decline in estrogen in postmenopausal women is strongly linked to a progressive decrease in bone density, raising the likelihood of losing teeth and contributing to several oral and facial issues.

CLINICAL PRESENTATION AND ORAL MANIFESTATIONS OF MENOPAUSE

The most common oral symptoms during menopause include burning, pain, dryness, altered taste perception, and progressive alveolar bone loss associated with osteoporosis. Carranza described a specific condition, menopausal gingivostomatitis, seen in menopausal and postmenopausal women. Clinically, the gingiva and oral mucosa appear dry, shiny, and pale to reddish in colour, and they bleed easily on probing. In some cases, fissuring may occur in the mucobuccal fold, closely resembling changes seen in the vaginal mucosa. Patients often complain of a persistent burning sensation, heightened sensitivity to thermal stimuli, and abnormal taste perceptions described as "salty," "peppery," or "sour." Reduced ability to perceive sweetness may lead to increased sugar intake, predisposing to caries.

Effect on Oral Mucosa

The changes that occur in the vagina and oral mucosa during menopause are similar, and both are strongly associated with estrogen deficiency. These include decreased keratinisation and thinning of the oral epithelium. These atrophic changes may put women at risk of neurological disorders such as idiopathic neuropathy and autoimmune lesions such as oral lichen planus (OLP), benign mucosal pemphigoid, and pemphigus vulgaris.[8]

Gingivostomatitis

Menopausal gingivostomatitis is characterised by erythematous, easily bleeding gingiva that progresses to a diffusely atrophic, pale-appearing mucosa. Some women also present with senile atrophic gingivitis, in which the gingival tissues appear abnormally pale. Others may develop menopausal desquamative gingivostomatitis, which is marked by

redness, dryness, a shiny mucosa, peeling with bleeding, and burning sensations.[9] When fungal superinfection is confirmed by culture, topical antifungal agents such as nystatin or clotrimazole may provide symptom relief. In addition, hormone therapy with estradiol has been found beneficial in certain cases, particularly in women with identifiable estrogen receptors in the oral epithelium.[10]

Burning Mouth Syndrome (BMS)

BMS typically begins in middle to later adulthood, with a mean age of onset of 55–60 years, and is rare before age 30. It predominantly affects peri- and postmenopausal women.[11] BMS, also known as stomatodynia, stomatopyrosis, glossopyrosis, or glossalgia, is a common oral symptom of menopause. It occurs most often in women in their 40s or 50s. BMS is defined by a persistent burning sensation in the oral cavity, without any associated systemic disease, abnormal test results, or clinical lesions in the oral mucosa. Women who were perimenopausal or postmenopausal experienced oral discomfort at a considerably higher proportion (43%) than those who were premenopausal (6%).[12] The tongue aches the most, but the lips, palate, gums, and parts of the mouth that support dentures can also hurt. Symptoms frequently emerge three to twelve years following the commencement of menopause. Case- control research conducted by Gao et al. revealed that menopausal women with BMS exhibited lower estradiol levels and higher follicle-stimulating hormone (FSH) levels than women without oral symptoms.[13] Management is primarily symptomatic and multidisciplinary. Topical local anaesthetic gels such as lidocaine may be used for short-term episodic pain relief. Topical desensitising agents, such as capsaicin, may be beneficial in selected patients by reducing peripheral nociceptor sensitivity, although tolerability can limit their use. Persistent or chronic pain often requires centrally acting neuromodulator agents, such as low-dose tricyclic antidepressants, Serotonin–norepinephrine reuptake inhibitors (SNRIs), or gabapentinoids, rather than benzodiazepines, which are not recommended for long-term pain control due to limited efficacy and risk of dependence. Hormone therapy (systemic or local, where indicated) may provide partial symptomatic benefit in hormonally mediated conditions by improving tissue trophicity and reducing nociceptive sensitivity. Still, it should be considered adjunctive rather than definitive therapy.

Effect of Menopause on Salivary Parameters

Xerostomia, subjective dry mouth, often accompanied by thick or mucoid saliva, is a common oral complaint during the menopausal transition and after menopause. Several observational studies have shown that postmenopausal women have reduced stimulated and unstimulated salivary flow, particularly from the submandibular and sublingual glands, compared with premenopausal women, even after accounting for medication use.[14,15] Declining salivary flow compromises saliva's protective functions, buffering capacity, antimicrobial activity, lubrication, and remineralisation, thereby increasing susceptibility to root caries, oral discomfort, dysphagia, taste alteration, oral candidiasis, and periodontal disease. Alterations in salivary composition have also been reported, including changes in calcium concentration and reductions in antimicrobial proteins such as lysozyme, which may further impair oral defence mechanisms.[16,17] Reduced salivary flow disrupts oral microbial homeostasis, favouring the proliferation of organisms such as Candida albicans and cariogenic bacteria.[15] Management is primarily symptomatic and preventive, and includes frequent water sipping, sugar-free chewing gums or lozenges (preferably xylitol-based), saliva substitutes, and meticulous oral hygiene. Topical fluorides (toothpastes, gels, or varnishes) are recommended for caries prevention, particularly for exposed root surfaces. Chlorhexidine, when used intermittently and judiciously, may reduce plaque burden and the risk of root caries. Pharmacological sialogogues such as pilocarpine or cevimeline may be considered in selected women with significant symptoms, while recognising contraindications and limited menopause-specific trial data. Overall, optimal plaque control and preventive dental care remain central to reducing oral morbidity in postmenopausal women.

Effect on Chemosensory System

Menopausal changes may also affect the chemosensory system:

- *Gustatory:* Women may experience phantom tastes or reduced sensitivity to sucrose.
- *Olfactory:* A decline in olfactory performance has been observed.

Effect on Jaw Bone

In postmenopausal women, the coexistence of osteoporosis and periodontitis often intensifies the inflammatory response to dental plaque.[18,19] Clinically, this manifests as decreased bone mineral density (BMD) in the alveolar

crestal and sub-crestal regions, increased bleeding on probing, and loss of dentoalveolar bone height. Birkenfeld (1999) reported a clear association between systemic osteoporosis and alveolar bone resorption.[19] Research suggests that after age 50, the mandibular cortical bone becomes increasingly porous, particularly in the alveolar region, contributing to a progressive decline in bone mass. Consequently, affected women face a greater risk of premature loss of posterior teeth. A continued reduction in BMD may eventually result in edentulism and severely resorbed alveolar ridges, compromising the suitability of conventional dentures and limiting options for dental implant therapy.

Menopausal status and hormone therapy (HT) also appear to influence the longevity of implants. Maxillary failures are more prevalent among postmenopausal women not on HT (13.8%) than among premenopausal women (6.3%) and postmenopausal women on HT (8.1%). [20] These findings indicate that the absence of estrogen and the alterations in the bones that occur following menopause may be risk factors for implant failure, particularly in the maxillary bone.

Effect on Periodontium in Menopausal Women

The gingiva, periodontal ligament, cementum, and alveolar bone make up the periodontium, which provides teeth with their vital supporting structure. By regulating inflammatory mediators, vascular permeability, and fibroblast growth and differentiation, sex steroid hormones play a crucial role in maintaining periodontal health. Osteoblasts and fibroblasts in periodontal tissues contain estrogen receptors that respond to changes in a woman's hormone levels throughout her reproductive life, thereby affecting the integrity of her periodontal tissues.[21,22]

Following menopause, the prevalence and severity of periodontal disease increase significantly compared to the premenopausal stage.[23] The Scardina and Messina study revealed notable variations in vascular parameters, including loop diameter, labial mucosal vessel tortuosity, and periodontal mucosal density, between postmenopausal and premenopausal women.[24] Their findings support the idea that study group tissues may be more prone to inflammation than controls. Additionally, evidence links alveolar bone resorption to systemic osteoporosis. According to Kribbs, the likelihood of tooth loss was almost three times higher for women with advanced osteoporosis than for those in good health.[25]

ORAL MANIFESTATIONS OF OTHER DISEASES EXACERBATED BY MENOPAUSE

Although several other conditions with dental symptoms become more common around menopause, little is known about their connection to estrogen deficiency.

Sjögren's Syndrome: This autoimmune condition can cause xerostomia, or dry mouth, which raises the risk of cavities, periodontal disease, and oral candidiasis. It is more prevalent around menopause.[26]

Pemphigus Vulgaris: An autoimmune condition causing painful mucosal ulcers in the mouth, including on the cheeks, palate, lips, and gums.[27]

OSTEOPOROSIS

Osteoporosis is a common condition in postmenopausal women, characterised by reduced bone density and an increased risk of fractures. Systemic osteoporosis, which leads to widespread bone loss, may increase the risk of advanced alveolar bone loss and reduced bone mineral density.[28] This, in turn, can lead to early tooth loss, leaving women edentulous. Estrogen deficiency upregulates immune cells (macrophages and monocytes) and osteoclasts, thereby increasing the production of bone-resorbing cytokines.[29]

OSTEONECROSIS

In postmenopausal women, osteonecrosis of the jaws is observed in patients treated with bisphosphonates for osteoporosis.[30] These drugs are endogenous pyrophosphate analogues that bind to bone and inhibit osteoclast function, thereby lowering bone turnover and reducing active remodelling in areas characterised by excessive bone resorption. Osteonecrosis of the maxilla caused by oral bisphosphonate therapy is less frequent than that caused by systemic bisphosphonate therapy.

Although the risk of maxillary osteonecrosis in patients treated for osteoporosis is very low, several factors have been associated with an increased risk. Refer to Table 1.

Table 1: Possible risk factors for the development of maxillary osteonecrosis

Chemotherapy	Cancer	Immunotherapy	Corticosteroids
Female sex: estrogens	Old age	Neurological damage	Variations in atmospheric pressure
Osteoporosis	Osteoarthritis	Hypersensitivity reactions	Hemodialysis
Blood dyscrasias	Vascular diseases	Coagulation alterations	Systemic lupus erythematosus
Alcohol abuse	Smoking	Hypothyroidism	Storage diseases
Arterial hypertension	Malnutrition	Infections	Diabetes mellitus
Chronic inactivity	Hyperlipidemia & adipose emboli	Drepanocytosis (sickle cell diseases)	Gaucher's disease
Human immunodeficiency virus infections	Dental risk factors: periapical disease, periodontal disease, dental abscesses, and surgery affecting bone, trauma caused by poorly fitting dentures, traumatising exostosis		

Table 2: Proposed new classification of maxillary osteonecrosis due to bisphosphonates and its treatment

Clinical Stage	Manifestations	Treatment
Stage 1	Bone exposure with necrotic bone or a small ulceration of the oral mucosa without exposure of necrotic bone. Both symptomatic.	Daily 0.12% chlorhexidine rinseand follow-up.
Stage 2A	Bone exposure with necrotic bone or a small oral fistula without exposure of necrotic bone,but exhibiting symptoms. Controlled with antibiotics and antiseptics, the lesions do not worsen.	Daily 0.12% chlorhexidine rinse, antibiotics, analgesics and follow-up.
Stage 2B	Bone exposure with necrotic bone or a small oral fistula without exposure of necrotic bone, but exhibiting symptoms. Not controlled with drug treatment, the lesions worsen, and pain is difficult to control.	Daily 0.12% chlorhexidine rinse, antibiotics, analgesics and surgery, with elimination of the necrotic bone.
Stage 3	Mandibular fracture, extraoral fistula, osteolysis extending to the inferior margin.	Daily 0.12% chlorhexidine rinse, antibiotics, analgesics and wide surgery with bone resections.

The risk-predicting capacity of each of these factors has not been established, but it is extremely low in absolute terms. The following criteria must be met to establish a diagnosis of maxillary osteonecrosis: current or past treatment with bisphosphonates; the presence of one ormore ulcerated lesions on the alveolar mucosa, with the exposure of maxillary or mandibular bone; exposed bone of necrotic appearance; spontaneous presentation of the lesions or, more frequently, manifestation after dentoalveolar surgery (particularly extractions); and the absence of healing for a period of at least 6 weeks.[28] Table 2 presents the clinical stages and associated treatment options.

DENTAL MANAGEMENT DURING MENOPAUSE

A comprehensive clinical history must be gathered for all menopausal women, including a meticulous assessment of mucosal membranes, periodontal and dental health, and salivary flow (quantity and quality). When surgery involving underlying bone is planned, including periodontal surgery, implants, and extractions, medications should be administered with caution, particularly bisphosphonates, other immunosuppressants, and corticosteroids. In these situations, gentle care and atraumatic methods should be used. In certain circumstances, counselling during dental treatment has helped achieve the expected results. Also, it is very important to keep dental plaque levels low by using the right oral hygiene tools (such as interproximal brushes, dental floss, brushing frequency, and technique) and chemotherapeutic medicines like chlorhexidine digluconate. These compounds reduce dental plaque accumulation, improve periodontal health, and prevent caries (by reducing Streptococcus mutans), particularly root caries, which are more common in older adults.[31] To prevent dental cavities, it is also a good idea to use toothpastes, varnishes, or gels containing fluoride. Refer to Box 1.

Box 1 : Preventive strategies to maintain oral-dental health in the monopause

- Careful periodontal monitoring and excellent oral hygiene are especially important for postmenopausal women
- See a dental professional for cleaning at least twice a year
- See a periodontist immediately for
  - Bleeding gums during brushing
  - Red, swollen or tender gums
  - Gums that have pulled away from the teeth
  - Persistent bad breath
  - Pus between the teeth and gums
  - Loose or separating teeth
  - A change in the way your teeth fit together when you bite
  - A change in the fit of your dentures
- *Keep your dental professionals informed about any medications you are taking and any changes in your health history*
- *Brush and floss properly every day*
- *Eat a well-balanced diet*
- *Avoid sugary or starchy snacks*

TOBACCO AND ARECA NUT CHEWING

In India, the habit of chewing tobacco and areca nut creates additional oral health hazards, and its prevalence tends to increase with age among women. Areca nut and tobacco chewing had adverse effects on teeth: a significantly higher proportion of chewers exhibited dental attrition compared to non-chewers. Further analysis showed no significant difference in attrition among quid types, including maya, gutkha, and mixed chewers. Sensitivity to cold beverages was also significantly higher among chewers, indicating detrimental effects on oral tissues and function.[32]

Areca nut chewing is strongly implicated in the development of oral potentially malignant disorders such as oral leukoplakia and oral submucous fibrosis (OSMF), and continued habitual chewing significantly increases the risk of progression to oral squamous cell carcinoma.[33] The World Health Organisation (WHO) and International Agency for Research on Cancer classify betel quid with and without tobacco, including areca nut products, as carcinogenic to humans, contributing substantially to the high burden of oral cancer in South Asian populations.[34]

SYNOPSIS

- Menopause can have a big impact on oral and dental health. But all of these problems, from losing teeth to getting an oral infection, can be treated and managed to keep your mouth healthy.
- Psychological difficulties are as important as physical ones, and dental professionals should not only treat clinical concerns but also be mindful of their patients' feelings.
- Adding counselling and patient education to regular dental care can greatly enhance treatment outcomes and overall patient satisfaction.
- Regular dental visits, careful oral hygiene, and professional prophylaxis remain very important for maintaining your mouth;s health throughout and after menopause.s.

RESEARCH AGENDA

Registry of osteonecrosis and association with bisphosphonates.

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RESPIRATORY SYSTEM

Keywords: Respiratory system, asthma, chronic obstructive pulmonary disease, sleep apnoea and menopause

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INTRODUCTION

The menopausal transition marks a critical physiological milestone in a woman's life, characterised by the permanent cessation of ovarian function and a consequent decline in circulating estrogen and progesterone levels. While its effects on the reproductive, skeletal, and cardiovascular systems are well recognised, emerging evidence highlights menopause as a pivotal period that also influences respiratory health.

Sex hormones exert significant regulatory effects on airway tone, immune responses, and pulmonary vasculature, shaping susceptibility to and progression of various respiratory diseases. The withdrawal of these hormones during menopause can alter airway reactivity, inflammatory patterns, and ventilatory control, predisposing women to conditions such as asthma, chronic obstructive pulmonary disease (COPD), sleep-disordered breathing, interstitial lung disease (ILD), and lung cancer. Furthermore, the interplay between ageing, hormonal decline, and comorbidities such as obesity, gastroesophageal reflux, and cardiovascular disease amplifies respiratory morbidity in postmenopausal women. Despite these associations, the respiratory implications of menopause remain under-recognised and understudied, leading to gaps in diagnosis and management. Understanding the complex and nuanced relationship between menopause and pulmonary function is therefore essential for timely intervention, personalised treatment, and improving quality of life in ageing women. This review explores the effects of menopause-related hormonal changes on the respiratory system, the timing of menopause (early vs. late), the impact of menopause on major respiratory diseases, the underlying mechanisms, screening and clinical management considerations, and the role of menopause in respiratory disease.

Menopause : Effect On Respiratory Physiology

With menopause, alterations in the levels and nature of hormones are universally seen in women. There is a sharp fall in the estradiol (E2) levels, resulting in predominance of estrone (E1) levels. Progesterone levels also drop abruptly. LH and FSH levels are raised due to loss of hypothalamic negative feedback by sex steroids. Estrogen acts as a bronchodilator by multiple mechanisms, including reducing intracellular calcium in bronchial smooth muscle, β2 receptor-mediated bronchodilation, stimulating endothelial Nitric oxide (NO) synthase, leading to increased production of NO, a smooth muscle relaxant, and direct action via estrogen receptors.[1] It also maintains alveoli by acting on estrogen receptor α and β1 and modulates the immune system.[2] Therefore, a lack of E2 is associated with airway hyperresponsiveness and systemic inflammation, including lung inflammation, resulting in poor lung function.[3,4] Progesterone directly stimulates central chemoreceptors, causing increased ventilatory drive in response to Co2. Progesterone is also a direct smooth muscle relaxant. Its absence, therefore, blunts the ventilatory response, leading to hypoventilation and a higher resting PaCO2. Refer to Table 1

Table 1 – Effect of hormones on respiratory function and changes seen at menopause

Hormones	Respiratory function	Mechanisms	Changes in menopause
Estrogen	a. Bronchodilation	↓ Intracellular Ca2+ ↑ß2 receptor, ↑eNOS ↑ ER α, ↑ERß	Accelerated decline in lung function (Adjusted for smoking and age)[3,4]
	b. Modulates immune response	In asthma patients, high estrogen promotes TH2 inflammation & low estrogen promotes	↑Airway hyper-responsiveness

Menopause And Respiratory Diseases

Asthma: Hormonal changes are key to the pathogenesis of asthma in this age. Estrogen, as an immune enhancer, shifts inflammation toward the TH2 pathway. So, its decline should lead to fewer asthma symptoms. But it has a bronchodilatory effect that goes away with its deficit. A population-based study has found that asthma prevalence rises in perimenopausal and menopausal women compared to menstruating women.[7] Peri and post-menopausal women suffer from a more symptomatic form of asthma.[7,8] Asthma tends to be more severe and poorly controlled in post-menopausal women.[9] Increased risk of exacerbation and hospital admission is seen in them.[10] With increasing age, post-menopausal women tend to suffer more from Gastroesophageal Reflux Disease (GERD), cardiovascular comorbidities, which also contribute to worsening asthma. Interestingly, the asthma phenotype in postmenopausal women is non-TH2. Women in this age group usually present with a neutrophilic type of asthma.[11] This explains the absence of atopy and family history of asthma in these women and poor symptom control with asthma treatment, particularly inhaled corticosteroids (ICS).[12] Treatment with menopause hormone theraphy (MHT) is associated with higher asthma risk, increased asthma symptoms and reduced asthma control.[13,14]

Asthma treatment in menopausal women should follow the standard 5-step incremental approach with Maintenance and Reliever Therapy (MART) (single combination of inhaled maintenance with anti-inflammatory reliever therapy). The preferred Metered Dose Inhaler (MDI) contains a combination of formoterol and budesonide, or their equivalents. For stage 1 and 2 asthma, the MART Inhaler is used as needed for symptomatic relief. MART Inhaler with Low dose ICS is prescribed for stage 3 & Medium dose ICS for stage 4 asthma. In stage 5, severe asthma treatment includes combinations of high-dose ICS, low-dose oral corticosteroids, biologicals and other medications. Ensuring adherence to treatment and teaching proper inhaler technique are imperative, especially for elderly women. Comorbidities and treatable traits like smoking cessation, heart failure, obesity,[13] Obstructive Sleep Apnoea, GERD, allergic rhinitis, anxiety and depression[15] should be optimally managed.

COPD: Strong evidence exists that early menopause(<45 years of age) entails a clinically significant fall and precipitous rate of decline in lung function[16] compared to women who had a normal or late menopause (>45 years of age). In the Tasmanian longitudinal health study cohort (TASH), coupling lung function from menarche to menopause, the study found lower postbronchodilator FEV1 (Forced Expiratory Volume 1) in 1st Second (168ml; 95% CI (273-63) and Low FVC (Forced Vital Capacity) (186ml; 95% CI (302-70) associated with menopause. Although the FEV1/FVC ratio didn't change. This finding held up after adjustment for confounding variables, including age and smoking habits. Among COPD phenotypes, emphysema predominates in smokers, and chronic bronchitis predominates in never-smoking post-menopausal females. Higher risk of worsening COPD (including emphysema and chronic bronchitis) is found regardless of the cause of menopause, natural or surgical menopause.[17] Losing lung function in COPD patients with menopause can be detrimental. Asymptomatic or mildly symptomatic COPD patients can become more symptomatic, end up in exacerbation and increased health care utilisation, increased morbidity and mortality.

So, spirometry monitoring could be advised for COPD patients to detect a rapid decline in lung function and prompt referral to a pulmonologist.

Standard treatment for COPD includes stage-based pharmacological and non-pharmacological interventions according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. These interventions help preserve lung function and reduce the risk of future exacerbations. Pharmacological treatment includes MDI with a combination of Long Acting Beta Agonist (LABA) + Long-Acting Muscarinic Antagonist (LAMA) ±ICS (based on GOLD A/B/E staging, eosinophil count, number and nature of previous exacerbation in the last year) with additional treatment of Azithromycin, Roflumilast or biologic (Dupilumab) for recurrent exacerbators. Non-pharmacologic therapies, including smoking cessation, Long-Term Oxygen Therapy (when indicated), vaccinations, domiciliary Non-Invasive Ventilation (when indicated), and pulmonary rehabilitation, are achievable and provide a mortality benefit in addition to triple inhalational therapy.

Sleep Disordered Breathing (SDB) and Obstructive Sleep Apnoea (OSA): The prevalence of sleep apnoea in menopausal women increases compared with premenopausal women after adjusting for age, BMI and other confounders.[18,19]

Proposed mechanisms to explain these findings are alterations in sex hormones at menopause, leading to redistribution of fat in a cephalad direction and loss of progesterone- mediated blunting of the ventilatory response to apnoea. Interestingly, surgical menopause is associated with a higher prevalence of OSA than natural menopause, possibly due to a sudden decline in sex hormones.[20] While OSA is the most prevalent SDB, Insomnia and restless leg

syndromes are also reported in menopause and may have an effect on OSA. Age and BMI are the two strongest risk factors of OSA, along with mood disturbance like depression.[21] Excessive visceral body fat is another independent risk factor for OSA beyond BMI.[19]

Given the detrimental cardiovascular and metabolic effects of OSA, it is needless to say that screening for OSA by Polysomnography (PSG) is needed in post-menopausalwomen, particularly for those with complaints of disturbed sleep. Once OSA is diagnosed, it is classified into mild, moderate, and severe grades based on the Apnoea Hypopnoea Index (AHI).

Treatment with lifestyle modifications, weight loss and nocturnal Positive Airway Pressure therapy (PAP) is effective in post-menopausal OSA. Postural OSA needs simple posture control. Oral appliances and other adjunctive therapies are advised for people intolerant to PAP therapy. Surgery remains the last resort option for refractory OSA if symptoms persist despite optimised therapy. Various surgical modalities are available depending on the anatomical site of obstruction, such as nasal surgeries, tonsillectomy, uvulopalatopharyngoplasty, and maxillomandibular advancement. Although MHT may reduce OSA symptomthes, but risks far outweigh the benefits, and it is not routinely recommended.[22]

ILD: ILDs are a heterogeneous group of diseases. Very scant data is available regarding menopause and ILDs. Incidence of Idiopathic Pulmonary Fibrosis (IPF), which is one of the most common ILDs, increases with age. Menopause naturally increases the prevalence of IPF. The association is in part due to the influence of age, but also due to the lack of sex hormones in menopause. Sex hormones are found to be protective against lung fibrosis.[23] Among Connective Tissue Disorders (CTD) related ILD, Systemic sclerosis (SSc) related ILD (SSc-ILD) is most studied with menopause. SSc-ILD in Postmenopausal females is more likely to be limited cutaneous SSc with anticentromere antibody positivity than in premenopausal females.[24] Patients with early menopause have more ILDs.

Early menopause is an independent risk factor for low Diffusing Capacity of the Lung for Carbon Monoxide (DLCO).[24] Diagnosis of ILD requires High-Resolution Computed Tomography of the Thorax (HRCT) thorax, which is the imaging modality of choice. Pirfenidone and Nintedanib are the only approved drugs for Idiopathic Pulmonary Fibrosis (IPF). For SSc ILD, many immunosuppressants can be used, including mycophenolate mofetil (MMF) or Rituximab as first-line and Cyclophosphamide, Nintedanib, or azathioprine as second-line options.[25] Along with treating primary autoimmune disease, it is also important to treat complications of pulmonary hypertension, cutaneous vasoconstriction and GERD associated with SSc. Nonpharmacological treatments like recommended vaccinations, smoking cessation and pulmonary rehabilitation improves outcome in ILD as in all chronic respiratory diseases.

Lung Cancer: Hormonal involvement in lung cancer pathogenesis was suggested by experimental studies finding progesterone and estrogen receptors in the lung. However, study results are contradictory, with late age of menopause showing increased,[26,27] decreased[28,29] and no change [30,31] in risk of lung cancer. Risk for lung cancer was increased among postmenopausal women compared to premenopausal women by 44% when adjusted for age and smoking[32] in a meta-analysis. Studies on lung cancer with the use of hormone replacement therapy (HRT) also have contradictory results; Some studies showed increased risk,[33,34] few showed decreased risk,[35,36] and others found no change,[37-39] in cancer risk. Screening for lung cancer with Low Dose Computed Tomography (LDCT) annually in smokers is not yet implemented in India. But the Centres for Disease Control (CDC) recommendation is to screen people between [50-80] years of age with LDCT who have smoked[20] pack years or more and are either current smokers or have quit smoking within the past15 years. Once a lung nodule is identified, establishing a histopathological diagnosis and staging are the key next steps for making treatment decisions.

Menopause significantly influences respiratory health through hormonal alterations that affect disease susceptibility, phenotype, and outcomes. A decline in lung function is noted with the onset of menopause. This has widespread implications: reduced lung function worsens all existing respiratory illnesses. Menopause thus comes up as a risk factor for increased respiratory morbidity and mortality. Asthma prevalence and severity increase in peri- and postmenopausal women, likely due to loss of estrogen's bronchodilatory and immunomodulatory effects. Postmenopausal asthma often presents as non-Th2, neutrophilic inflammation, therefore less responsive to corticosteroids, with comorbidities such as GERD and obesity worsening symptom control. In COPD, early menopause accelerates lung function decline, independent of smoking, with emphysema predominating in smokers and chronic bronchitis in nonsmokers. Sleep-disordered breathing, particularly OSA, becomes more prevalent postmenopausally due to hormonal loss, altered fat distribution, and diminished ventilatory drive, warranting screening in symptomatic menopausal women. Limited evidence suggests menopause may contribute to the pathogenesis and progression of

ILD, especially SSc-related ILD, through loss of antifibrotic hormonal effects. The role of menopause in lung cancer risk remains controversial, with studies reporting inconsistent associations. Overall, menopause profoundly influences the pathogenesis, phenotype, and management of respiratory disease. Clinicians should adopt individualised, hormone-aware approaches that emphasise early screening, optimal control of comorbidities, and appropriate, timely referral to pulmonologists.

SYNOPSIS

- Menopause represents a critical transition influencing multiple respiratory conditions, underscoring the need for sex-specific research.
- The bronchodilator effect of estrogens decreases after menopause, predisposing to various lung pathologies.
- Vigilant screening and management of respiratory disease in accordance with standardised guidelines are important.
- Management of comorbidities and cautious use of HRT (if indicated otherwise) in optimising respiratory outcomes in postmenopausal women.

RESEARCH AGENDA

Asthma Phenotype and Severity Across Menopause

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GASTROINTESTINAL SYSTEM

24

INTRODUCTION

Natural menopause represents a complex biological transition rather than an isolated event. Beyond its reproductive implications, menopause induces significant systemic alterations, including those affecting the gastrointestinal (GI) system.[1] Although menopause has traditionally been associated with vasomotor, bone, metabolic, and cardiovascular effects, it represents a far more comprehensive physiological transition with wide-ranging systemic consequences. One of the most responsive yet historically under-recognised organ systems is the GI tract. The GI system, with its extensive integration of endocrine, neural, muscular, and immune networks, is profoundly influenced by declining ovarian hormone levels.[2]

Emerging evidence demonstrates that the postmenopausal gut undergoes a coordinated neuroendocrine and immune metabolic reprogramming that affects multiple domains, including motility, epithelial barrier integrity, visceral nociception, microbial composition, and overall disease susceptibility. These changes have significant clinical relevance, particularly because many women present in midlife with new-onset or exacerbated GI symptoms.[3] A comprehensive understanding of the GI consequences of menopause is therefore essential for clinicians to accurately evaluate, diagnose, and manage gastrointestinal complaints in the postmenopausal population.

Gastrointestinal Motility

Sex steroid receptors are widely distributed throughout the gastrointestinal tract, including the epithelium, smooth muscle layers, enteric nervous system, and the mucosal immune compartment. The functional consequence is that estrogen and progesterone can influence gut motor patterns, sensory thresholds, and inflammatory signalling through both neuronal and immune pathways. Ovarian hormones modulate nitric oxide (NO) containing inhibitory neurons within the myenteric plexus and influence mast cell density and responsiveness in the gastrointestinal mucosa.[4,5] These pathways connect menopausal hormone withdrawal directly to changes in neuromuscular coordination, visceral sensitivity, and symptom expression.

Esophageal Motility And Reflux

Direct physiologic data evaluating menopause specific effects on esophageal motility and transient lower esophageal sphincter relaxations remain limited. However, epidemiologic patterns are consistent: ageing and reduced physical activity correlate with increased prevalence of gastrointestinal reflux disease (GERD) in women, probably mediated by ageing-related visceral adiposity, higher intra-abdominal pressure, and increased reflux events.[6] In both sexes, hiatal hernia and elevated body mass index (BMI) are strongly associated with GERD. Notably, the BMI reflux relationship appears more pronounced in women than in men, suggesting sex-specific differences in fat distribution, hormonal modulation of sphincter tone, and symptom perception.[7]

Gastric Emptying And Upper GI Symptom

Gastric emptying of solids and liquids is consistently slower in women than in men.[8-10] This difference is often attributed to prolonged proximal gastric relaxation and reduced postprandial contractility of the distal stomach in women. Scintigraphic emptying curves for men and women typically diverge around 50 minutes after ingestion, highlighting sustained sex differences in gastric motor physiology.[11] Symptom perception also differs: women generally report earlier and more intense sensations of satiety and abdominal pressure during fasting, and after meals report more prolonged fullness and higher nausea prevalence than men.[4] Women also exhibit lower basal and maximal gastric acid output, correlating with smaller gastric surface area and reduced parietal cell volume relative to body size.[12] These differences are clinically important because symptom burden does not map perfectly to objective motor delay, especially in functional dyspepsia and gastroparesis-like syndromes.

Menopause And Hormone Therapy: Divergent Effects On Gastric Motility

During menopause, gastric emptying tends to accelerate and may approximate patterns observed in men. In contrast, postmenopausal women receiving menopause hormone therapy (MHT) demonstrate slower gastric emptying

resembling premenopausal physiology.[13] This strongly supports a modulatory role of estrogen/progesterone on gastric motor regulation. However, symptoms do not always worsen after menopause. Some data suggest postmenopausal individuals may experience less severe gastroparesis symptoms than those in premenopause, implying that menopause-related changes in visceral sensitivity, central symptom processing, or comorbidity patterns may modify the clinical expression of delayed emptying.[14]

Lower GI Motility, Visceral Sensitivity, and the Menopausal Brain Gut Axis

With menopause, declining estrogen levels reduce inhibitory neuromodulation within the enteric nervous system and alter serotonin and nitric oxide signalling. These changes may partially normalise transit in some individuals, but can coexist with heightened visceral pain perception. Estrogen withdrawal is associated with lower nociceptive thresholds via reduced estrogen receptor–mediated modulation at dorsal root ganglion neurons and spinal pain pathways, thereby contributing to visceral hypersensitivity.[3]

Clinically, this can present as a paradox: modest transit improvement alongside increased bloating, discomfort, and pain, as sensory amplification becomes the dominant driver of symptoms. Menopause is associated with neuroendocrine changes that affect autonomic regulation, stress responsivity, and emotional processing. Estrogen modulates the HPA axis, corticotropin-releasing hormone signalling, and limbic circuits involved in pain modulation. Loss of estrogen can increase stress reactivity and alter central pain processing, amplifying GI symptom perception even when objective motility changes are modest.[15]

In functional GI disorders, this central contribution is clinically visible: postmenopausal women with functional disorders can report greater symptom severity and poorer quality of life compared with premenopausal counterparts, even when disease activity or motility parameters are similar.[16]

Microbiota And Hormone Interactions: Possible Links To Motility And Sensitivity

The gut microbiota undergoes age- and hormone-related shifts in composition and diversity. Estrogen influences microbial diversity both directly (through receptor-mediated effects on the intestinal epithelium) and indirectly (via bile acid metabolism and immune regulation).[17-20] Menopause associated estrogen reduction has been linked to decreased diversity, altered Firmicutes-to-Bacteroidetes ratios, and increased pro-inflammatory taxa. These microbiota changes may influence motility by altering short-chain fatty acid production, enteroendocrine signalling, and mucosal immune activation. While causality remains incompletely established, emerging evidence supports a biologically credible model in which menopause-related dysbiosis contributes to constipation, bloating, and visceral hypersensitivity in susceptible individuals.[21-27]

Clinical implications: Pre-menopausal women are known to have higher levels of estrogen and progesterone than post-menopausal women. Studies have demonstrated that pre-menopausal women subsequently have slower gastric emptying than post-menopausal women. After menopause, estrogen and progesterone levels decrease significantly, thereby improving gastric emptying. However, many post-menopausal women are prescribed MHT by their clinicians. Some studies have demonstrated that post-menopausal women taking MHT have delayed gastric emptying, whereas others have demonstrated MHT with estrogen to be a potential remedy for gastroparesis.

New or worsening GI symptoms during menopause should not be automatically attributed solely to age. Hormonal withdrawal, neuroimmune modulation, changes in the microbiota, and central pain amplification can all contribute. Non-hormonal strategies targeting visceral hypersensitivity, stress modulation, diet, physical activity, and microbiota-directed approaches may be particularly valuable in postmenopausal patients. MHT may partially restore premenopausal motility patterns in women using it for established indications, but should not be initiated solely for gastrointestinal symptoms.

Gastrointestinal Reflux Disease and Menopause

GERD is among the most prevalent GI disorders worldwide, affecting roughly one in five adults in Western populations.[28] Historically, sex- and menopause-specific patterns were under-examined, but accumulating evidence indicates that menopausal status is an independent modifier of GERD prevalence, symptom burden, and complication risk in women. Observational survey data involving nearly 500 women across reproductive stages demonstrate that perimenopausal and postmenopausal women have significantly higher GERD symptom prevalence than premenopausal women. They are also more likely to carry a GERD diagnosis. Symptom burden correlates with higher

body weight and alcohol consumption, emphasising the interaction between menopausal biology and established lifestyle risk factors. Typical manifestations included overt reflux and nausea, and postmenopausal women were nearly three times more likely to report symptoms than non-menopausal women.[29] A critical clinical signal in this cohort was under-recognition: despite frequent symptoms, nearly 80% of affected women had never received a formal GERD diagnosis.[29]

This aligns with broader concerns that reflux symptoms in women may be minimised or not escalated to diagnostic evaluation. Large population analyses reinforce menopause as a strong independent risk factor. In a cohort of more than 180,000 women, postmenopausal status was associated with an approximately 3.5-fold higher adjusted risk of GERD than premenopausal status. Notably, menopause was a stronger independent association than smoking, alcohol intake, or type 2 diabetes mellitus.[30] Beyond symptoms, postmenopausal women with GERD have a higher likelihood of complications, including erosive esophagitis, peptic strictures, and Barrett's esophagus.[30]

This matters because it implies menopause may influence not only symptom perception but also mucosal injury and disease progression. The use of nonsteroidal anti-inflammatory drugs with hormone therapy increases GERD. The mechanisms are likely multifactorial. Estrogen influences GI motility, visceral sensitivity, and lower esophageal sphincter (LES) function. A proposed pathway is estrogen-associated increase in nitric oxide bioavailability: estrogen exposure correlates with elevated plasma NO levels, which promote LES relaxation and reflux permissiveness.[31] Menopause also tends to be accompanied by central adiposity and altered esophageal clearance and sensitivity, which can amplify both reflux burden and symptom perception.

MHT may further modify gastrointestinal risk profiles. Observational studies suggest that postmenopausal women using exogenous hormones have a higher prevalence of GERD and reflux symptoms compared with non-users.[30] Pooled evidence from systematic reviews and meta-analyses indicates that current or prior hormone therapy use is associated with a modestly increased risk of GERD or reflux symptoms, with an adjusted odds ratio of approximately 1.3. Furthermore, postmenopausal women taking the same dose of estrogen in combination with the progestin levonorgestrel exhibited lower plasma nitric oxide levels than those taking estrogens alone. The evidence from these studies is strengthened by the meta-analysis, which showed postmenopausal estrogen alone use was associated with higher odds of GERD than combined estrogen plus progestogen.[32]

These findings underscore the need for well-designed prospective studies with standardized exposure definitions. Clinically, menopause should be recognised as a meaningful, sex-specific modifier of reflux risk. Postmenopausal women may warrant a lower diagnostic threshold, particularly in the presence of refractory symptoms or alarm features. Counselling regarding hormone therapy should include discussion of potential reflux-related effects, especially in women with pre-existing GERD.[18,31,33] If appropriate, providers should seek alternative MHT, such as progesterone-only therapy, in patients already suffering from reflux-related symptoms, given its reduced risk for GERD, Barrett's esophagus, and esophageal stricture.[34,35]

Esophageal Adenocarcinoma (EAC) and Menopause

EAC has risen sharply in incidence over recent decades in Western countries and is among the fastest-growing GI malignancies. [36-38] The established risk factors include chronic GERD, central obesity, and tobacco exposure. Despite shared risk exposures across sexes, EAC demonstrates one of the most striking sex disparities in GI oncology, with male-to-female incidence ratios approaching 7–8:1 in many populations.[37,39,40] Women develop EAC at a substantially older age than men, with an estimated delay of ~15–20 years (often reported as ~15–17 years in detailed analyses).[39,40] This temporal delay has led to the hypothesis that endogenous estrogens may protect against progression along the reflux-Barrett's adenocarcinoma sequence. The loss of estrogen after menopause is a biologically plausible contributor to the convergence of risk later in life.

Experimental and clinical observations support plausibility: estrogen signalling may modulate epithelial proliferation, inflammation, oxidative stress, DNA damage responses, apoptosis, and immune surveillance within esophageal tissue. These pathways could reduce the likelihood that chronic reflux-related injury evolves toward neoplasia during the premenopausal period. Human observational data are limited but suggest that menopausal hormone therapy may be associated with a modest reduction in EAC risk. A population-based cohort study reported a reduced incidence of EAC among postmenopausal women using MHT compared with never-users. In detailed cohort work from Sweden evaluating large populations of women exposed to systemic MHT over time, current or prior MHT

use was associated with reduced EAC risk (adjusted hazard ratio ~0.78), even after adjustment for GERD, obesity, and type 2 diabetes, with effects observed across estrogen-only and combined regimens.[41] However, absolute EAC incidence in women remains low, limiting power for dose–response and duration analyses. Further, these associations do not outweigh known MHT risks in other organ systems and should not be interpreted as a basis for prescribing MHT solely for cancer prevention. Hormonal associations appear weaker or inconsistent for esophageal squamous cell carcinoma compared with adenocarcinoma, consistent with distinct pathogenic pathways and supporting the concept that any estrogen-linked protection is more relevant to the reflux–Barrett's–adenocarcinoma axis.[42]

Clinical implications: Even though overall EAC incidence is lower in women, postmenopausal women with long-standing GERD constitute a clinically relevant at-risk group for Barrett's esophagus and malignant progression, and delayed diagnosis can occur if reflux symptoms are under-investigated in women. Menopausal status, GERD duration, obesity, and hormone exposure should be integrated into individualised risk assessment and decisions around endoscopic evaluation and surveillance.

Gastric Cancer and Menopause

The incidence of gastric cancer shows sex- and age-related variation, raising the question of whether menopausal status modifies risk. A nationwide Korean cohort study evaluated >2.4 million women aged ≥ 40 years who underwent standardised national health screening, categorised as pre-/perimenopausal or postmenopausal. Over a mean follow-up of ~8.3 years, the cumulative incidence of gastric cancer was nearly threefold higher in postmenopausal women (0.92%) compared with pre/perimenopausal women (0.33%).[43] This difference persisted after adjustment for age and clinical variables, supporting the view that menopause is a biologically relevant risk modifier rather than merely a proxy for ageing.

Metabolic dysfunction: Within postmenopausal women, type 2 diabetes independently increased gastric cancer risk (hazard ratio ~1.15), and incidence rose progressively from normoglycaemia to prediabetes to diabetes suggesting a graded relationship between metabolic dysregulation and carcinogenesis. Menopause-associated estrogen deficiency is commonly accompanied by visceral adiposity, insulin resistance, dyslipidaemia, and chronic low-grade inflammation, plausibly intensifying proliferative and oxidative pathways in susceptible gastric mucosa.

Lifestyle risk context and key limitations: Obesity, tobacco use, and heavy alcohol intake were also associated with increased risk in postmenopausal women in this dataset.[43] Biologically, loss of estrogen's anti-inflammatory/antioxidant effects may heighten vulnerability to these exposures. However, the cohort lacked Helicobacter pylori status, an essential determinant of gastric cancer and did not capture diet, histologic subtype, or anatomic location, limiting mechanistic interpretation.[43] Future studies integrating H. pylori, hormonal profiles, metabolic markers, and tumor biology are needed to clarify whether estrogen deficiency is directly carcinogenic or primarily amplifies metabolic/lifestyle pathways.

PANCREATICOBILIARY DISEASE AND MENOPAUSE

Gallstone Disease

Gallstone disease demonstrates a strong female predominance and is influenced by age, metabolic status, and hormonal milieu, making menopause a key period for disease expression.

Epidemiology and metabolic correlates: In a cohort of 1,337 patients with type 2 diabetes, gallstone disease was significantly more common in women (29%) than men (22%; P = 0.003), and prevalence increased with age; elevated BMI and family history were additional risk factors.[44] Physical activity appears protective. In a cohort of 8,010 postmenopausal individuals, lower physical activity was independently associated with increased gallstone risk: women in the two lowest activity quartiles had 59% and 57% higher odds, respectively, compared with the highest quartile.[45] This supports the role of energy balance and sedentary behaviour in postmenopausal biliary pathology.

Mechanisms: estrogen and lithogenic bile: Estrogen increases hepatic cholesterol synthesis and secretion and can reduce bile salt and phospholipid proportions, producing cholesterol-supersaturated bile that promotes crystal nucleation and gallstone formation.[46,47] Estrogen also impairs gallbladder motility, increasing stasis. Although endogenous estrogen declines after menopause, this theoretical reduction in lithogenic drive may be offset by age-related metabolic shifts such as visceral adiposity, insulin resistance, dyslipidaemia and by exogenous estrogen exposure via MHT.

MHT and gallbladder disease: robust evidence of increased risk: A USPSTF systematic review (including 20 RCTs totaling 39,145 participants and three cohort studies totaling 1,155,410 participants) found estrogen-only MHT increased gallbladder disease risk vs placebo; combined estrogen–progesterone therapy also increased risk, with annualized incidence 1.31% vs 0.84% in placebo (hazard ratio 1.57, 95% CI 1.36–1.80), translating to ~260 excess cases over 5.6 years.[48] Much of this evidence derives from WHI datasets, which did not consistently stratify by dose, formulation, or route, and adherence varied, limiting precision in some subgroup estimates. A large prospective cohort (>45,000 postmenopausal women) found increased cholecystectomy risk among MHT users, largely confined to unopposed oral estrogen. The estimated absolute impact was approximately one excess cholecystectomy per 150 women treated with unopposed oral estrogen over five years. [49]

Clinical implication: Gallstone disease is a tangible adverse outcome of MHT, particularly oral estrogen, and should be explicitly considered during shared decision-making. Weight management, physical activity, and glycaemic control remain practical risk-mitigation strategies.

Biliary Tract Cancers

Biliary tract malignancies show sex differences: gallbladder cancer is more common in women, whereas cholangiocarcinoma, ampullary cancers, and mixed-type biliary tumours occur more frequently in men.[50] This distribution implies tissue-specific interactions between hormones and the environment.

Cohort evidence: no uniform increase, but confounding by gallstones/cholecystectomy is central: A Swedish matched cohort (290,186 HRT users; 870,165 non-users; 2005–2012) found no overall increase in biliary tract cancer risk among systemic MHT users.[51] Gallbladder cancer odds appeared reduced among MHT users, but this lost significance after adjusting for gallstone disease. MHT exposure in this cohort was strongly associated with gallstone disease (OR 6.95, 95% CI 6.64–7.28). This supports a plausible indirect pathway: increased gallstone disease → increased cholecystectomy → reduced gallbladder cancer risk by organ removal prior to malignant transformation. Extrahepatic bile duct cancer odds were 0.83 in MHT users, and no major differences emerged when stratified by estrogen-only vs combined regimens.[51]

Case–control evidence: gallbladder cancer risk may increase with combined/oral MHT, while cholangiocarcinoma signals may differ: A large nested case–control study (1,682 biliary tract cancer cases with 8,419 controls) reported that combined estrogen–progesterone MHT was associated with nearly twofold increased gallbladder cancer risk (OR 1.97), and oral MHT with even higher gallbladder cancer risk (OR 2.28).In contrast, estrogen-only and non-oral preparations were associated with reduced cholangiocarcinoma risk, suggesting the route first-pass hepatic exposure) may be critical. No association was observed for ampullary or mixed-type tumours. Dose, duration, prescription number, and time since last use did not meaningfully modify risks in this analysis.[51]

Notably, the increased gallbladder cancer risk with combined/oral MHT was observed independent of gallstone status, implying mechanisms beyond gallstone-driven inflammation, potentially including direct hormonal effects on bile composition or biliary epithelial proliferation. These findings support the hypothesis that transdermal MHT may be safer for women at high baseline biliary malignancy risk, because it avoids first-pass hepatic estrogen exposure.[50]

Research gap: Because biliary cancers are relatively rare and MHT exposure is heterogeneous, conclusions remain constrained. Future prospective studies with standardised hormone exposure and careful adjustment for gallstones and metabolic confounders are needed.

Acute Pancreatitis

An age-matched Danish population-based case–control study (1,054 acute pancreatitis cases; 10,540 controls) found no significant association between current MHT use and acute pancreatitis risk, consistent across gallstone-related and alcohol-related etiologies. A modest increase among former users was suggested but may reflect confounding or reverse causation (discontinuation due to metabolic abnormalities such as hyperlipidaemia).[52]

Rarely, estrogen-associated pancreatitis occurs most often in women with severe hypertriglyceridaemia. Case reports and small series describe estrogen-induced elevations in triglycerides via increased hepatic VLDL production and reduced lipoprotein lipase activity, precipitating pancreatitis through capillary obstruction, ischemia, and free fatty acid–mediated acinar injury.[53-55] Observational studies show that MHT, particularly oral estrogen, can raise triglycerides in some women, whereas transdermal estrogen tends to be more lipid-neutral due to reduced first-pass hepatic effects.[56]

Clinical implication: Routine MHT does not mandate pancreatitis surveillance in the general population, but baseline and follow-up lipid monitoring should be considered in women with known hypertriglyceridaemia, prior estrogen-related lipid derangements, or idiopathic pancreatitis history, and non-oral routes may be preferable when HRT is indicated.[53-56]

INTESTINAL DISEASE AND MENOPAUSE

Menopause influences intestinal physiology through hormonal withdrawal, immune regulation, neuromodulation, shifts in the microbiome, and changes in nutritional absorption and bone metabolism. Several intestinal disorders show menopause-relevant patterns in prevalence, severity, or complications.

Coeliac Disease

Coeliac disease is now recognised as frequently presenting in adulthood and often with non-classical/extraintestinal manifestations. Untreated disease causes malabsorption of iron, folate, fat-soluble vitamins (A, D, E, K), and calcium, contributing to anaemia, metabolic bone disease, and reproductive disturbances.[57,58] Epidemiologically, women are more commonly diagnosed. In a population-based incidence cohort (282 patients), 65% were women; women were diagnosed at a younger age than men (44.5 vs 48.9 years; P = 0.03), with many female diagnoses occurring during perimenopause and some after menopause.[59]

Reproductive associations have been variably reported. Some studies suggest a shortened reproductive lifespan (delayed menarche, earlier menopause), but robust case–control data (288 coeliac women vs 586 controls) found no difference in age at menopause or in the proportion with early/premature/surgical menopause.[60,61] Nonetheless, women with coeliac disease had higher rates of menstrual abnormalities (delayed menarche, irregular cycles, dysmenorrhoea, abnormal flow, prolonged bleeding, intermenstrual bleeding).[61] Skeletal outcomes are central: osteoporosis/osteopenia are more prevalent and severe in coeliac disease.[62,63] In postmenopausal women, estrogen deficiency synergistically magnifies fracture risk, making coeliac disease a high-value diagnosis to consider in older women with bone disease.

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a chronic condition caused by an inappropriate immune response in the gastrointestinal tract. Its cause, while not well understood, is likely multifactorial, with possible contributions including genetic factors, faecal microbiota properties, gut epithelial characteristics, and immune properties. IBS demonstrates sex differences in phenotype. A meta-analysis of 22 studies found women are more likely to report abdominal pain and constipation, while men are more commonly reported to have diarrhoea predominant symptoms. Menstrual-cycle symptom worsening is reported in both IBS and healthy women, supporting hormonal modulation of symptoms.[64]

Menopause-specific data are emerging. A controlled study using Rome criteria found postmenopausal women with IBS had significantly greater symptom severity (P = 0.003) and worse physical health-related quality of life (QoL) (P = 0.048) than premenopausal women with IBS; comparable age-group differences were not observed in men.[65] This pattern supports menopause-related changes in brain–gut signaling and visceral pain processing. However, not all cohorts identify reproductive hormones as the dominant determinant. In the Seattle Midlife Women's Health Study (291 women), stress-related tension independently predicted constipation severity, and cortisol was inversely related to constipation. For diarrhoea severity, stress-related tension and advancing age were significant predictors; reproductive hormone levels were not independent predictors.[65] This underscores the practical reality: during menopause, stress physiology and central processing can dominate bowel habit changes, even when hormone effects remain biologically plausible.

Microscopic colitis

Microscopic colitis predominantly affects older adults and is common in postmenopausal women. Prospective Nurses' Health Study data showed that current MHT use was associated with an increased risk of microscopic colitis (HR 2.64) compared with never use, with risk rising with longer duration and declining after discontinuation, suggesting a reversible exposure effect. Prior oral contraceptive use also increased the risk (HR 1.57). Notably, age at menarche, parity, age at menopause, and menopause type were not associated, pointing toward exogenous hormone exposure as the key hormonal modifier rather than intrinsic reproductive history.[66]

Clinical implication: In postmenopausal women, intestinal complaints often reflect layered influences: hormonal deficiency, immune and microbiome shifts, central stress physiology, and nutritional compromise. Coeliac disease should be actively considered in unexplained bone loss or anaemia; IBS may worsen via brain–gut mechanisms; microscopic colitis appears hormonally sensitive with MHT as a clinically meaningful risk exposure.

Diverticular Disease and Menopause

Diverticulitis increases with age and is common in postmenopausal women, likely influenced by changes in connective tissue integrity, immune modulation, and microbiota composition.[67-69] Prospective Nurses' Health Study (65,367 postmenopausal women) data link MHT exposure to diverticulitis risk: both current and past MHT users had a higher incidence than never-users.[70] This association occurred with estrogen-only and combined regimens and was not modified by age, BMI, prior OC use, fibre intake, or duration, suggesting a threshold/permissive effect rather than a cumulative dose response. Proposed mechanisms include estrogen-mediated immune effects and connective tissue remodelling, though definitive pathways remain uncertain. Clinically, MHT exposure should be considered in the risk assessment of postmenopausal women with acute or recurrent diverticulitis.[7]

Inflammatory Bowel Disease and Menopause

The menopause and irritable bowel disease (IBD) relationship is incompletely defined due to heterogeneous designs and outcomes, but several clinically relevant signals exist. A retrospective cohort comparing women with and without IBD found a small but statistically significant earlier mean menopause age in IBD (50.0 vs 51.5 years; P = 0.006), without BMI differences.[71] The clinical significance is uncertain, and causality cannot be inferred. In a small retrospective study (65 women), flare frequency after menopause did not differ from premenopause; interestingly, MHT use was associated with reduced disease activity, attributed to estrogen's anti-inflammatory properties.65 Kane et al. found a protective effect of MHT on disease activity in post-menopausal women with irritable bowel disease (IBD). In this study, post-menopausal women on MHT were 80% less likely to have an IBD flare.[72] Post-menopausal women with IBD who were on MHT showed an improvement in their disease activity based on physician global assessment scores, compared to post-menopausal women with IBD who were not on MHT. Pre-menopausal disease activity seemed to be higher in patients who underwent MHT compared to the controls. Conversely, prospective data from the Nurses' Health Study (108,844 postmenopausal women without prior IBD) found that MHT was associated with an increased risk of developing ulcerative colitis (not Crohn's disease), with risk increasing with longer use and declining after discontinuation; no major difference between estrogen-only and combined formulations.[73] This suggests that exogenous hormones may influence immune pathways relevant to ulcerative colitis initiation while potentially exerting different effects in established disease, highlighting the complexity of timing and context.

Menopause and quality-of-life burden in established IBD: In a study of 71 women, greater IBD severity correlated with worse menopause-specific QoL across psychosocial, physical, and sexual domains, while vasomotor symptoms were not clearly affected by IBD activity.[74]

Genitourinary and sexual symptoms are particularly important. In a CCFA Partners cohort survey (1,250 women),41% with active disease reported at least one moderate-to-severe vulvovaginal symptom. Except for vaginal dryness, these symptoms were more common with active disease than remission. After adjusting for menopausal status, active IBD remained independently associated with symptom burden, which significantly reduced sexual interest and activity; postmenopausal estrogen deficiency likely amplifies this vulnerability.[75]

Cardiovascular outcomes in postmenopausal IBD: WHI-based analysis (134,022 participants; 1,367 with self-reported IBD) found no significant differences in coronary heart disease, venous thromboembolism, or peripheral arterial disease after adjustment. An age-adjusted increase in ischemic stroke risk (HR 1.41; 95% CI 1.06–1.88) lost significance after additional adjustment for socioeconomic factors, rheumatologic comorbidities, and traditional risk factors[76]

Interpretation is limited by self-report, cohort demographics, missing covariates (e.g., psoriasis), and minimal biologic therapy exposure due to pre-biologic era enrollment.[77] Menopause intersects with IBD through immune modulation, symptom burden, sexual health, and therapy decisions. MHT may reduce activity in some women with established disease, yet may increase ulcerative colitis risk in previously unaffected women. Individualised decisions should integrate disease phenotype, symptom profile, thrombosis risk, and quality-of-life priorities.[73-77]

Colorectal Cancer (CRC) and Menopause

Colorectal cancer (CRC) represents a major cause of cancer-related morbidity and mortality in women, and accumulating evidence suggests that menopausal hormone exposure significantly influences CRC risk. In contrast to several other gastrointestinal malignancies, MHT appears to confer a protective effect against CRC, particularly with combined estrogen–progestin formulations. A comprehensive meta-analysis encompassing 20 observational studies demonstrated that any lifetime exposure to MHT, whether estrogen-only or combined estrogen–progesterone therapy, was associated with a reduced risk of CRC.[78]

This protective association has been further substantiated by randomized trial data.The U.S. Preventive Services Task Force (USPSTF) 2022 evidence update, drawing largely from the Women's Health Initiative (WHI), reported that women randomized to combined estrogen–progestin therapy (n = 16,608) experienced a significantly lower incidence of CRC compared with placebo over a median follow-up of 5.6 years. The absolute CRC incidence was 0.59% in the MHT group versus 0.93% in the placebo group, corresponding to a hazard ratio of 0.62 (95% CI 0.43–0.89). In contrast, estrogen-only therapy did not significantly reduce CRC risk when compared with placebo, highlighting a potential role for progestins in mediating the protective effect.[48]

Mechanisms: receptor biology and anti-neoplastic signaling:The mechanistic basis for MHT associated CRC risk reduction remains incompletely elucidated, but several biologically plausible pathways have been proposed. Estrogen and progesterone exert their effects through nuclear hormone receptors expressed in colonic epithelial cells, particularly ERβ. Activation of these receptors has been shown to promote DNA repair, enhance pro-apoptotic signaling, suppress oncogenic pathways, regulate cell-cycle progression, and modulate epigenetic mechanisms, including microRNA expression and DNA methylation patterns.[78] Collectively, these effects may slow adenoma progression and reduce malignant transformation within the colonic epithelium.

Genetics and gene–environment interaction: Emerging evidence indicates that genetic susceptibility modifies the magnitude of CRC risk reduction associated with MHT. A genome-wide interaction analysis identified specific genetic variants, including loci within GRIN2B and DCBLD1, that interact with HRT exposure to influence CRC risk.[79] Building on this observation, investigators evaluated the joint effects of MHT use and a polygenic risk score (PRS) derived from 141 CRC-associated single-nucleotide polymorphisms.

The analysis included 28,486 postmenopausal women of European ancestry, with CRC risk estimated over a 30-year horizon beginning at age 50 years.[80] Logistic regression models demonstrated a statistically significant interaction between PRS and MHT exposure. Notably, women in the highest quartile of genetic risk derived the greatest absolute benefit from MHT use. Among these high-risk individuals, the 30-year cumulative CRC risk was 2.4% lower in women using any form of MHT compared with non-users ($P = 1.83 \times 10^{-14}$).[80]

These findings suggest that MHT may partially attenuate genetically determined CRC susceptibility.However, several limitations warrant consideration. The PRS and study cohorts were population-specific, potentially limiting generalizability to non-European populations. In addition, MHT exposure was self-reported in some datasets, introducing the possibility of recall or misclassification bias.[80]

Clinical implication: MHT should not be prescribed solely for CRC prevention, but CRC risk reduction especially with combined therapymay be a meaningful ancillary consideration within a broader individualized risk–benefit assessment (cardiovascular, thrombotic, breast cancer, biliary risks).

Faecal Incontinence and Menopause

Faecal incontinence affects an estimated 2–7% of the general population, rising with age, and is particularly prevalent among hospitalized patients and long-term care residents. Beyond physical symptoms, the psychosocial burden is severe, with embarrassment, anxiety, fear of public episodes, and social withdrawal.[81]

Diet and stool consistency and fibre as a protective factor Modifiable lifestyle factors, particularly dietary fibre intake, appear to influence faecal continence in older women. A large prospective cohort study of 58,330 elderly women (mean age 73 years) demonstrated a protective association between long-term dietary fibre intake and faecal incontinence risk. Women in the highest quintile of fibre consumption experienced an 18% lower overall risk of faecal incontinence compared with those in the lowest quintile. The benefit was most pronounced for liquid stool incontinence, with a 31% risk reduction observed in women with the highest fibre intake.82 These findings suggest that fibre may improve stool consistency and colonic transit dynamics, thereby reducing incontinence episodes.

MHT exposure: Hormonal status and exogenous hormone exposure also appear to influence faecal continence in postmenopausal women. In a large observational study involving 55,828 women, faecal incontinence was more frequently reported among current and former users of MHT compared with never-users.[83] The association was strongest among women receiving combined estrogen–progesterone therapy, whereas those using estrogen-only formulations exhibited a comparatively lower risk. Importantly, the risk of faecal incontinence showed a duration-dependent relationship with MHT exposure, increasing with longer periods of use and declining with greater time elapsed since discontinuation.[83] These findings suggest a potentially reversible hormonal effect on anorectal continence mechanisms, possibly mediated through estrogen- and progesterone-related changes in pelvic floor musculature, connective tissue integrity, or neuromuscular control.

Constipation–incontinence overlap: Constipation and faecal incontinence frequently coexist and may represent overlapping manifestations of pelvic floor dysfunction or disordered colonic motility. A cross-sectional survey of 2,319 participants identified white race, menopause, and constipation as independent risk factors for faecal incontinence.After adjustment for these variables, constipation remained a strong predictor, with constipated women significantly more likely to experience faecal incontinence than those without constipation.[84] This association is consistent with mechanisms such as over flow incontinence, rectal hyposensitivity, and impaired evacuation, which are more prevalent in older and postmenopausal populations.

Clinical implication: proactive screening, attention to constipation management, fibre optimization, and careful consideration of MHT risk/benefit are key in postmenopausal women with incontinence.

Liver Disease and Menopause

Menopause alters immune responses, fibrogenesis, metabolic regulation, and hepatic injury pathways. Sex differences in liver disease epidemiology and outcomes often become more pronounced after menopause as estrogen-mediated protective effects decline.

Viral hepatitis

The natural history of hepatitis C virus (HCV) infection demonstrates consistent sex-related variation. Women exhibit higher rates of spontaneous viral clearance compared with men, an effect attributed in part to estrogen-mediated immune modulation.[85] In women who remain chronically infected, fibrosis progression is slower during the premenopausal period. Following menopause, however, this protective effect is lost, and progression to cirrhosis accelerates, approximating rates observed in men.[86] Similar sex-based differences have been reported in chronic hepatitis B virus (HBV) infection. Women experience fewer hepatic flares and show lower rates of viral reactivation after hepatitis B antigen seroconversion when compared with men.[86-89] These findings suggest that endogenous female sex hormones play a protective role in immune-mediated liver injury and viral control.

Alcohol-associated liver disease

Women sustain greater hepatic injury than men for the same quantity of alcohol consumed. This may be attributed to differences in metabolism, body composition, and estrogen-related sensitization of hepatocytes to oxidative injury.[90] Menopause may further remove hepatoprotective influences, potentially amplifying vulnerability.

Metabolic dysfunction–associated steatotic liver disease (MASLD) and fibrogenesis after menopause

Over the period of time following the Delphi [91] consensus terminology of fatty liver has been changed to metabolic dysfunction associated steatotic liver disease (MASLD) and metabolic dysfunction associated steatotic hepatitis. This was to remove the stigma of the term fatty and incorporate metabolic dysfunction in terminology.[91] In premenopausal women with MASLD/MASH progression to fibrosis and further cirrhosis is slow but postmenopause this progression accelerates. The pattern is similar to the progression in HCV infection.[92] The prevalence of MASLD significantly increases across the menopausal stage starting from the menopause transition. This includes natural, surgical menopause and also premature ovarian insufficiency.[93] It has also been shown that older postmenopausal women with MASLD have a higher all cause and liver related mortality as compared to men. This indicates that estrogen deficiency is a modifier of the disease course. A large meta-analysis incorporating 12 observational studies demonstrated a robust association between menopause and MASLD, with a pooled odds ratio of 2.37 (95% CI 1.99–2.82) The association between menopause and MASLD was seen after adjuting the confounding risk factors of

age and traditional metabolic risks. However, between-study heterogeneity was high, reflecting differences in diagnostic criteria, population characteristics, and adjustment strategies.[94] These changes may be due to visceral fat redistribution, insulin resistance, dyslipidaemia, and systemic inflammation accompanying estrogen deficiency seen in postmenopause. These changes promote enhanced delivery of free fatty acids to liver, increasing triglyceride accumulation in hepatocytes. Estrogen is hepatoprotective by decreasing inflammation, reducing oxidative stress and improving insulin sensitivity. It also suppresses the activation of hepatic stellate cell activation and thus slows fibrogenesis. Loss of protective effects of estrogen after menopause accelerates progression from steatosis to steatohepatitis and then to fibrosis and cirrhosis.[94]

Autoimmune cholestatic disease and bone health synergy

Autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC) predominantly affect women and are associated with hepatic osteodystrophy, compounded by postmenopausal estrogen deficiency and malabsorption of fat-soluble vitamins in cholestasis.[95,96]

Liver Transplantation, Menopause, and Long-Term Systemic Outcomes

Survival and age-related outcomes: The outcome and prognosis following liver transplant is different in both men and women.[97] Women have a better outcome following liver transplant. However, advanced recipient age (>65 years) is associated with poorer graft and patient survival irrespective of sex.[98] Age-related immune senescence, comorbidities, and frailty likely contribute to these outcomes.Metabolic dysfunction is seen to happen after liver transplant. 5-10% of patients progress to cirrhosis. MASH develops after liver transplant. This is seen more in women after menopause.[99,100] The development of metabolic syndrome is associated with higher cardiovascular and cerebrovascular disease risks.[101]

Bone loss after liver transplantation: High doses of immunosuppressive therapy and sterioids are given post transplant to prevent graft rejection. These accelerate bone loss.[102,103] In a background of menopause with estrogen deficiency this effect is compounded. The risk of osteoporosis and fractures increases. Early bone health assessment and preventive strategies for bone loss should be followed.

Primary biliary cholangitis (PBC) and bone microarchitecture

PBC is a chronic cholestatic autoimmune liver disease that predominantly affects women, most commonly presenting after the age of 40 years, with a striking female-to-male prevalence ratio of approximately 9:1.[104] The disease is frequently complicated by metabolic bone disease, which represents a major source of morbidity, particularly in postmenopausal women. Women with untreated PBC have been shown to lose bone mass at approximately twice the rate of age-matched female controls, underscoring the combined skeletal impact of cholestasis and estrogen deficiency.[105] In postmenopausal women, estrogen deficiency further amplifies skeletal vulnerability, emphasizing the need for early bone health assessment, fracture risk stratification, and targeted preventive strategies in women with PBC

HCV, Menopause Timing, and Drug-Induced Liver Injury (DILI)

HCV fibrosis progression and potential MHT benifit : disease progression to fibrosis is slower in women during the premenopausal period however it acceerates after menopause demonstrating protective effect of endogenous estrogens. In a prospective cohort study of 251 women with chronic HCV infection, the severity of hepatic fibrosis was independently associated with longer duration of infection (>15 years), higher body mass index, advanced hepatic steatosis, and menopausal status.

Menopausal women on HRT also had a lesser severity of fibrosis as compared to non users. This showed that estrogens suppress hepatic stellate cell activation and modulate the profibrotic cytokine signaling and decrease fibrosis.[106] Women with HCV infections had increased vasomotor symptoms and earlier menopause.[107] This signifies that chronic liver disease disrupts estrogen metabolism, production of sexhormone binding globulin and affects reproductive ageing and menopausal symptoms.

Drug induced liver injury and postmenopausal vulnerability

Women suffer more drug induced liver injury as compared to men and this rises after menopause.

Women also have 1.5-1.7 times higher risk of adverse drug reactions overall.[108,109] The mechanism for a higher

predisposition to DILI in women maybe due to difference in pharmokinetics, fat distribution which may increase exposure to lipophilic drugs. Also hormonal differences increase gastric emptying and intestinal transit time affecting absorption of the drugs.[110-112]

Immune differences are also relevant: stronger antibody responses and higher autoimmune predisposition may increase immune-mediated hepatotoxicity risk.[113,114] DILI with autoimmune features (drug-induced autoimmune hepatitis or drugs triggering classical AIH) is more common in women, with median age ~53 years, aligning with postmenopause and supporting the concept that estrogen withdrawal alters immunoregulation.[114]

Bariatric Surgery in Post menopausal women

The Malabsorption-Osteoporosis Continuum: Perhaps the most critical concern for the gastroenterologist is the "double hit" of surgical malabsorption and estrogen deficiency on the skeletal system. Estrogen is fundamentally bone-protective; its loss during menopause accelerates RANKL-mediated osteoclast activity. When this is coupled with a Roux-en-Y Gastric Bypass (RYGB) or Bilio-pancreatic Diversion (BPD), which bypasses the duodenum, the primary site for active calcium transport,the risk for secondary hyperparathyroidism and accelerated bone resorption becomes profound. Clinical evidence suggests that postmenopausal women undergoing malabsorptive procedures experience significantly higher rates of fragility fractures compared to their premenopausal counterparts. Therefore, the transition from calcium carbonate to calcium citrate is mandatory, as the latter does not require an acidic gastric environment for absorption, which is lacking in the post-bariatric stomach.[115-117]

Gastroesophageal R eflux and Procedural Selection: Menopause is an independent risk factor for the development and exacerbation of Gastroesophageal Reflux Disease (GERD), likely due to the loss of the protective effects of progesterone and estrogen on the lower esophageal sphincter (LES) and the redistribution of fat to the visceral compartment. In the context of bariatric surgery, the choice of procedure is paramount. While Sleeve Gastrectomy (SG) is often preferred for its technical simplicity, it is associated with increased intraluminal pressure and can worsen reflux in the menopausal patient. In contrast, the Roux-en-Y Gastric Bypass serves as a definitive anti-reflux procedure by diverting acid and bile away from the esophagus. For the postmenopausal woman with pre-existing hiatal hernia or esophagitis, RYGB remains the preferred surgical approach to prevent long-term complications such as Barrett's esophagus.[116,117]

Sarcopenic Obesity and Nutritional Management: The synergistic effect of age-related muscle loss (sarcopenia) and the rapid weight loss following bariatric surgery poses a significant risk to the functional status of postmenopausal women. The decline in growth hormone and estrogen further impairs protein synthesis. Postoperative nutritional strategies must therefore prioritize high-biological-value protein intake to mitigate the loss of lean muscle mass. Furthermore, the altered pharmacokinetics of the post-bariatric gut must be considered if MHT is prescribed. Oral estrogens may have erratic absorption due to reduced gastric surface area and altered intestinal transit times; thus, transdermal delivery systems are often recommended as the gold standard to ensure therapeutic stability and bypass hepatic first-pass metabolism.[117]

Gastrointestinal Disease and Bone Health in Postmenopausal Women

Osteoporosis prevalence and mechanistic basis: Osteoporosis is defined by reduced bone mass, impaired microarchitecture, and increased fracture susceptibility. It affects up to 50% of white women older than 50 years and is a major driver of vertebral, hip, and distal radius fractures.Bone remodeling depends on balance between osteoclast resorption and osteoblast formation; aging shifts this balance toward bone loss.[118-120] Menopause is a key inflection point: estrogen decline increases RANKL and decreases osteoprotegerin, promoting osteoclast differentiation, activity, and survival.[121]

GI diseases as cause of secondary osteoporosis: Secondary osteoporosis is common in gastrointestinal diseases due to inflammation, malabsorption, reduced activity, and medication exposures (notably glucocorticoids and immunosuppressants).[121]

IBD and fractures: IBD also is associated with increased fracture risk . this may be due to inflammation, malnutrition, calcium/vitamin D malabsorption, hypogonadism micorbiome shifts and glucocorticoid exposures. Osteoclastic activity increases and muscle strength decreases.[122]

Coeliac disease and bone fragility: Coeliac disease is associated with low bone mineral density. At diagnosis, 38–72% of coeliac patients have low BMD, even without overt GI symptoms.Fracture risk is increased by 43–92% vs controls.[123-

[125] Villous atrophy impairs calcium absorption → hypocalcaemia → secondary hyperparathyroidism → osteoclast-mediated resorption.[126] Chronic inflammation and micronutrient deficiency further damage bone; postmenopausal estrogen deficiency magnifies this harm.

H. pylori and bone: H. pylori infection hasbeen associated with osteopenia/osteoporosis in observational studies and meta-analyse.[126] CagA-positive strains may confer higher skeletal risk; in a meta-analysis including >24,000 participants, CagA-positive infection was linked to ~42% higher osteoporosis risk vs uninfected controls.[127] Proposed mechanisms include systemic inflammation, oxidative stress, impaired gastric acidification affecting calcium absorption, and altered endocrine signaling.[128]

The gut microbiome as a bone regulator: The gut microbiota influences host development and immune tone, and signals to distant organs.[129-131] Experimental and clinical data suggest microbiome composition can modulate bone via immune pathways, short-chain fatty acids, calcium absorption, and systemic inflammation.This is particularly relevant in menopause and chronic GI disease where dysbiosis is common, creating a plausible triad: menopause → microbiome shifts + immune activation → altered bone turnover and fragility.[130-135] In postmenopausal women, GI disease and osteoporosis frequently coexist and may exert additive or synergistic effects on fracture risk. Judicious steroid use, calcium/vitamin D optimization, and timely DXA screening are essential, especially in IBD, coeliac disease, cholestatic liver disease, and in those on long-term immunosuppression.

SYNOPSIS

- Menopause with its decreasing estrogen levels modifies gastrointestinal function and disease through various pathways. It affects motility, visceral sensitivity, metabolic regulation, microbiota and immune signaling.
- Menopausal status may normalize some motor patterns it also meaningfully influences the epidemiology and outcomes of reflux disease, functional bowel disorders, hepatobiliary pathology, and selected gastrointestinal cancers.
- Recognizing these hormone-related effects can prevent diagnostic delay and therapeutic oversimplification.
- A menopause-informed approach,integrating hormonal context, metabolic health, and brain–gut mechanisms,offers a more precise framework for managing gastrointestinal disease in women across midlife and beyond.

RESEARCH AGENDA

Prevalence and presentation of GERD in peri and postmenopausal women in Indian context

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RENAL SYSTEM

Keywords: Menopause, renal dysfunction, chronic kidney disease, menopause hormone therapy

INTRODUCTION

Menopause marks a critical transition in a woman's life, influencing multiple organ systems, including the kidneys.[1] Estrogen appears to modulate renal physiology, and as estrogen levels decline, the kidneys may become increasingly susceptible to endothelial dysfunction, oxidative stress, and inflammatory signalling, thereby potentially accelerating both the structural and functional trajectories of age-related renal decline.[2]

Epidemiological evidence suggests that menopause is independently associated with a greater fall in estimated glomerular filtration rate (eGFR) and a higher prevalence of Chronic Kidney Disease (CKD), even after adjusting for confounders such as age, hypertension, diabetes, and obesity.[3-5] A shorter reproductive lifespan, and thus reduced cumulative estrogen exposure, may be associated with a higher incidence of CKD.[4,6] Women bear a significant but often under-recognised burden of CKD. Women of reproductive age group with CKD are prone to menstrual disorders, infertility and premature ovarian insufficiency (POI).[7,8] CKD often remains asymptomatic until late stages, underscoring the need for large-scale strategies to detect early disease, slow its progression, and improve cardiovascular outcomes.[8,9] Regular monitoring of renal function and early detection of impairment are particularly essential in postmenopausal women.[10]

RENAL PHYSIOLOGY AND MENOPAUSE

Studies have suggested that estrogen and estrogen receptors (ERs) play key roles in many physiological processes in the kidney, including mitochondrial homeostasis, endothelin-1 regulation, repair, regeneration, and phosphorus homeostasis.[2] Premenopausal women generally exhibit lower blood pressure and a lower prevalence of hypertension compared to men, largely due to the protective effects of estrogen.[9] This advantage diminishes after menopause, when declining estrogen levels may lead to a more rapid rise in blood pressure, which may be comparable to or exceed that of age-matched men. These patterns are thought to reflect, at least in part, sex-related differences in renal physiology, including modulation of the renin–angiotensin–aldosterone system (RAAS), endothelin (ET) pathways, and tubular transport mechanisms.[9]

Estrogen has been shown to interact with the renin-angiotensin system (RAS), which controls blood pressure, renal function, and fluid balance. Angiotensin-converting enzyme 2 (ACE2) converts angiotensin II, a peptide that promotes vasoconstriction and inflammation, into angiotensin (1-7), which has vasodilatory and anti-inflammatory effects. Experimental evidence suggests that estrogen upregulates ACE2 expression, thus increasing the formation of protective angiotensin (1-7) and contributing to improved vascular and renal function. The Mas receptor (MasR) is the primary receptor for angiotensin (1-7), mediating its effects. Estrogen upregulates MasR expression, thus enhancing the effect of angiotensin (1-7). The angiotensin II type 1 receptor (AT1R) is responsible for the vasoconstrictive, pro-inflammatory, and oxidative stress-promoting effects of angiotensin II. Estrogen has been shown to downregulate AT1R expression, thereby reducing angiotensin II binding and its detrimental effects on vascular and renal function. Through modulation of the renin–angiotensin system, estrogen may contribute to a shift toward vasodilatory and anti-inflammatory effects in the vascular and renal compartments by boosting beneficial pathways (ACE2/MasR) and reducing harmful ones (AT1R).[9] In addition to this, estrogen has been implicated in nitric oxide (NO)-mediated vasodilation and enhanced renal sodium excretion.

Androgens have been associated with increased activity of renin, angiotensin II, and aldosterone, as well as increased epithelial sodium channel (ENaC) expression, thereby enhancing renal sodium reabsorption and contributing to higher blood pressure.[9] In contrast, estrogenic influences are more commonly linked to vasodilatory pathways and natriuresis, highlighting sex-related differences in the regulation of blood pressure and sodium homeostasis.[9]

The menopausal transition (MT) is accompanied by changes in the hormonal milieu that may influence the RAAS and vascular function. In parallel with advancing age, postmenopausal women tend to exhibit lower eGFR and a higher prevalence of hypertension, impaired fasting glucose, and metabolic syndrome.[11] A cross-sectional study of 3,918

women aged 40–55 years found that menopause was linked to a 2.32 ml/min/1.73 m^2 decrease in eGFR, even after accounting for age, body composition, and metabolic factors. Menopausal women also had a 51% higher likelihood of having an eGFR below 90 ml/min/1.73 m^2. These findings indicate that menopause and estrogen deficiency may independently contribute to reduced kidney function, beyond the effects of changes in body composition, fat distribution, and metabolism that occur during the MT.[3]

Higher circulating follicle-stimulating hormone (FSH) levels have been independently associated with indicators of renal dysfunction in postmenopausal women. Across menopausal stages, rising FSH concentrations have been linked to higher serum creatinine and lower eGFR, with women in the highest FSH categories showing a greater likelihood of reduced kidney function or CKD compared to those with lower FSH levels.[11] Advancing age appears to further aggravate this relationship, suggesting that elevated FSH, in addition to estrogen loss, may contribute to renal function decline after menopause.[11]

Longitudinal data from the Michigan cohort of the Study of Women's Health Across the Nation (SWAN), which followed women through midlife, demonstrate a gradual decline in kidney function. In this cohort, lower FSH levels and higher sex hormone–binding globulin (SHBG) concentrations were associated with higher eGFR.[1] Importantly, although eGFR was associated with FSH and SHBG levels, the rate of decline in renal function was consistent with that expected from ageing alone, underscoring renal ageing as the primary driver, with menopausal hormonal changes acting as modifying rather than causative factors.

CHRONIC KIDNEY DISEASE AND MENOPAUSE

The MT is accompanied by changes in ovarian function that may influence renal and cardiovascular physiology, potentially increasing vulnerability to CKD and related metabolic disturbances. CKD affects approximately 11–13% adults worldwide, with prevalence varying by sex. In a recent systematic review and meta-analysis of community-based studies from India (2011–2023), the pooled prevalence of CKD was 13.51% among women and 14.80% among men.[12] CKD represents a substantial health and economic burden, conferring increased risks of cardiovascular disease (CVD), premature death, and reduced quality of life (QoL).[8,9] CKD-related mineral and bone disorder (CKD-MBD) further contributes to osteoporosis, vascular calcification, and higher mortality.[13]

Pathophysiology of CKD in Relation to Menopause: Both early natural and early surgical menopause are associated with an increased risk of CKD.[6] Women with CKD exhibit higher luteinizing hormone (LH) and FSH levels, along with lower testosterone and estradiol concentrations compared with women without CKD, highlighting the bidirectional relationship between sex hormones and kidney health.[6] Experimental and clinical evidence suggests that estrogen deficiency may contribute to renal oxidative stress, inflammation, apoptosis, and fibrotic pathways, processes which are implicated in CKD progression. Disruption of estrogen ER signalling has been linked to acute kidney injury and several chronic kidney disease states, including diabetic nephropathy, lupus nephritis, and IgA nephropathy.[2]

Beyond estrogen deficiency, emerging evidence implicates a potential role for FSH in renal fibrosis and CKD progression, revealing new endocrine mechanisms in postmenopausal CKD. Experimental studies indicate that FSH can act on renal tubular cells, promoting profibrotic signalling and IL-8–mediated inflammatory responses, pointing to a novel mechanism of kidney injury after menopause.[14]

In ovariectomized animal models, these renal pathological changes were reversed by bone marrow-derived mesenchymal stem cell (BM-MSC) exosomes. Improvements in renal function and reductions in fibrosis and apoptosis support the concept of a potential therapy to protect kidney structure and function in postmenopausal women.[15]

Risk factors for Chronic Kidney Disease:

Gender: Women have a higher prevalence of advanced CKD, whereas men experience faster progression, higher mortality, and increased cardiovascular risk.[16,17] Postmenopausal women are less likely to undergo screening or receive timely treatment and face greater barriers to renal transplantation.[17] Elderly women more frequently opt for conservative care and report lower quality of life on renal replacement therapy (RRT), while men tend to start RRT earlier. These disparities reflect both biological and socio-cultural factors, highlighting the need for sex- and gender-sensitive approaches to CKD care.

Sex- and menopause-specific risk factors for CKD: Lower lifetime exposure to endogenous estrogen has been associated with a higher risk of CKD in women. In a 15-year prospective cohort study of 3,043 women, shorter duration of endogenous estrogen exposure (< 11 years) was linked to a higher incidence of CKD, particularly before 45 years of

age.[18] Additional reproductive factors, including early menopause, hysterectomy or bilateral oophorectomy before 45-50 years, younger age at first childbirth, and early initiation of menopause hormone therapy (MHT), have also been associated with increased CKD risk, underscoring the complex relationship between reproductive history, hormonal exposure, and renal ageing.[19,20]

Obesity: may contribute to renal inflammation and lipid dysregulation, effects which may be further amplified after menopause.[21]

Sleep: Poor sleep quality, short sleep duration, and reduced sleep efficiency have been linked to reduced renal function in postmenopausal women. Observational data suggest that MHT may attenuate this association and be protective. Thus, sleep health and MHT may help mitigate renal decline in later life.[22]

Impact of Chronic Kidney Disease

In women, CKD has systemic consequences, with important effects on reproductive, skeletal, and cardiovascular health.

Reproductive Health and Early Menopause In CKD: Menstrual disorders, infertility, and features of POI are common but often underrecognized in women with CKD.[23] When CKD develops during the reproductive years, it can have a profound impact on ovarian function, with menopause occurring on average approximately 5 years earlier than in the general population, at a reported mean age of around 45.5 years.[24] Early menopause has been described across all stages of CKD (stages 3–5D). [10] A diagnosis of CKD during the reproductive years has been associated with a 2.64 times higher risk for early menopause.[25]

In women with advanced CKD (stage 5 or receiving dialysis), disruption of the hypothalamic-pituitary-ovarian axis leads to menstrual irregularity and an early menopause like state.[10] The uremic milieu, together with hyperprolactinemia and increased levels of endorphins and leptin, impairs the pulsatile secretion of gonadotropin-releasing hormone.[10] This results in abnormal LH and FSH release, loss of the normal pre-ovulatory rise in estrogen and progesterone, and consequent chronic anovulation and amenorrhoea.[10]

Diagnosing menopause in premenopausal-age women with CKD stage 5D can be challenging, as the traditional definition of menopause is not fully applicable in this population.[10] Menstrual function may resume with hormone replacement therapy, intensive dialysis, or following kidney transplantation, indicating that ovarian suppression in advanced CKD may be functional, rather than permanent.[10,23] In CKD, nephrology clinics should routinely record gynaecological and reproductive history, age at menopause, and history of MHT use.

CKD-Related Mineral and Bone Disorder (CKD-MBD) CKD patients have a higher risk of fracture than the general population across all age groups. Osteoporosis is a disorder of the bone that reduces bone strength, as measured by bone mass and quality. Renal osteodystrophy (ROD) refers specifically to the skeletal component of CKD-MBD and encompasses a spectrum of bone histological abnormalities related to altered turnover and mineralisation. Therapies to protect against fractures must be personalised and based on bone turnover and mineralisation.[26]

The effect of menopause on CKD-MBD is poorly defined, and there are no longitudinal studies of changes in bone density, bone quality, or CKD-MBD-related metabolic parameters during the menopause transition in women with CKD. Skeletal fragility in women with advanced CKD is multifactorial and complex, driven by the combined effects of postmenopausal osteoporosis, medication effects, and CKD-MBD. Uraemic inflammation, hormonal imbalances, and medications such as corticosteroids accelerate bone loss.[27] ROD, a low-turnover bone disease, along with secondary hyperparathyroidism, contributes to cortical bone resorption, further weakening bone and making fractures common.[25,27] CKD has been associated with greater tooth loss in postmenopausal women, especially those aged 66-79 years.[28]

In women with CKD, disturbances in calcium–phosphorus homeostasis, parathyroid hormone excess, and vitamin D deficiency contribute to CKD-MBD, resulting in impaired bone quality and increased fracture risk.[29] CKD-MBD is a systemic condition that impacts both the skeletal and cardiovascular systems and can occur at any stage of CKD.[26] It arises from a combination of traditional and CKD-specific risk factors that affect skeletal and cardiovascular systems.[26] CKD-specific factors include disturbances in mineral metabolism (calcium, phosphate, parathyroid hormone (PTH), 25-hydroxyvitamin D [25OHD], Fibroblast growth factor 23 [FGF-23]), uremic toxins and altered function in immune, endocrine, neurohormonal, and gut systems.[26]

Diagnosis of CKD-MBD relies on a multi-modal approach.[26] Biochemical assessment can provide information on calcium, phosphorus, 25 (OH) D, parathyroid hormone, FGF-23, and markers of bone formation and resorption. Thoracic or lumbar spine X-rays and dual-energy X-ray absorptiometry (DXA) are used to evaluate bone structure and bone mineral density (BMD). Histomorphometry analysis of bone biopsies in selected cases provides detailed insight into bone turnover and architecture.[30]

CKD-Associated Cardiovascular Disease: is the primary cause of mortality in postmenopausal women with CKD.[13] In addition to traditional risk factors, women with CKD are exposed to non-traditional cardiovascular risk factors (CRFs), including inflammation and calcium-phosphate imbalance.[13] Vascular calcification in CKD is a complex, multisystem disease.[26] Declining kidney function, reflected by a lower eGFR, is associated with an increased risk of heart failure, particularly heart failure with preserved ejection fraction (HFpEF). Clinically, women with CKD require careful monitoring for signs of heart failure.[31]

Cardiovascular risk stratification in women with CKD - Routine evaluation of the 10-year cardiovascular mortality risk using traditional calculators is not required for women with CKD stages 3–5.[32] Risk assessment depends on reduced eGFR and the severity of albuminuria, both of which independently and substantially increase cardiovascular morbidity and mortality.[32]

- Women with mildly reduced kidney function (eGFR 45–59 mL/min/1.73 m^2; CKD G3a) and normal albumin excretion (< 30 mg/g) have at least a moderate cardiovascular risk, which rises to high risk when albuminuria is present.
- An eGFR below 45 mL/min/1.73 m^2 (CKD G3b) is associated with high to very high cardiovascular risk, even in the absence of significant albuminuria.
- Women with advanced CKD (eGFR < 30 mL/min/1.73 m^2; CKD G4–G5), as well as those with severely increased albuminuria (≥300 mg/g) at any stage of CKD, should be considered at very high cardiovascular risk.

Cardiovascular imaging, such as vascular calcification evaluation or echocardiography, is used to assess cardiovascular involvement.[26] This integrated diagnostic strategy enables a comprehensive understanding of CKD-MBD, allowing targeted management.

Sexual Dysfunction: Sexual dysfunction is common in women with CKD and is driven by hypoestrogenism, leading to vaginal dryness and dyspareunia, uraemia, and treatment- related factors.[10] Approximately 55% of women with CKD report difficulties with sexual arousal, and difficulty achieving orgasm is also frequently reported.[33]

MANAGEMENT OF POSTMENOPAUSAL WOMEN WITH CHRONIC RENAL DISEASE

Screening for CKD and Referral to a Nephrologist: Women older than 50 years, particularly those with hypertension and/or diabetes mellitus, should be routinely screened for kidney disease.[25] Referral to a nephrologist is recommended in the presence of marked albuminuria (urine albumin-to-creatinine ratio >300 mg/g), a decline in eGFR of at least 25% or any eGFR <30 mL/min/1.73 m^2, haematuria or newly diagnosed nephrolithiasis, suspected hereditary kidney disease, or renal dysfunction of unclear aetiology.[25]

Regular assessment of the major CRFs, early evaluation of bone health, and careful consideration of MHT for menopausal symptoms should be integral components of the comprehensive multidisciplinary management plan for postmenopausal women with CKD.[25, 34-37] In the presence of comorbidities such as diabetes, dyslipidaemia, and hypertension, an individualised approach is essential.[38,39]

- *Lifestyle modifications* including weight optimisation, regular physical activity, exercise (at least 150 min per week or as tolerated), smoking cessation, moderation of alcohol intake, and dietary mod ications (daily sodium intake of <2 g).[25]
- *Therapeutic interventions* such as optimal control of blood sugar, blood pressure, and lipids.[40] Use of RAAS blockade when indicated. In women with established CVD, low-dose aspirin may be considered.
- *MHT:* In postmenopausal women with one or two CRFs who experience severe menopausal symptoms, transdermal MHT may be considered.[25] In women with established CVD, long-standing diabetes mellitus, or three or more CRFs, local (vaginal) estrogen therapy is preferred for the management of genitourinary symptoms.

Preventive Strategies in Postmenopausal Women with Chronic Kidney Disease and High or Very High Cardiovascular Risk:[25]

- Lipid management should aim for an Low density lipoprotein (LDL)-cholesterol target of <1.8 mmol/L (70 mg/dL) in those at high cardiovascular risk and <1.4 mmol/L (55 mg/dL) in those at very high risk. In non–dialysis-dependent women, statin therapy, with or without ezetimibe, is recommended. Women initiating dialysis while already receiving lipid-lowering therapy may continue treatment; however, initiation of statins during ongoing dialysis in the absence of clinical atherosclerotic CVD is not recommended.
- In the presence of albuminuria, RAAS inhibition should be considered regardless of blood pressure. Target systolic blood pressure (SBP) <130 mmHg when tolerated. In kidney transplant recipients, a target SBP <130 mmHg and diastolic blood pressure (DBP) <80 mmHg is recommended.
- HbA1C target is <6.5% to <8.0%. For women with type 2 diabetes mellitus or non-diabetic kidney disease, an eGFR >20 mL/min/1.73 m^2, or coexisting heart failure, sodium glucose co-transporter 2 (SGLT2) inhibitors should be considered for combined renal and cardiovascular protection. Additional therapies, including GLP-1 receptor agonists, mineralocorticoid receptor antagonists, and antiplatelet agents, may be used according to individual clinical indications and risk profiles.

Management of Osteoporosis in Postmenopausal Women with Chronic Kidney Disease

Management should be individualised according to the CKD stage.[27] In women with CKD stages G1–G3, osteoporosis assessment and treatment generally follow recommendations for the general population.[25] In advanced CKD (stages G4–G5), with or without biochemical abnormalities, management should be undertaken in collaboration with a renal specialist, with optimisation of CKD-MBD treatment.[25,27]

- Lifestyle modification: All women should receive lifestyle and supportive measures, including adequate calcium intake (800–1200 mg/day). In postmenopausal women with CKD stages 1–3, vitamin D is usually given at 1000–2000 IU/day. In CKD stages 4–5, vitamin D alone is insufficient; active vitamin D analogues are required, with close monitoring. Encourage weight-bearing exercise, fall-prevention strategies, and smoking cessation.[25]
- Pharmacological therapy: should be individualised, balancing fracture risk against potential adverse effects. MHT prevents postmenopausal osteoporosis and fractures; estrogen replacement should be considered in premenopausal women with amenorrhoea, without contraindications.[10] When indicated, osteoporosis treatments such as denosumab, parathyroid hormone analogues, or romosozumab may be safely considered, with careful monitoring in women with advanced CKD.[25] No dose adjustment is required for denosumab or romosozumab in CKD; however, close monitoring for hypocalcaemia is required in women with creatinine clearance (CrCl) < 30 mL/min or those on dialysis.[10] Potential adverse events include the risk of hypocalcaemia, atypical fractures, and osteonecrosis of the jaw with denosumab; hypotension with teriparatide; and hypocalcaemia and adverse cardiovascular events with romosozumab.[25] Particular attention should be paid to rebound bone loss after discontinuation of denosumab or romosozumab. Teriparatide may require dose adjustment; treatment duration is limited to 24 months; and it is contraindicated in CKD stages 4–5D.[10] Bisphosphonates, alendronate and zoledronic acid, may be used for the treatment of osteoporosis in postmenopausal women with CKD when CrCl is ≥ 35 mL/min, with no dose adjustment required. Their use is not recommended in patients with a CrCl < 35 mL/min. Use of bisphosphonates is generally contraindicated in CKD stages G4 to G5.[10]
- Raloxifene: Selective estrogen receptor modulators, such as raloxifene, may offer fracture protection and potential renal benefits in selected populations.[23] It increases BMD at the hip and spine and reduces the risk of vertebral fractures in women with CKD without increasing adverse effects.[41] In postmenopausal women, including those on haemodialysis, raloxifene also improves trabecular bone density, reduces bone resorption markers, and may slow the progression of albuminuria in those with diabetes.[42,43] In a recent meta-analysis, raloxifene in postmenopausal women with end-stage renal disease (ESRD) significantly increased BMD at the lumbar spine (SMD 3.30; 95% CI 3.21–3.38) and at the femoral neck (SMD 3.29; 95% CI 3.21–3.36) compared with placebo.[44]

- Management of CKD- MBD[26,30] The aim is to slow progression and reduce fracture risk, cardiovascular events, and mortality through individualised care. CKD-associated osteoporosis management should consider fracture risk, bone turnover, CKD stage, and mineral metabolism, with correction of vitamin D d iciency, maintenance of calcium–phosphate balance, monitoring of PTH levels, and use of calcimimetics or parathyroidectomy for secondaryhyperparathyroidism in CKD G5D.[26]

Management of Vasomotor Symptoms in Chronic Kidney Disease

Menopause Hormone Therapy

Although endogenous estradiol appears to be renoprotective, evidence regarding the renal effects of exogenous MHT remains inconsistent.[45,46] At present, there are no CKD-specific guidelines for MHT use, and available studies report variable effects on kidney function, cardiovascular risk, and fracture outcomes, likely due to variations in formulation, route of administration, type of progestogen, timing of initiation, and underlying renal function.[19,23,47] MHT is primarily indicated for the relief of vasomotor symptoms. In women with CKD, doses of 17β-estradiol generally recommended are 50–70 % lower than those used in women with normal kidney function, with no clear CKD stage–specific cut-offs.[25] Data on progesterone dosing in CKD are limited, although the risk of fluid retention may be increased in women with underlying kidney disease.[25] The transdermal route is preferred for women at high or very high cardiovascular risk. Women receiving calcineurin inhibitors (cyclosporine, tacrolimus) should have estradiol levels closely monitored after initiation of MHT, due to potential pharmacokinetic interactions that may alter hormone metabolism.[25]

In women with CKD, including advanced stages, treatment with MHT has been associated with improvements in QoL and selected surrogate bone and cardiovascular markers in limited observational studies. However, an elevated risk of thrombosis with oral estrogens has also been reported.[47,48] Observational cohort data suggest that later age at menopause or earlier initiation of MHT is associated with a reduced risk of CKD and ESRD, suggesting a possible protective, but non-causal, role of female hormones in kidney health.[19] In a large observational cohort of 1.46 million postmenopausal Korean women followed for nine years, MHT use was associated with approximately a 30% lower risk of developing ESRD, with greater benefit observed with longer MHT duration, suggesting a renal-protective effect of estrogen.[37] MHT has been associated with a lower risk of CKD-related cognitive dysfunction in postmenopausal women.[49]

Due to the absence of definitive trial data, MHT regimens in women with CKD should be individualised, taking into account cardiovascular and thrombotic risk, stage of kidney disease, symptom burden, and patient preference. In women with premature or early menopause, protection of renal function may be considered as a potential additional benefit of MHT.[25] The possibility that low-dose MHT might improve sexual function in postmenopausal women with CKD remains biologically plausible but is not supported by direct, high-quality studies.[10]

Non-hormonal therapy in Chronic Kidney Disease

Non-hormonal treatments for vasomotor symptoms and osteoporosis are not contraindicated in women with CKD; evidence from large CKD-specific RCTs is limited.[25,50,51] Dose adjustments of non-hormonal preparations should be guided by the patient's creatinine clearance or eGFR.

UROLITHIASIS

Long-term observational data from the Nurses' Health Study II indicate that postmenopausal women had a 27% higher incidence of kidney stones than premenopausal women, with a further increase in risk after surgical menopause.[52] Hormone therapy was not associated with a significant change in stone risk.[52] Among postmenopausal women, urolithiasis is more frequently associated with uric acid stone composition, diabetes, hyperuricemia, and reduced kidney function. Both postmenopausal status and hyperuricemia are independent risk factors for uric acid stones.[53] These women often require more invasive procedures and have lower self-voiding rates, highlighting the need for tailored management to protect renal function.[53] Early recognition and individualised evaluation are essential to prevent recurrence and preserve renal function in postmenopausal women with urolithiasis.

SYNOPSIS

- Menopause marks an important physiological transition that can influence kidney function, as loss of estrogen's protective effects may contribute to endothelial dysfunction, oxidative stress, and progressive renal ageing.
- Population studies show that menopause is linked to lower eGFR and a higher prevalence of CKD, particularly in women with early or surgical menopause and shorter lifetime exposure to estrogen. Estrogen supports key renal and vascular pathways including the renin–angiotensin–aldosterone system, nitric oxide signalling, and sodium balance. Rising follicle-stimulating hormone levels after menopause may further impair kidney function.
- CKD in postmenopausal women has multisystem effects, including early menopause, cardiovascular disease, osteoporosis, CKD–MBD, sexual dysfunction and cognitive impairment.
- Screening and early detection of CKD are integral to management, particularly in women with cardiometabolic risk factors. Management requires a multidisciplinary, individualised approach that addresses cardiovascular risk reduction, bone health, and the cautious use of menopause hormone therapy, based on renal function and overall risk profile.
- Osteoporosis management in women with CKD requires stage-specific evaluation, integration with CKD-MBD assessment, and individualised use of anti-osteoporotic therapies in collaboration with nephrology care.

RESEARCH AGENDA

Large, prospective studies to clarify the impact of menopause on CKD and the role of MHT in this population.

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IMMUNE SYSTEM

Keywords: Menopause,estrogen withdrawal, immune regulation, autoimmune disease, rheumatoid arthritis, systemic lupus erythematosusy

INTRODUCTION

Menopause is a major biological transition in a woman's life, marked by the permanent cessation of ovarian follicular activity and a sustained decline in estrogen and progesterone levels. Beyond vasomotor and urogenital symptoms, menopause exerts profound effects on immune regulation, musculoskeletal health, pain perception, metabolism, and vascular biology. These changes are particularly relevant to systemic rheumatic diseases (SRDs), many of which show strong female predominance, characteristic age-related shifts in incidence, and clear links to reproductive milestones. For gynaecologists, understanding the intersection between menopause and rheumatology is essential, as gynaecological encounters often precede or coincide with the onset or progression of rheumatic disease.

This chapter provides an integrated, clinically oriented overview of how menopause influences the epidemiology, pathophysiology, and clinical expression of major systemic rheumatic diseases, with a particular focus on rheumatoid arthritis (RA), osteoarthritis (OA), Sjögren's syndrome (pSS), systemic sclerosis (SSc), gout, fibromyalgia (FMS), and bone health.

OVERVIEW OF THE IMMUNE SYSTEM

The immune system is a complex network of cells, tissues, and soluble mediators that protects the host against pathogens and maintains homeostasis. It is broadly divided into innate and adaptive immunity. Innate immunity provides the first line of defence through physical barriers, phagocytic cells (such as macrophages and neutrophils), natural killer (NK) cells, and inflammatory cytokines. Adaptive immunity involves antigen-specific responses mediated by T and B lymphocytes, leading to immunological memory. Hormonal, genetic, and environmental factors, including sex hormones such as estrogen and progesterone, tightly regulate immune responses.[1]

IMMUNO-ENDOCRINE CHANGES ACROSS MENOPAUSE

Estrogens exert complex, dose-dependent immunomodulatory effects. At physiologic concentrations, estradiol generally promotes immune tolerance, enhances regulatory T-cell function, and suppresses excessive Th1- and Th17-mediated inflammation. Estrogens can regulate macrophage function, both inflammatory and non-inflammatory cytokine production, T cell differentiation towards Th1, Th2, or Treg cells, and B cell function, influencing antibody production. Estrogens, particularly estradiol (E2), play a significant role in regulating macrophage biology. They influence macrophage differentiation by regulating macrophage colony-stimulating factor (M-CSF). In certain settings, estrogens also regulate the recruitment of monocytes and macrophages to sites of inflammation, infection, or tumors.[1] Estrogens also influence cytokine production by macrophages, with both positive and negative effects, depending on factors such as estrogen type, exposure duration, macrophage origin, and estrogen levels. Progesterone further reinforces immune quiescence by modulating antigen-presenting cells and cytokine balance. The menopausal transition, characterised by fluctuating and ultimately low estrogen levels, disrupts these regulatory pathways and shifts immune responses toward a more pro-inflammatory state.[1]

In parallel, menopause is associated with changes in adipose tissue distribution, insulin sensitivity, oxidative stress, and neuroendocrine signaling, all of which influence pain perception, musculoskeletal integrity, and cardiovascular risk. These systemic effects provide a biological framework for the observed clustering of autoimmune disease onset and symptom exacerbation in the years surrounding menopause.

Estrogens exert complex, dose-dependent immunomodulatory effects. At physiologic concentrations, estradiol promotes immune tolerance, enhances regulatory T-cell (Treg) function, and suppresses excessive Th1- and Th17-mediated inflammation.[2,3] Estrogens regulate macrophage function, including inflammatory and anti-inflammatory cytokine production, T-cell differentiation toward Th1, Th2, or Treg phenotypes, and B-cell activity, thereby influencing antibody production (Fig. 2).[2,4] Estradiol (E2) plays a central role in macrophage biology by influencing differentiation and function through estrogen receptor-mediated regulation of macrophage colony-stimulating factor (M-CSF) and cytokine signaling pathways. Depending on estrogen concentration, duration of exposure, and cellular

context, estrogen may exert either pro- or anti-inflammatory effects[3,5] Progesterone further promotes immune quiescence by modulating antigen-presenting cell function and maintaining cytokine balance.[6]

The menopausal transition(MT), characterized by fluctuating and ultimately declining estrogen levels, disrupts these regulatory mechanisms and shifts immune responses toward a pro-inflammatory state.[3,7] Concurrently, menopause is associated with adverse changes in adipose tissue distribution, insulin sensitivity, oxidative stress, and neuroendocrine signaling, contributing to increased cardiometabolic and inflammatory disease risk and providing a biological basis for the increased incidence and exacerbation of autoimmune diseases during this period.[7]

PREDISPOSITION TO INFECTIONS AND IMPAIRED VACCINATION RESPONSES IN POSTMENOPAUSAL WOMEN

Postmenopausal women face an increased risk of infections and reduced vaccine efficacy due to diminished estrogen levels, which cause vaginal atrophy, higher PH, and immunosenescence (age-related immune decline). A second peak in HPV prevalence occurs post-menopause. Women over 45 have a 4-fold higher risk of acquiring HIV compared to younger women.[8] Studies show that postmenopausal women may not develop robust protection from standard vaccine doses and show decreased antibody reponse to vaccines such influenza and pneumococcus. Low estrogen is a key cause of impaired immunity suggested by research models using 17β-estradiol replacement restoring the antibody responses to vaccines.[9]

HORMONE THERAPY AND IMMUNE FUNCTION

Menopause hormone therapy (MHT) has been investigated for its potential to modulate immune responses in postmenopausal women. Estrogen therapy may reduce levels of pro-inflammatory cytokines and improve immune cell function. However, the effects of MHT on immunity are complex and influenced by factors such as dose, route of administration, timing of initiation, and individual health status. While MHT may confer some immunological benefits, it must be balanced against potential risks, including thromboembolism and hormone-dependent cancers.[3,10]

ESTROGEN AND COVID

Estrogen provides immune protection against COVID-19 primarily through anti-Inflammatory effects, reducing cytokine storm severity by inhibiting pro-inflammatory cytokines like IL-6 and TNF-α while promoting regulatory T-cell responses and antibody production[11]. Premenopausal women, with higher endogenous estrogen levels, show lower infection severity and mortality compared to men or postmenopausal women, linked to estrogen's downregulation of ACE2 receptors thereby reducing viral entry and modulation of innate immunity pathways like TLR7.[12] Studies suggest potential benefits of MHT in low- estrogen states, though clinical trials are needed to confirm safety and efficacy.[13]

RHEUMATOID ARTHRITIS AND MENOPAUSE

Epidemiology and Timing of Onset: Rheumatoid arthritis shows a distinct sex- and age-specific incidence pattern, with a second peak in women occurring in the postmenopausal period. Large population-based cohorts demonstrate that early menopause and a shorter reproductive lifespan are associated with increased risk of seronegative RA and postmenopausal-onset RA (PMORA).[14-17] Conversely, cumulative lifetime estrogen exposure appears protective in some observational studies. However, genetic analyses suggest that the timing of menarche and menopause alone may not be causally sufficient to explain RA risk.[18]

Serologic Phenotypes and Menopause: Menopause appears to influence RA phenotypes differentially. Several cohorts have shown stronger associations between early menopause and Anti-citrullinated protein antibody (ACPA)- negative inflammatory arthritis than with ACPA-positive disease[14,15]. This observation supports the concept that hormonal withdrawal may preferentially affect innate and stromal immune pathways rather than autoantibody-driven adaptive immunity.

Disease Activity and Symptom Burden: Postmenopausal women with RA frequently report higher pain scores, worse patient global assessment, and greater functional impairment compared with premenopausal women, even when objective inflammatory markers are similar. Recent data indicate that early menopause is independently associated with higher disease activity indices and pain, suggesting contributions from central sensitization, altered nociception, and estrogen-dependent neuromodulation rather than inflammation alone.[17]

Hormonal Therapies and RA Risk: Exogenous hormone exposure has divergent effects depending on life stage and formulation. Oral contraceptive use is generally associated with reduced RA risk, particularly during active use, whereas MHT has been linked to increased risk of late-onset RA in some cohorts.[19] Notably, prolonged MHT use in women with later menopause may confer protective effects in selected populations, underscoring the complexity of cumulative exposure, timing, and individual susceptibility. Women with RA and menopausal symptoms, especially with osteoporosis risk, can be given MHT.

SJÖGREN'S SYNDROME AND MENOPAUSE

Primary Sjögren's syndrome frequently manifests or worsens in midlife women. Epidemiologic studies indicate that reduced lifetime estrogen exposure is associated with increased risk of Primary Sjögren's syndrome (pSS), and menopausal status correlates with greater severity of sicca symptoms.[20,21] Vaginal dryness in pSS reflects both estrogen deficiency and systemic exocrinopathy, and is associated with neuropathy and reduced quality of life. For gynecologists, distinguishing genitourinary syndrome of menopause from autoimmune-mediated sicca is critical, as management strategies differ and often require multidisciplinary collaboration.[22] Data on HT influence are limited, and HT may be considered if there are no contraindications and after individual risk assessment. There is no evidence of disease exacerbation with MHT, and it appears to have a neutral effect on the disease.

SYSTEMIC SCLEROSIS AND MENOPAUSE

Systemic sclerosis exhibits significant shifts in menopause-related phenotypes. Registry data indicate that postmenopausal women, particularly those with early menopause, have a higher prevalence of interstitial lung disease (ILD), pulmonary hypertension, and vascular complications. These findings support the concept that estrogen withdrawal may accelerate vasculopathy and fibrotic pathways in genetically susceptible individuals. The SPRING-SIR registry analysis of 1538 Italian women with Ssc revealed that postmenopausal patients had higher rates of limited cutaneous SSc (70.5%), anti-centromere positivity (35.1%), interstitial lung disease, and gastrointestinal involvement compared with premenopausal patients[23]. Early menopause (before age 45, in 14.4%) independently predicted digital ulcers, reduced DLCO, vasculopathy, and ILD even after adjustments. These findings highlight the need for routine assessment of menopausal history in SSc risk stratification and targeted screening[24]. MHT is not absolutely contraindicated but should be used with caution. MHT, preferably transdermal, may be considered only for severe menopausal symptoms after individualised risk assessment, with particular caution or avoidance in women with pulmonary arterial hypertension, severe vasculopathy like significant Raynaud's/ischemic complications, or high thrombotic risk.

LUPUS ARTHRITIS AND MENOPAUSE

Systemic lupus erythematosus(SLE), particularly lupus arthritis, shows a distinct hormonal relationship. Estrogen stimulates B cells and autoantibody production. Consequently, many women with SLE experience an improvement in disease activity after natural menopause[25] Studies report lower SLE disease activity indices and fewer flares post-menopause. However, damage accrual may continue. MHT in postmenopausal SLE patients can precipitate mild-to-moderate flares.[26]

Postmenopausal women with SLE are at particularly high risk for osteoporosis and fractures. Estrogen deficiency, chronic inflammation, vitamin D deficiency, and prolonged glucocorticoid therapy synergistically impair bone density. Immune-mediated cytokines such as IL-1 and TNF-α further promote osteoclast activation and bone resorption.[27] Musculoskeletal pain and stiffness may persist or worsen after menopause, even in the absence of active synovitis, reflecting cumulative joint damage and age-related degenerative changes.

HT, particularly when combined with estrogen and progesterone, appears to be effective in alleviating menopausal symptoms in SLE patients. For inactive or low-activity SLE patients, the risk of flare seems to be very low. More studies are needed to establish the safety of HT prescriptions across their various formulations.[28] However, HT should be avoided or used with extreme caution in women with antiphospholipid antibodies or a history of thrombosis due to the elevated risk of venous and arterial events.[29]

SPONDYLOARTHROPATHIES AND MENOPAUSE

Data on menopause in spondyloarthropathies (SPA)are limited, but emerging evidence parallels RA/PsA. Estrogen appears to have an anti-inflammatory effect in SpA. An experimental arthritis model showed that estrogen suppressed

SpA-related inflammation. In contrast, estrogen deficiency worsened the disease.[30] Clinically, lower estrogen levels correlate with higher inflammation and symptoms, while estrogen replacement improves outcomes in some women with SpA. Loss of estrogen's bone-protective effects also contributes to osteoporosis risk. Estrogen appears to have an anti-inflammatory effect in SpA.[18] MHT is not containdicated and is neutral to the disease progression.

GOUT, METABOLISM, AND MENOPAUSE

Although traditionally considered a male-predominant disease, gout incidence increases substantially in women after menopause. Estrogen promotes renal urate excretion, and its decline contributes to rising serum uric acid levels. Large cohort studies confirm increased gout risk with early menopause and shorter reproductive lifespan, while certain hormone therapy formulations may modify this risk.[31]

FIBROMYALGIA AND PAIN AMPLIFICATION

Fibromyalgia is highly prevalent in peri- and postmenopausal women, increasing linearly with age, from premenopause to peri- and then to postmenopause.[32] Studies indicate that functional impairment in postmenopausal FMS is largely independent of body mass index, suggesting a prominent role for neuroendocrine and central pain-processing mechanisms rather than structural factors alone.[33] MHT is not contraindicated and may be used as an adjunctive, symptom-modulating treatment in women with bothersome menopausal symptoms, as estrogen can influence central pain processing and sleep, potentially improving sleep quality, fatigue, and pain perception, although MHT is not disease-modifying for fibromyalgia.

AUTOIMMUNE SKIN DISEASES IN MENOPAUSE

Autoimmune skin diseases are conditions in which the immune system mistakenly targets components of the skin, leading to chronic inflammation and varied clinical manifestations, such as rashes, plaques, blisters, and pigment changes.[34] These diseases disproportionately affect women, and the perimenopausal and postmenopausal periods represent critical phases of immune and hormonal transition that may influence disease onset, severity, and clinical course.[35]

The interplay between sex hormones and vitamin D: declining estrogen during menopause may exacerbate immune dysregulation, while inadequate vitamin D further impairs immune homeostasis. Together, these hormonal and micronutrient factors contribute to the sex bias, age distribution, and clinical severity observed in autoimmune skin disorders.[36]

Common Autoimmune Skin Diseases in Menopausal Women

Several autoimmune skin diseases can arise or change in clinical behavior around menopause:

PSORIASIS

A chronic autoimmune disease characterized by hyperproliferative, scaly plaques on the skin. Psoriasis and Menopause. Psoriasis, a prevalent T helper 17 (Th17)-driven autoimmune skin disease, exhibits variable clinical expression during menopause due to estrogen's immunomodulatory effects. Declining estrogen levels post menopause disrupt immune balance, reduce skin barrier integrity, and promote Th1/Th17 inflammation, often exacerbating plaques, inducing new flares, or diminishing treatment response in affected women. Concurrently, menopausal symptoms like stress, sleep disruption, and weight gain act as triggers, while thinner, drier skin heightens irritation. Management emphasises topical therapies, photoprotection, biologics for refractory cases, and non-hormonal menopause relief to mitigate inflammatory synergy.[37]

MHT lacks formal guideline-specific recommendations for patients with psoriasis due to limited high-quality data, but expert consensus and emerging evidence advise individualised assessment that weighs menopausal symptom severity against potential psoriasis risks. Large cohort studies indicate that HRT increases incident psoriasis risk in postmenopausal women (adjusted HR 1.22–1.48, with a greater increase with duration ≥5 years), but patient-reported data show neutral effects on existing psoriasis severity in most cases (62–73% unchanged).[38-40]

CUTANEOUS LUPUS ERYTHEMATOSUS AND SYSTEMIC LUPUS ERYTHEMATOSUS

SLE frequently manifests with characteristic skin lesions, such as the malar "butterfly" rash across the cheeks and

nasal bridge, discoid plaques with scarring and dyspigmentation, and photosensitive eruptions, affecting up to 80% of patients at some point in their disease course. These cutaneous features, classified as lupus-specific (acute cutaneous lupus erythematosus [ACLE], subacute cutaneous lupus erythematosus [SCLE], and chronic cutaneous lupus erythematosus [CCLE]) or nonspecific (vasculitic lesions or alopecia), arise from immune complex deposition, inflammation, and autoantibody-mediated damage exacerbated by ultraviolet exposure.[41]

Menopause introduces hormonal shifts, particularly declining estrogen levels, which may influence SLE activity. While estrogen promotes B-cell activation and autoimmunity, potentially worsening skin flares during the premenopausal years, postmenopausal reductions in estrogen often correlate with decreased overall disease severity and fewer exacerbations, though skin involvement can persist or evolve independently.[42]

MHT remains controversial in women with SLE due to risks of disease flares and thrombosis, though it may be cautiously considered for severe vasomotor symptoms in those with stable, inactive disease and no antiphospholipid syndrome (APS). Similar to oral contraceptive use, postmenopausal SLE patients face heightened arterial or venous thrombosis concerns, necessitating the lowest effective dose for the shortest duration if initiated; trials like SELENA demonstrated increased mild-to-moderate flares but no significant rise in severe activity or SLE Disease Activity Index (SLEDAI) scores, while meta-analyses indicate an elevated flare risk (relative risk 1.96).[26,43,44] Contraindications include active SLE, anti-phospholipid antibody (aPL) positivity, or APS owing to prothrombotic effects and insufficient safety data, with prolonged estrogen exposure linked to higher odds of discoid lupus (adjusted odds ratio 2.8). Safer regimens favour transdermal estradiol paired with micronised progesterone or dydrogesterone to minimise the risk of venous thromboembolism and coagulation activation compared with oral routes.[44]

DERMATOMYOSITIS (DM)

An autoimmune condition affecting both skin and muscle, presenting with characteristic rash patterns (heliotrope rash and Gottron's papules). Sex hormones appear to influence disease expression, with a higher female predominance suggesting sex-specific immune modulation.[44] No randomized clinical trials confirm the safety of MHT in dermatomyositis patients. However, in the absence of hypercoagulable states (antiphospholipid antibodies) or other contraindications, MHT is likely safe for managing menopausal vasomotor symptoms.[45]

SCLERODERMA

Localised scleroderma causes skin and subcutaneous fibrosis, mimicking systemic sclerosis histologically, but lacks Raynaud's, digital ischemia, or organ involvement. HT has the same effect as in systemic sclerosis.[46]

LICHEN PLANUS

A chronic inflammatory and autoimmune dermatologic condition with violaceous, pruritic papules and plaques. Although its exact cause remains unclear, it typically involves aberrant T-cell responses against basal keratinocytes. The incidence of oral lichen planus (OLP) is higher among perimenopausal women compared with the general population and shows a significant association with increasing severity of depression. In this group, LP may be mediated by decreased estrogen and progesterone levels, either directly or indirectly through the induction of depression, which may act as a triggering factor.[47]

Additional disorders, such as vitiligo (melanocyte destruction), pemphigus (autoantibodies against desmosomal proteins), and other autoimmune blistering diseases, may also present or change course during the menopausal years.[48] There remains considerable debate about the use of OCPs and HRT in individuals with autoimmune skin conditions. Nonetheless, it is well established that their use is contraindicated in patients with APS or APL Ab-positive.[45]

Clinicians should be vigilant for new or worsening skin manifestations in menopausal women, especially persistent rashes, plaques, or blistering that are unresponsive to usual dermatologic treatments. Referral to a dermatologist and appropriate immunologic evaluation can facilitate early diagnosis and management.

EMERGING THOUGHTS

Recent comprehensive reviews have highlighted that altered estrogen receptor (ER) signalling, rather than estrogen deficiency alone, may influence immune-cell differentiation and function across multiple immune lineages.[49] The actions of endogenous estrogens are mediated by ERα, ERβ, and the G protein–coupled estrogen receptor, with effects

that are cell-specific, receptor-specific, and context-dependent, providing a biological framework for understanding immune variation across the female life course, including the menopausal transition. Increasing attention has focused on the immune effects of pharmacologic modulation of ER signalling, including aromatase inhibitors, selective estrogen receptor modulators (SERMs), and selective estrogen receptor degraders (SERDs). These agents have been shown to alter immune-cell composition and function in experimental and disease-specific settings and may contribute to the observed sex-based differences in response to immune checkpoint inhibitor therapies. While these observations are relevant to the development of ER-targeted therapies, particularly in oncology, the current evidence remains preclinical. These data should not be extrapolated to support immune-modulating indications for routine MHT, and clinical decisions regarding MHT should continue to be guided by established menopausal indications and individual risk assessment.

CLINICAL IMPLICATIONS

Gynaecologists are often the first clinicians to encounter women during the menopausal transition. Awareness of rheumatic disease manifestations allows timely referral, coordinated care, and informed counselling regarding MHT and bone health, sexual function, and long-term disease risk. Menopause should be approached as a window of opportunity for comprehensive, life-course-oriented care in women at risk for immune-mediated inflammatory diseases.[17,48]

SYNOPSIS

- The immune system consists of innate and adaptive arms that maintain host defense and immune homeostasis.
- Sex hormones, particularly estrogen and progesterone, are major regulators of immune tolerance and inflammation.
- Physiologic estrogen promotes regulatory T-cell function and suppresses excessive Th1/Th17-mediated inflammation.
- Estrogen regulates macrophage differentiation, recruitment, and cytokine production in a dose- and context-dependent manner.
- Progesterone reinforces immune quiescence by modulating antigen-presenting cells and cytokine balance.
- The menopausal transition disrupts immuno-endocrine regulation, shifting immunity toward a pro-inflammatory state.
- Menopause is associated with metabolic, neuroendocrine, and oxidative changes that amplify inflammation and pain.
- These systemic changes contribute to increased autoimmune disease onset and symptom exacerbation around menopause.
- MHT may partially restore immune regulation but has variable effects depending on formulation, timing, and patient risk.
- Estrogen confers relative protection against severe COVID-19 through anti-inflammatory effects and innate immune modulation.
- Rheumatoid arthritis shows a second incidence peak post-menopause, particularly seronegative and postmenopausal-onset disease.
- Postmenopausal women with RA often report higher pain and disability despite similar inflammatory markers.
- Reduced lifetime estrogen exposure is associated with increased risk and severity of Sjögren's syndrome.
- Early menopause in systemic sclerosis is linked to increased vasculopathy, interstitial lung disease, and fibrotic complications.
- In SLE, disease activity often improves after natural menopause, though damage accrual may continue. MHT may be cautiously considered in stable, inactive SLE but is contraindicated in antiphospholipid antibody–positive patients.

- Estrogen deficiency may worsen inflammation and bone loss in spondyloarthropathies. Declining estrogen increases gout risk by reducing renal urate excretion.
- Fibromyalgia is common in peri- and postmenopausal women and reflects central pain amplification rather than inflammation alone.
- Autoimmune skin diseases frequently emerge or change course around menopause, requiring careful hormonal, dermatologic, and immunologic assessment.

RESEARCH AGENDA

Optimal MHT formulations and routes in immune-mediated disease

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Section 6

SAXUAL HEALTH

27. Sexual Health in Mid-life

SEXUAL HEALTH IN MIDLIFE

Keywords: Menopause, sexuality, classification, diagnosis, management

27

INTRODUCTION

Sexuality is an integral component of healthy human life, and there is no biological or psychosocial justification for menopausal or older women to forgo sexual activity if they wish to remain sexually active. Women's sexuality is multifaceted, shaped by the complex interplay of biological factors, psychological well-being, interpersonal relationships, cultural norms, and life experiences. According to the World Health Organisation (WHO) working definition, sexual health is a state of physical, emotional, mental, and social well-being in relation to sexuality, not merely the absence of disease or dysfunction. It requires a positive and respectful approach to sexuality and sexual relationships, the possibility of pleasurable and safe sexual experiences, and freedom from coercion, discrimination, and violence. The attainment and maintenance of sexual health are closely linked to the recognition and protection of sexual rights (WHO, 2006a).[1] From this holistic perspective, sexual health extends beyond reproductive function and disease prevention to encompass well-being across the life span.[2]

This is particularly relevant at midlife and after menopause. In 1994, the WHO declared that the right to sexual health is a fundamental human right. Recognising sexual health as a lifelong human right is essential to addressing the needs and experiences of women during the menopausal transition (MT) and menopause. Contrary to earlier ageist stereotypes, contemporary evidence from Western populations shows that sexual interest, intimacy, and expression often persist well into advanced age among healthy individuals. Early landmark work by Bretschneider and McCoy found that adults aged 80–102 years continued to report sexual desire, non-coital intimacy, masturbation, and intercourse, challenging the notion of inevitable sexual extinction with ageing.[3] Subsequent population surveys and systematic reviews have confirmed that although sexual frequency gradually declines with age, sexual activity and sexual well-being remain common and meaningful across the later decades of life.[4-6]

Importantly, modern research highlights a shift in Western cultural understanding, from viewing sexuality in older age as aberrant to recognising it as a multidimensional component of healthy ageing, shaped by physical health, emotional intimacy, relationship quality, inclusivity of diverse sexual identities, and evolving social norms. These findings underscore that ageing and menopause do not eliminate sexuality but rather transform its expression over time.[5]

Menopause is associated with a broad range of physical, physiological, and psychological changes that can adversely affect sexual function and overall well-being.[7] Although sexual symptoms increase with age, labelling them as sexual dysfunction (SD) requires the presence of personal concern or distress.[8] Sexual distress is most prominent in midlife, declines with advancing age, and is strongly influenced by partner-related factors.[9] A biopsychosocial assessment and a focused physical examination help healthcare providers (HCPs) provide appropriate advice and treatment to support sexual well-being.[10,11] Genitourinary syndrome of menopause (GSM) and hypoactive sexual desire disorders (HSDD) are the two most common causes of female sexual dysfunction (FSD), significantly affecting quality of life (QoL) around menopause.[10,12] These conditions frequently coexist and often extend beyond desire-related symptoms to affect arousal, orgasm, and overall sexual satisfaction.[10]

EPIDEMIOLOGY OF FEMALE SEXUAL DYSFUNCTION: GLOBAL AND INDIAN PERSPECTIVES

Despite the common assumption that sexual interest declines after menopause, sexuality remains highly important for many midlife women. In the Study of Women's Health Across the Nation (SWAN), over 75% of midlife women reported sexual activity as moderately to extremely important.[13] Despite this interest, sexual function commonly declines across the MT, with higher rates of dysfunction reported in postmenopausal women. Globally, the prevalence of FSD in postmenopausal women is high and variable, with most studies reporting rates exceeding 50% and some as high as 80–90%, depending on the population studied and the assessment tools used.[14] A systematic review found that FSD is a significant public health problem that affects 41% of premenopausal women around the globe.[15]

In a cohort of sexually active middle-aged women from Chile (40-64 years), 51.3% reported SD, with risk increasing with age and menopausal status.[16] Data from the Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking (PRESIDE) study, a large population-based survey (N=50,001), showed that although sexual problems increase with advancing age, sexual distress peaks during midlife, particularly during the MT. Women aged 45–64 years reported the highest prevalence of distressing sexual symptoms, particularly low sexual desire and arousal difficulties, highlighting menopause as a critical window for clinical intervention.[8]

In a clinic-based study from Malaysia, 85.2% of postmenopausal women were found to have FSD, with dissatisfaction, arousal, and desire being the most affected domains.[17] A multicentre Italian study of midlife women reported a 70.6% prevalence of SD, rising from 55% in 40-45-year-olds to 82.8% in those aged 52-55 years ($P < 0.01$).[18] Evidence from large reviews indicates that menopausal status, ageing, and sociodemographic factors strongly influence the risk of FSD across different cultural settings. A systematic review of 54 studies from 17 countries reported prevalence rates ranging from 37.3 to 78.2% in perimenopausal women, and between 9% to 89% in postmenopausal women. This highlights the high global burden and variability of FSD in menopausal women.[14] Another review and meta-analysis of 37 studies, including 9,982 postmenopausal women, found that approximately 65% experienced SD, with a higher risk observed among older women and those with lower educational levels.[19]

Indian studies consistently report a high burden of FSD, with prevalence ranging from 66% to 81% among postmenopausal women; estimates vary by setting and instrument. In a tertiary medical clinic in South India, 75% of women had FSD, affecting all sexual domains and occurring more frequently in women over 40 years of age, and in those with lower educational levels.[20] In North India, most postmenopausal women screened positive for dysfunction on the FSFI, with higher dysfunction reported with increasing age and longer duration since menopause; the authors also highlighted sociocultural inhibition and hesitancy to discuss sexual problems as potential contributors to the observed burden and measurement challenges.[21] Community and rural clinic studies similarly document a substantial symptom burden, including declines in sexual activity with increasing years since menopause and notable rates of dyspareunia/vaginal dryness and reduced libido among sexually active women.[22,23]

Two multicentre hospital-based studies conducted under the aegis of the Indian Menopause Society (IMS) provide complementary, non-overlapping insights. In the IMS McCoy questionnaire-based study, the overall sociodemographic profile did not significantly influence sexual function.[24] Perimenopausal women had better overall sexual function than menopausal women, and urogenital atrophy was associated with poorer sexual function. In women with monogamous relationships, the partner-related domain remained stable from perimenopause to menopause.[24] The IMS Indian Midlife Registry GSM study quantified the time course of key GSM symptoms, reporting that vaginal dryness (35%) and dyspareunia (23.4%), classic GSM features, were most prominent in early postmenopause (within 8 years of the final menstrual period) and declined thereafter.[25] Reduced libido/arousal (10.2%) was also reported, but should be interpreted as part of broader SD rather than GSM-specific.[25] Overall, Indian evidence supports early postmenopause as an important clinical window for proactively identifying GSM-related symptoms (dryness, dyspareunia) and broader sexual concerns, using sensitive, clinician-initiated enquiry and validated tools adapted for the local context.[24,25]

FEMALE SEXUAL RESPONSE

The normal female sexual response is complex and varies widely among women. Masters and Johnson first described a linear four-phase model based on physiological responses, comprising excitement, plateau, orgasm, and resolution. However, this model gave no importance to sexual desire or libido.[26] To incorporate psychological factors, Kaplan later proposed a three-phase model of desire, arousal, and orgasm, highlighting sexual desire as a key initiating factor and forming the basis of DSM-III and DSM-IV classifications.[27]

More recently, Basson's circular, intimacy-based model conceptualises female sexual response as non-linear, integrating interpersonal, contextual, psychological, and biological factors, with desire often emerging in response to emotional closeness rather than preceding sexual activity.[28] These models show that female sexual response is multidimensional and should be understood using a biopsychosocial approach, especially at midlife and after menopause.[11]

CLASSIFICATION OF SEXUAL DYSFUNTION

According to the American Psychiatric Association classification, the Diagnostic and Statistical Manual of Mental

Disorders, Fifth Edition, Text Revision (DSM-5-TR) 2022, which retains the DSM-5 2013 diagnostic structure for SD, the female sexual disorders are classified as follows:

FSD Disorders (DSM-5 / DSM-5-TR)[29,30]

- *Female Sexual Interest/Arousal Disorder (FSIAD):* includes HSDD and female sexual arousal disorder (FSAD). It is characterised by reduced or absent sexual interest or arousal, present for ≥6 months and causing marked distress.
- *Female Orgasmic Disorder (FOD):* is defined as a marked delay in, reduced frequency of, or absence of orgasm, or markedly reduced intensity of orgasmic sensations.
- *Genito-Pelvic Pain/Penetration Disorder (GPPPD):* encompasses difficulties with vaginal penetration, vulvovaginal or pelvic pain, fear or anxiety about pain, and pelvic floor muscle tightening.
- *Substance/medication-induced sexual dysfunction:* it includes dysfunction attributable to a substance or medications like Selective Serotonin Reuptake Inhibitors (SSRIs), and some antihypertensives.
- *Other specified or unspecified SD.*

DSM-5-TR requires symptoms to be present for at least six months, to occur in the majority of sexual experiences, and to be associated with clinically significant distress.[12] While DSM-5-TR acknowledges the influence of ageing, relationship factors, medical conditions, and sociocultural context, it is primarily a psychiatric classification system and does not specifically address hormone-related or genitourinary mechanisms relevant to menopause. A key limitation for menopause practice is the merger of HSDD and FSAD into a single diagnosis. Desire and arousal are related but distinct entities with differing etiologies, risk factors, and treatment responses, and the combined construct has not been uniformly adopted in pharmacological interventional trials in women.

The International Society for the Study of Women's Sexual Health (ISSWSH) classification continues to recognise HSDD as a distinct diagnosis, reflecting real-world clinical experience.[31] The Global Consensus Position Statement recommends this approach on the Use of Testosterone Therapy for Women (2019), endorsed by the International Menopause Society, the Endocrine Society, and the International Statistical Classification of Diseases and Related Health Problems, 10th Revision International Classification of Diseases (ICD-10) system, which is used worldwide for both medical and psychiatric diagnoses.[32,33] For routine menopause care, a sexual health assessment guided by the ISSWSH and the ICD-11 aligns closely with the realities of menopause care by prioritising the identification of treatable biological contributors,recognising the interaction of hormonal changes, genitourinary health, physical health, psychological factors, relationship context, and sociocultural influences, and noting that symptoms may fluctuate over time. It reduces unnecessary psychiatric labelling and supports early, preventive intervention.[34–36] Sexual health is evaluated across four functional domains and interpreted in the context of individual distress and personal meaning:

- *Sexual desire disorder*
  - HSDD
  - *Sexual aversion disorder*
- Sexual arousal disorder
- Orgasmic disorder
- Sexual pain disorder
  - Dyspareunia
  - Vaginismus
  - Other sexual pain disorders

SD may be lifelong or acquired, generalised or situational (limited to certain types of stimulation, situations, or partners), psychological or physical, or a combination of factors. The symptoms must persist for at least 6 months, and at least 75% of sexual experiences and must cause clinically significant distress.[12] The associated distress or impairment may be mild, moderate, or severe.

Hypoactive Sexual Desire Disorder

HSDD, the most common SD in women, may be associated with negative emotional and psychological states, and medical conditions, including depression. This underscores the importance of comprehensive clinical evaluation to identify contributory and potentially reversible factors.[37] Sexual desire is regulated by central nervous system pathways that balance excitatory and inhibitory neurotransmitter activity. Dopamine, norepinephrine, testosterone, estrogen, and progesterone are excitatory, whereas serotonin, prolactin, and opioids are inhibitory of sexual desire and response. In HSDD, this balance may be disrupted, resulting in reduced sexual excitation, increased inhibition, or both.[38] These neurobiological changes may be reinforced over time through experience-dependent neuroplasticity and are consistent with observed differences in brain function and structure in women with HSDD.[37]

HSDD is characterised by a persistent (≥6 months) reduction or absence of sexual desire, manifesting as reduced or absent spontaneous sexual thoughts or fantasies, diminished responsive desire to erotic stimuli, or difficulty maintaining interest during sexual activity.[34] It may also present as a loss of desire to initiate or participate in sexual activity, including avoidance of situations that could lead to sexual activity, provided these behaviours are not secondary to sexual pain disorders. These symptoms must be accompanied by clinically significant personal distress, such as frustration, grief, feelings of incompetence or loss, sadness, sorrow, or worry.[34]

The ISSWSH process of care (POC) for HSDD provides evidence-based guidance for diagnosing and managing HSDD.[37] The POC begins with a routine inquiry about sexual concerns, with a focus on low sexual desire or interest. Diagnosis involves distinguishing generalised acquired HSDD from other causes of low sexual desire by a thorough sexual history and/or a clinician administered tool, the Decreased Sexual Desire Screener (DSDS).[37] A biopsychosocial assessment is then used to identify potentially modifiable factors, guiding initial management with education and targeted interventions. When needed, additional treatments, including sex therapy, centrally acting agents, and hormonal therapy, are introduced, with treatment selection decided based on menopausal status.[37]

Genitourinary Syndrome of Menopause

Vulvovaginal atrophy, a key component of GSM, affects approximately half of postmenopausal women and commonly presents with vaginal dryness, irritation, burning, and dyspareunia. GSM increases the risk of SD because dyspareunia and reduced lubrication also impair arousal, orgasm, and sexual satisfaction, leading to decreased motivation for continued sexual activity.[39] Treating GSM can alleviate this problem. For details of GSM, refer to Chapter 10.

Low Sexual Desire in Menopause

GSM and HSDD may coexist, or one condition may precipitate symptoms of the other.[10] Women with HSDD may engage in sexual activity despite low interest, resulting in reduced arousal, leading to vaginal dryness and dyspareunia. Women with GSM may initially have a normal desire that may decline secondary to worsening vaginal dryness and pain with intercourse.[10] In peri- and postmenopausal women, GSM should be considered when the onset of low desire correlates with the development of GSM symptoms, suggesting GSM as the primary cause. When both conditions are present, a sequential approach is recommended, treating GSM first and reassessing sexual desire after symptom control to determine the need for further evaluation or intervention.[10]

Sexual Function: Determinants and Barriers

Sexual well-being during the MT and postmenopause is shaped by a complex interplay of biological, psychological, relational, medical, and sociocultural factors, with wide interindividual variability. Sexual function at menopause depends as much on non-medical influences as on hormonal changes, and the contribution of these determinants should not be underestimated.[36,40] Declining estrogen levels lead to genitourinary changes such as vaginal dryness, dyspareunia, reduced lubrication, and diminished genital sensitivity, which are central contributors to FSD. Estrogen deficiency results in reduced genital vascularity, thinning of the vaginal epithelium, loss of elasticity, and narrowing of the vaginal vault, often leading to painful intercourse and reduced sexual response.[40,41] Lower estradiol levels are associated with a greater symptom burden, while age-related androgen decline, largely independent of menopause, further contributes to reduced desire, impaired arousal, orgasmic difficulties, and diminished sexual satisfaction.[42]

Psychological responses to menopause are heterogeneous. While some women report positive changes, such as freedom from fear of pregnancy and greater intimacy, others experience anxiety related to ageing, fear of pain, altered body image, or perceive menopause as a cue to disengage from sexual activity. Mood disorders and depression,

common during midlife, further impair desire, arousal, and satisfaction.[36,40] Relationship quality, partner age and health, sexual communication, and relationship duration strongly influence sexual activity, and declines in women's sexual frequency with age may partly reflect partner-related factors. Women's sexual health may be negatively affected by their partners' SD, such as erectile dysfunction, premature ejaculation, or HSDD.36 Sociocultural context, including stigma associated with ageing and menopause, financial stress, domestic violence, restrictive beliefs, and life-course transitions such as the "empty nest", also plays a significant role.[43]

Sexual health in midlife is also influenced by comorbid medical conditions (including cardiovascular disease, diabetes, arthritis, and neurological disorders), commonly used medications (particularly SSRIs), and surgical interventions involving the breast or genital tract. Depression and urinary incontinence have particularly strong negative effects on sexual desire, the frequency of sexual activity, and satisfaction, independent of other comorbidities.[44] Women with multiple chronic health conditions are at increased risk of SD.[45] Overall sexual satisfaction in women appears to be more strongly influenced by multimorbidity than by age.

Despite the high prevalence of sexual concerns, disclosure barriers substantially limit recognition and care. Very few women discuss their sexual concerns with their HCPs. Many women do not voluntarily disclose sexual problems because of embarrassment, lack of awareness that symptoms are treatable, or the belief that sexual changes are a normal and unavoidable part of ageing; sociocultural norms reinforce these barriers.34 HCP-related barriers, such as limited time, inadequate training, personal discomfort, and age-related stereotypes, further contribute to under-recognition and undertreatment.[46] Proactive, sensitive, and non-judgmental enquiry by clinicians is therefore essential to identify reversible conditions, particularly GSM, and to integrate sexual health into routine menopause care. HCPs should play an active role in discussing sexual health, enabling women to express concerns comfortably and facilitating accurate diagnosis and effective management of female sexual problems.[34,44]

CLINICAL ASSESSMENT

History

As many women may hesitate to raise sexual concerns, clinicians should proactively invite discussion by asking a simple, open-ended question such as, "Do you have any concerns related to sexual activity?" A comprehensive sexual history is vital to the assessment of sexual concerns around menopause. In addition to identifying the primary symptom, a focused sexual history should assess each domain of the sexual response cycle, including desire, arousal, and orgasm, as well as the presence of sexual pain.10 The history should also include screening for mental health concerns (such as depression or anxiety), religious or cultural influences, and the quality of the sexual relationship, including the partner's physical, mental, and sexual health, where relevant. The timing of symptom onset, particularly in relation to the MT, the duration, and whether symptoms are persistent or context-specific (generalised or situational), are key elements of the history. Assessing personal or relational distress is essential, as it is required for diagnosis.[34] For many women, reduced libido or arousal is not perceived as problematic and does not require intervention unless it causes personal concern or distress.

A holistic biopsychosocial approach is necessary to fully understand and treat this key component of midlife women's well-being.[47] Careful consideration of each of these domains is required for a comprehensive assessment and individualised management.[12] Clinical history-taking should be structured around these key influences.[11]

- *Biological factors* include gynaecological and obstetric history, such as menstrual disorders, endometriosis, infertility, pregnancy and mode of delivery, timing and type of menopause, premature ovarian insufficiency, pelvic floor disorders, genital prolapse, urinary incontinence, and prior pelvic surgery. Hormonal use includes contraceptives, hormone replacement therapy, and anti-estrogenic or anti-androgenic medications. Sexual function may also be affected by cancer treatments (surgery, chemotherapy, radiotherapy), comorbidities and related medications, endocrine disorders (thyroid disease, hyperprolactinaemia, diabetes), neurological or psychiatric illness, chronic pain conditions, and the use of psychotropic drugs.
- *Psychological factors* include poor self-esteem, negative body image, mood and anxiety disorders, personality traits, attitudes towards ageing and menopause, past sexual experiences, sexual orientation and roles, and a history of sexual trauma or abuse.
- *Sociocultural influences* shape sexual attitudes and behaviours and include gender norms and inequalities, cultural or religious beliefs, work-related stress and life events, social support, and access to healthcare.

- *Relational factors* to consider include partner availability, the partner's health, and the quality of communication and emotional intimacy. Assessment of the partner's physical health and sexual function is an important component of a comprehensive evaluation of women's sexual health.[37]

Measurement of Sexual Function

Several validated instruments are available to assess female sexual function.

- *The McCoy Female Sexuality Questionnaire (MFSQ)* is one of the earliest validated instruments developed to assess female sexual function and satisfaction, particularly in midlife, menopause, and hormone therapy.[48] The questionnaire evaluates sexual interest/desire, arousal, vaginal lubrication, orgasm, sexual enjoyment, and relationship satisfaction. It also explores attitudes towards sexuality and the perceived importance of sexual activity. Responses are recorded on Likert-type scales, allowing both domain-specific and overall assessments of sexual function.[24] The MFSQ has been widely used in menopause-related research, especially in studies evaluating the effects of estrogen therapy and other hormones on sexual function. It is less detailed and standardised than the FSFI, and cut-off scores for diagnosing SD are not well established. Despite these limitations, the MFSQ remains useful for capturing subjective sexual well-being and treatment-related changes in sexual function among midlife and postmenopausal women.
- *Female Sexual Function Index (FSFI)* is currently the most widely used tool in both clinical practice and epidemiological studies, clinical trials, and menopause research. The FSFI is a 19-item self-reported questionnaire that evaluates six domains of sexual function: desire, arousal, lubrication, orgasm, satisfaction, and pain. Each item is rated on a Likert scale based on sexual experiences over the preceding four weeks. Domain scores are calculated using standardised weighting factors and summed to generate a total score ranging from 2 to 36, with lower scores indicating poorer sexual function.[49] The FSFI has been extensively validated in different populations and cultural settings and is commonly used to identify women at risk of SD, monitor changes over time, and evaluate treatment outcomes.[50]
- *Female Sexual Distress Scale (FSDS)* is a validated, self-reported instrument designed to assess sexually related personal distress in women, which is a key criterion required for the diagnosis of FSD. The original FSDS consists of 12 items, each rated on a 5-point Likert scale (0 = never to 4 = always), r lecting experiences over the preceding 30 days. Total scores range from 0 to 48, with higher scores indicating greater sexual distress. A commonly used cut-off score of≥15 suggests clinically significant sexual distress.[51]
- *FSDS-Revised (FSDS-R)* which is a revised version, includes 13 items and better captures distress related to low sexual desire, making it particularly relevant in midlife and postmenopausal women.[52] The FSDS and FSDS-R complement the FSFI by distinguishing between sexual symptoms and the distress they cause, thereby helping in identifying women who meet the diagnostic criteria for SD and guiding appropriate counselling and treatment.
- *Decreased Sexual Desire Screener (DSDS)* is a brief, validated clinician-administered tool used to screen for acquired, generalised HSDD in women. It consists of five yes/no questions and assesses low sexual desire with associated personal distress, while helping exclude other causes such as medical conditions, medications, relationship issues, or psychosocial stressors.[53] The DSDS supports, but does not replace, a clinical diagnosis, and is particularly useful in midlife and menopausal women to identify distressing low desire within a biopsychosocial assessment framework.

Physical Examination

A focused physical and pelvic examination is essential in the evaluation of SD in midlife and postmenopausal women. The pelvic examination allows assessment of clitoral adhesions or phimosis, clitoral atrophy, urethral meatal prolapse, telescoping of urethral meatus, labial resorption, vulvar dystrophies and dermatoses, vulvovaginal atrophy, dryness, mucosal fragility, infection, pelvic floor muscle tone (high tone pelvic floor dysfunction), and pain-triggering sites in the vulva, vagina (vulvodynia) and pelvis (pudendal nerve disorder).[37] Measurement of vaginal pH can provide supportive evidence of estrogen deficiency, with values > 5 indicative of vaginal atrophy. A general physical examination is important to identify comorbid medical conditions that may contribute to SD.

Laboratory Studies

Laboratory evaluation should be selective and clinically indicated. Measurement of serum follicle-stimulating hormone (FSH) and estradiol may help to confirm menopausal status when in doubt. Routine androgen testing is not

recommended, as no circulating androgen cutoff reliably distinguishes women with and without SD. Sex hormone binding globulin (SHBG) and prolactin may be assessed in selected cases. Testing for sexually transmitted infections and other vaginal pathogens can help in the evaluation of sexual pain.[37] Additional investigations should be directed toward excluding relevant comorbidities, such as endocrine or metabolic disorders, based on clinical findings.[37]

GENERAL MANAGEMENT OF SEXUAL DYSFUNTION IN MENOPAUSE

- Assess the patient's goals before starting treatment and use them to evaluate progress. Improvement may also be tracked using a validated sexual function questionnaire.
- Education and counselling are the first-line therapeutic strategies for menopause-related SD.[37] Providing information on normal sexual functioning and the importance of motivation and adequate sexual stimulation, while emphasising the role of age and relationship duration, may facilitate positive sexual behavioural changes.
- Modifiable risk factors, including mood disorders and antidepressant use, sedentary lifestyle, endocrine disorders (hyperprolactinemia, hypo- or hyperthyroidism, diabetes mellitus), and gynaecological or urological infections or diseases, should be appropriately investigated and managed.[37]
- Involving the partner may be beneficial to modify negative communication patterns, addressing partner-related SD, or reducing pressure or demanding sexual behaviours.[54]
- Psychological interventions for SD, such as cognitive behavioural therapy (CBT) and mindfulness-based therapy, have been developed to treat HSDD, arousal, and orgasmic disorders in women, independent of menopausal status. For a list of common psychosocial contributors to SDs in midlife and menopausal women and corresponding psychotherapeutic approaches, refer to Table 1.[55,56]

Table 1: Common psychosocial contributors to SDs in midlife and menopausal women and corresponding psychotherapeutic approaches[55,56]

Psychosocial contributor	Evidence-based psychotherapeutic treatment options
Sexual myths, misconceptions, and restrictive sexual upbringing	Psychoeducation; cognitive restructuring (CBT); exploration of emotional influences on sexual response
Negative emotions (anxiety, guilt, shame, disgust, aversion)	CBT; mindfulness-based interventions; graduated exposure and sensate focus
Performance anxiety	Sensate focus (non-demand touching); CBT targeting maladaptive cognitions; attentional refocusing techniques
Body image concerns	CBT; mindfulness-based body awareness; sensate focus
Relationship or marital distress	Couple therapy, sex therapy focused on communication and intimacy
Poor sexual knowledge or technique (self or partner)	Psychoeducation; guided exercises; sexual communication skills training
Environmental factors: Stress, fatigue, inadequate time together, insufficient childcare	CBT-based stress management; prioritisation and communication strategies
Fear of pain / genito-pelvic pain	CBT; graded exposure; pelvic-floor–informed sex therapy

Trauma and comorbid disorders: History of sexual abuse, sexual assault or other traumatic physical experiences	Trauma-focused CBT; referral to trauma-informed psychotherapy
Anxiety or depressive disorders	Evidence-based treatment per psychiatric guidelines; integration with sex therapy
Substance use disorder (drugs and alcohol).	Referral or substance abuse therapy
Relationship or marital distress	Couple therapy, sex therapy focused on communication and intimacy
Compulsive use of internet erotica	Stimulus control and relapse prevention, referral for psychopharmacology (SSRI)

MANAGEMENT OF HSDD

Systemic Testosterone

The only evidence-based indication for testosterone therapy in women is the treatment of HSDD. Transdermal administration of testosterone at doses targeting the normal premenopausal physiologic range has shown to improve sexual desire, arousal, pleasure, orgasm, and the frequency of satisfying sexual events.[32,57] Total serum testosterone concentrations should not be used to diagnose HSDD; instead, they should be measured at baseline and after approximately three months of treatment to avoid supraphysiological exposure. Therapy should be discontinued if no clinical benefit is observed after six months.[32]

Most national regulatory authorities do not approve testosterone formulations for use in women, except a 1% testosterone cream licensed in Australia. In clinical practice, approximately one-tenth of a standard male dose of 1% transdermal testosterone, approximately 300 mcg/day, is generally sufficient to achieve premenopausal physiological levels.[58] Male formulations may be used cautiously at female doses with regular monitoring of serum testosterone levels. The safety of testosterone therapy has not been established for long-term use.[32] However, short-term use of testosterone therapy (< 24 months) for the management of HSDD has not been associated with adverse cardiovascular disease events, cancer or any other serious adverse events. Evaluation of therapy response should be monitored clinically in terms of improvement of low sexual desire/wellbeing after 12 weeks of therapy, and signs of androgen excess with the measurement of total testosterone and SHBG every 6 months to avoid excessive dosing.[57] It should be explained to the patient that achieving an initial improvement in symptoms of HSDD with transdermal testosterone can take around 4–6 weeks; the peak improvement in sexual desire has been seen at 12–16 weeks.

Women receiving testosterone therapy should be monitored for androgen-related adverse effects, including acne and hirsutism, and for metabolic parameters, such as the lipid profile. Dose adjustment or discontinuation should be considered if supraphysiological levels or adverse effects occur. Testosterone is metabolised to estrogen, and thus abnormal uterine bleeding or breast symptoms, such as a lump or nipple discharge, may result and require appropriate evaluation. In the absence of an approved female-specific product, the off-label use of male testosterone formulations may be considered. Prescribing an approved male formulation is rare and should be considered only if serum testosterone concentrations are maintained within the physiological premenopausal female range (Expert Opinion). Testosterone levels in adult males are approximately 10 to 15 times higher than those in females.[59]

Flibanserin

It is an oral, non-hormonal, centrally acting, multifunctional serotonin agonist and antagonist (MSAA) agent administered at 100 mg once daily. It modulates neurotransmitters by decreasing serotonin and increasing norepinephrine and dopamine. It has been shown to increase the number of satisfying sexual events and sexual desire while reducing sexual distress. Flibanserin is associated with milder side effects such as dizziness, fatigue, nausea, sleepiness, and insomnia, while serious adverse events are similar to placebo. Its efficacy in postmenopausal women

has been demonstrated in an RCT (PLUMERIA), and it has recently received Food and Drug Administration (FDA) approval for use in postmenopausal women up to 64 years of age.[60-62]

Bremelanotide

Subcutaneous bremelanotide, a melanocortin receptor-4 agonist, is used as an on-demand subcutaneous injection taken approximately 45 minutes before anticipated sexual activity.[63] Common adverse effects include nausea, flushing, headache, and transient increases in blood pressure. In 2019, bremelanotide was approved by the FDA for the treatment of HSDD in premenopausal women only. For postmenopausal women, its use remains off-label. Flibanserin and Bremelanotide are prescribed only in cases of clinically diagnosed HSDD.

Menopause Hormone Therapy and Tibolone

Some oral estrogen and oral contraceptive pills increase SHBG and reduce free testosterone. If low libido or arousal occurs, consider stopping the oral contraceptive pill or switching to a non-oral menopausal hormone therapy (MHT).[64]

MHT can improve sexual function primarily by relieving GSM-related dyspareunia and may modestly benefit other sexual domains through improvements in overall well-being. A meta-analysis of 47 RCTs (N=35,912) found that estrogen therapy, combined estrogen–progestogen therapy, tibolone, and SERMs may slightly improve sexual function in peri- and postmenopausal women.[65] Although moderate to severe vasomotor symptoms remain the main indication for HT, women should be informed of its potential sexual health benefits. In women with low libido, the choice of HT should consider route and formulation, with preference for transdermal estrogen or tibolone. Tibolone, which has selective tissue estrogenic activity and mild androgenic effects, produces greater improvements in sexual function, particularly desire, arousal, and orgasm, than conjugated estrogen-medroxyprogesterone acetate (CE/MPA), and it also improves menopausal symptoms and overall well-being.[66] This benefit is attributed to increased free testosterone and reduced SHBG. Tibolone has emerged as a useful hormonal option for women with low libido.[67]

Phosphodiesterase inhibitors

Studies of oral sildenafil for the treatment of FSD have reported inconsistent results and are not currently recommended.[68,69] Topical sildenafil cream improved outcomes in women with female sexual arousal disorder, most significantly in those without concomitant orgasmic dysfunction.[70]

MANAGEMENT OF ORGASMIC DISORDER

Vibrators may improve the ability to achieve orgasm by increasing clitoral blood flow.

MANAGEMENT OF SEXUAL PAIN[70]

Local estrogen therapy remains the gold standard for the management of moderate to severe symptoms of vulvovaginal atrophy. Additional pharmacological options include the oral selective estrogen receptor modulator ospemifene and vaginal dehydroepiandrosterone (DHEA). Non-pharmacological approaches such as vaginal moisturisers and lubricants, and pelvic floor physical therapy are sufficient for women with mild to moderate GSM. Mechanical devices and vaginal laser therapy may also be considered. For further details, refer to Chapter 10.

PROVOKED PELVIC FLOOR HYPERTONUS

Provoked pelvic floor hypertonus (vaginismus) may be effectively treated with physical therapy. Specific techniques may include the use of vaginal dilators and myofascial release of muscle tension in the pelvic floor, thighs, and abdomen, with or without biofeedback. Other options include the use of benzodiazepines, hypnotherapy, and botulinum toxin type A injections.[71]

VULVAR PAIN SYNDROMES

Vulvar discomfort may result from irritant or allergic contact dermatitis, often associated with topical products, soaps, lubricants, incontinence-associated moisture, or prolonged use of sanitary pads. In such cases, identifying and eliminating the offending irritant, along with appropriate management of urinary incontinence, can lead to significant symptom improvement. When vulvar pain occurs in the absence of an identifiable cause (vulvodynia), management

requires a multidisciplinary approach, which may include pelvic floor physical therapy, psychological interventions such as CBT, and selected topical or systemic pharmacological treatments. Individualised assessment is essential to address contributing musculoskeletal, neuropathic, and psychosocial factors.[72]

SYNOPSIS

- Sexual health is a core component of women's well-being and assumes particular importance during midlife and menopause. Menopausal hormonal changes interact with psychological health, relationships, sociocultural context, and comorbidities to influence sexual function, and clinical significance is determined by associated personal distress rather than symptoms alone.
- FSD is common during the MT and postmenopause, with GSM and HSDD being the most prevalent and often coexisting conditions. Accurate differentiation is important, as GSM symptoms may secondarily reduce desire, and treating GSM frst often improves sexual function.
- Assessment should be biopsychosocial, incorporating a sensitive sexual history, focused examination, selective investigations, and validated tools to evaluate both sexual function and sexual distress. Management is multidisciplinary, with education and counselling as first-line interventions. Modifiable risk factors should be addressed, and psychological therapies should target psychosocial contributors. Local estrogen therapy remains the cornerstone of GSM management, and testosterone therapy is the only evidence-based hormonal treatment for distressing HSDD in postmenopausal women.
- Recognising sexual health as a lifelong aspect of women's health enables clinicians to manage SD and improve the quality of life for women during and after the MT.

RESEARCH AGENDA

A need for high-quality, long-term safety data on systemic testosterone therapy in women to support regulatory approval and the development of products specifically indicated for menopausal women.

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Section 7

BREAST CANCER

BREAST CANCER -INDIAN CONTEXT

Keywords: Epidemiology, risk factors, screening, prevention.

INTRODUCTION

Breast cancer is the most common cancer in females worldwide.[1,2] It is the most frequently diagnosed cancer among women in 157 of 185 countries.[1,2] Globally, breast cancer now represents one in four of all cancers in women.[1,2] India is the largest developing country and has a steadily rising incidence of breast cancer.[1,3] Refer to Figure 1

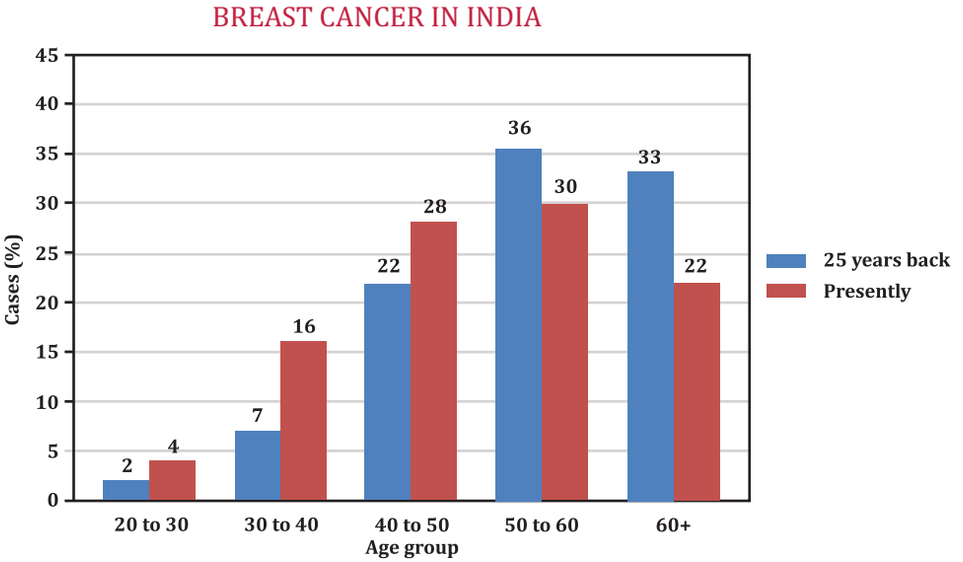

Figure 1: Trends in age distribution for breast cancer in India

Source: https://www.breastcancerindia.net/statistics/trends.html

EPIDEMIOLOGY

Breast cancer is the most common malignancy among women in urban India, accounting for approximately 25–32% of all cancers, whereas cervical cancer remains the leading cancer in rural women, with breast cancer ranking second.[3] According to the Global Cancer Observatory (GLOBOCAN) 2022, India records approximately 192,000 new breast cancer cases annually, with nearly 90,000 deaths, accounting for the highest cancer-related incidence and mortality among Indian women.[4,5] Breast cancer in India shows marked urban–rural and interstate variation. Age-adjusted incidence rates are highest in metropolitan and southern states such as Hyderabad, Chennai, Bengaluru, Delhi, and Chandigarh, while substantially lower rates are reported from rural registries, reflecting differences in lifestyle factors, reproductive patterns, awareness, screening uptake, and access to cancer care.[3] Projections indicate a continued rise in breast cancer burden, underscoring its growing public-health impact.[5]

Women in India are diagnosed with breast cancer nearly a decade earlier than their Western counterparts, with a substantial proportion presenting during midlife and beyond; the median age at diagnosis in India is approximately 49–53 years compared with 60–62 years in Western populations.[6-8] Epidemiologic data further indicate that 40–50% of Indian breast cancer patients are younger than 50 years, with up to 10–25% diagnosed before 40 years of age.[9,10] Tumours in younger women tend to be biologically more aggressive and are more frequently hormone- receptor negative, contributing to poorer outcomes. These women frequently present with advanced-stage III–IV of the disease.[6,11,12] The curative potential drops from 95% in Stage I to 21% in Stage IV.[10-13] For every two women diagnosed with breast cancer in India, one woman dies of it, increasing the mortality-to-incidence ratio.[14] Five-year survival for breast cancer in India is approximately 66%, substantially lower than that reported in high-income Western countries, which is around 90%. This disparity is largely attributable to late-stage presentation, with nearly 60% of Indian

patients diagnosed at locally advanced or metastatic stages, compared with approximately 28% in the United States.[3] Contributing factors include limited awareness, social and cultural barriers, delayed health-seeking behaviour, financial constraints, reliance on alternative therapies, and unequal access to specialised cancer care services.[15]

Beyond incidence and mortality, the burden of breast cancer in India is amplified by a large and growing survivor population. The estimated 5-year prevalence exceeds 750,000 women, reflecting substantial improvements in detection and treatment but also highlighting the need for long-term survivorship care.[4,5] Refer to Table 1

Table 1: Age-standardised incidence, mortality, and 5-year survival of breast cancer worldwide[1,4,16]

Indicator	India	Global	Low HDI countries	Very High HDI countries
Incidence rate (ASR per 100,000)	32.0	47.8	34.0	75.6
Mortality rate (ASR per 100,000 women)	15.10	13.6	19	11.5
5-Year Survival (%)	60-65	>72	40	85–90

ASR, age-standardised rate (WHO standard population); HDI, Human Development Index.

This epidemiological shift in breast cancer reflects the combined effects of urbanisation, changing reproductive patterns, increasing prevalence of lifestyle-related risk factors, improved detection of breast cancer in urban areas, and a concurrent decline in cervical cancer incidence attributable to reduced parity, improved hygiene, and opportunistic screening.[3-5]

BIOLOGIC SUBTYPES OF BREAST CANCER

Breast cancer is a heterogeneous disease characterised by both histologic types and biologic subtypes. Histologically, the majority of invasive breast cancers are classified as ductal carcinoma, accounting for 80% of invasive breast cancers, or from the glandular tissue itself, lobular carcinoma, accounting for 5% to 10% of invasive breast cancers. Independent of histologic type, breast cancers are further subdivided into biologic subtypes based on gene-expression profiling and, in routine clinical practice, by immunohistochemical (IHC) assessment of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2) and cell of origin, luminal or basal.[17,18] Importantly, molecular subtypes of ductal and lobular carcinomas include luminal A, luminal B, HER2-enriched, and triple-negative.[17,19]

While invasive lobular carcinoma is more commonly hormone receptor–positive and frequently corresponds to luminal subtypes, invasive ductal carcinoma shows greater biologic diversity and accounts for the majority of HER2-enriched and triple-negative tumours.[19-21] Luminal subtypes (ER and/or PR positive) constitute the majority of breast cancers and are generally associated with a favourable prognosis due to responsiveness to endocrine therapy. In contrast, HER2- enriched tumours lack hormone receptors but overexpress HER2 and, although biologically aggressive, benefit significantly from HER2-targeted therapies.[21]

Triple-negative breast cancer (TNBC), defined by the absence of ER, PR, and HER2 expression, represents the most aggressive clinical subtype,[20,22] occurring predominantly within invasive ductal carcinomas, although rare lobular TNBCs have been described.[20-22] TNBC accounts for approximately 12–17% of invasive breast cancers in Western populations and is associated with younger age at diagnosis, higher histologic grade, and more advanced stage at presentation.[22,23] Studies from India report a higher prevalence of TNBC, ranging from 20% to over 30%, largely within ductal carcinomas.[24-27]

This increased burden has been attributed to the younger age of onset, reproductive factors such as multiparity, lifestyle factors including obesity, socioeconomic determinants, limited screening, and possible genetic susceptibility in Indian and South Asian populations.[24-27] Ductal and lobular carcinomas describe tumour histology, whereas ER/PR/HER2-based subtypes describe tumour biology; both systems are complementary, but the biologic subtype primarily guides treatment and prognosis.

NONMODIFIABLE RISK FACTORS FOR BREAST CANCER

Age and Gender: Age is the strongest non-modifiable risk factor for breast cancer, with incidence increasing exponentially with advancing age.[1] In India, breast cancer presents at a younger age compared with high-income countries, with an increasing proportion of cases diagnosed before age 50, although age-specific incidence rates continue to rise with advancing age.[6] Breast cancer occurs approximately 100 times more frequently in women than in men. The risk of breast cancer increases markedly with age, such that a 70-year-old woman has an approximately ten-fold higher risk of developing breast cancer compared with a 30-year-old woman.[8]

Benign breast disease: The risk of invasive breast cancer is modestly increased in women with proliferative breast lesions without atypia, including complex fibroadenoma, moderate or florid ductal hyperplasia, sclerosing adenosis, and intraductal papilloma (relative risk [RR] 1.3–2.0). The risk is substantially higher in the presence of proliferative lesions with atypia, such as atypical ductal hyperplasia and atypical lobular hyperplasia (RR 4–6), and increases further to up to ten-fold when atypia is multifocal.[28] Refer to Chapter 29.

Family history: Approximately 5–10% of breast cancers are hereditary. Women with a first-degree relative diagnosed with postmenopausal breast cancer have an estimated 1.5–2-fold increased risk, while those with a first-degree relative affected by premenopausal breast cancer carry a higher relative risk of approximately 3.3. A history of breast cancer in two first-degree relatives increases the risk nearly fivefold.[29]

Hereditary cancer syndromes associated with breast cancer include hereditary breast and ovarian cancer syndrome (BRCA1/BRCA2), Cowden syndrome (phosphatase and tensin homolog [PTEN]), Li-Fraumeni syndrome (tumour protein p53 [TP53]), and hereditary diffuse gastric cancer (cadherin 1 [CDH1]).[30]

BRCA1 and BRCA2 mutations: Pathogenic variants in BRCA1 and BRCA2 are the most common causes of hereditary breast cancer, accounting for approximately 5–10% of all breast cancer cases.[31] Carriers of BRCA1 mutations have an estimated lifetime breast cancer risk of 60–72%, while those with BRCA2 mutations have a corresponding risk of 55–69%, substantially higher than the general population risk of approximately 12%.31 These pathogenic variants therefore confer a markedly increased lifetime risk, rather than a modest relative risk increase. Ethnic differences in mutation prevalence have been observed, with BRCA1 mutations reported more frequently among White populations and BRCA2 mutations more commonly identified in Asian populations, suggesting population-specific genetic susceptibility patterns.[32]

Menstrual factors: Early age at menarche (<12 years) is associated with an approximately 30% increased risk of breast cancer, while late age at menopause (>55 years) confers a 20–50% increased risk.[33]

Breast density on mammogram: High mammographic breast density is a strong independent risk factor for breast cancer. Compared with women with predominantly fatty breasts, those with slightly increased density have a relative risk of approximately 1.8, while women with extremely dense breasts have a relative risk approaching 4.6.[34]

Thoracic irradiation (Age 10–30 years): Women exposed to high-dose chest/thoracic radiation between ages 10–30 years for treatment of cancers such as Hodgkin lymphoma have a markedly increased subsequent breast cancer risk; long-term follow-up studies report standardised incidence ratios (SIRs) as high as more than 50 in some groups.[35]

MODIFIABLE RISK FACTORS FOR BREAST CANCER

Age at First Child: Women who are 30 years of age or older at the time of their first child's birth greater than 30 years of age have double the chance of developing breast cancer as compared to those who had their first child before the age of 20 years.[29,36]

Parity is inversely associated with breast cancer risk. Each full-term pregnancy is associated with an approximately 7% reduction in risk, and women with five or more children have nearly a 50% lower risk of breast cancer compared with nulliparous women, particularly when combined with prolonged breastfeeding.[37]

Hormone Therapy: Contraceptives: The magnitude of breast cancer risk associated with hormonal contraception varies by formulation. Contemporary cohort data demonstrate slightly higher risks with some oral combined and progestin-only formulations,[38] including desogestrel-containing pills and etonogestrel implants, Levonorgestrel-containing combined pills and intrauterine system[39,40] while no statistically significant increase has been observed with medroxyprogesterone acetate injections, the etonogestrel vaginal ring, or drospirenone- containing combined oral contraceptives.[41] Overall, the absolute excess risk remains small, particularly in younger women.[40]

Menopausal hormone therapy: The association between menopausal hormone therapy (MHT) and breast cancer risk is influenced by baseline risk, hormone formulation, duration of use, and patient age at initiation. Overall, the absolute increase in breast cancer risk with MHT is small, estimated at fewer than one additional case per 1,000 women aged 50–59 years per year of use. Evidence from randomised controlled trials indicates that combined estrogen–progestin therapy is associated with a modest increase in breast cancer incidence, whereas estrogen-only therapy, when used in appropriately selected women, is associated with a neutral or reduced risk.[42-44] The excess risk with combined therapy is largely confined to the period of use and declines after cessation, typically returning to baseline within approximately three years following short-term treatment. Tumours diagnosed during MHT use are more often estrogen receptor–positive and of lobular histology, suggesting promotion of pre-existing disease rather than initiation.[45,46] Current evidence supports individualised risk assessment before prescribing MHT, with attention to formulation, duration, and patient-specific breast cancer risk. The impact of MHT on breast cancer risk is complex, influenced by background risk, type of MHT, dose, duration of use, regimen, route of administration, and prior exposure. The incremental risk associated with MHT is minimal, with an estimated increase of fewer than 1 additional case per 1000 women aged 50–59 years annually.[42-46]

Breastfeeding: Women who do not breastfeed or breastfeed for shorter durations are at higher risk, and each additional year of breastfeeding reduces the risk by 4.3%. The longer women breastfeed, the more they are protected against breast cancer.[37]

Body Mass Index and Physical Activity: A higher body mass index (BMI) is associated with approximately a 12% higher risk per 5 kg/m^2.[47] Higher levels of physical activity show a dose-dependent reduction in breast cancer risk.[48]

Alcohol: Intake is associated with a dose-dependent increase in breast cancer risk; meta-analytic data indicate higher risk with increasing consumption, often more pronounced for postmenopausal breast cancer.[49]

RISK STRATIFICATION BASED ON RELATIVE RISK OF BREAST CANCER

Breast cancer risk can be stratified by the magnitude of the relative risk (RR) into high, moderate, and low categories.

High Risk: Factors conferring the highest risk (RR >4) include increasing age, biopsy-proven atypical hyperplasia, ductal or lobular carcinoma in situ, prior therapeutic thoracic irradiation before age 30 years, multiple first-degree relatives with breast cancer, a personal history of early-onset breast cancer, and the presence of high-penetrance pathogenic variants such as BRCA1, BRCA2, TP53, and CDH1.

Moderate risk: Factors (RR 2–4) include one first-degree relative with breast cancer, very dense breasts, late age at first full-term pregnancy, proliferative breast disease, and moderate- penetrance genetic variants such as checkpoint kinase 2 (CHEK2) and PTEN.

Low risk: Factors (RR 1.1–2.0) include reproductive, hormonal, and lifestyle exposures such as early menarche, late menopause, nulliparity, alcohol consumption, obesity in postmenopausal women, hormone therapy, and reduced physical activity. While many of these factors individually confer modest risk, their effects may be cumulative and are relevant for individualised breast cancer risk assessment and risk-reduction counselling.[40,50-53]

RISK-REDUCING FACTORS FOR BREAST CANCER DEVELOPMENT

Several factors are associated with a reduced risk of breast cancer (RR < 1). These include reproductive and hormonal factors such as early age at first full-term pregnancy (particularly before age 20 years) and breastfeeding, both of which confer a sustained protective effect. Lifestyle factors, including regular physical activity and maintenance of a healthy body weight, are also associated with lower breast cancer risk. Pharmacologic and surgical risk-reduction strategies, including the use of selective estrogen receptor modulators (for example, tamoxifen) and prior risk-reducing breast surgery or bilateral oophorectomy in appropriately selected high-risk women, significantly decrease breast cancer incidence. Additional factors associated with lower risk include low bone mineral density, prior

oophorectomy, and certain demographic characteristics such as Asian, Hispanic, or Pacific Islander ancestry. While individual protective factors may confer modest benefit, their effects may be additive and are relevant for comprehensive breast cancer risk assessment and counselling.[40,52,53]

RISK ASSESSMENT TOOLS

Breast cancer risk assessment tools are used to estimate an individual woman's likelihood of developing breast cancer and to identify those who may benefit from genetic counselling, enhanced surveillance, or risk-reduction interventions. These models integrate personal and family history, along with other high-risk features, to guide clinical decision-making.

Gail model: The Gail Model is a statistical breast cancer risk assessment algorithm developed in 1989 by Dr Mitchell Gail and colleagues at the Biostatistics Branch of the National Cancer Institute's Division of Cancer Epidemiology and Genetics. It was derived from a large screening study of 280,000 women aged 35 to 74.[54] However, the original model did not account for racial or ethnic differences, atypical hyperplasia, BRCA mutations, tamoxifen use, or prior ductal or lobular carcinoma in situ, limiting its applicability in high-risk women. The Gail model has been validated in diverse populations, including Indian women, demonstrating reasonable accuracy for breast cancer risk prediction in hospital-based settings.[55]

The Breast Cancer Risk Assessment Tool (BCRAT): also known as Gail Model 2, is a revised version of the original Gail model and is widely used to estimate 5-year and lifetime risk of invasive breast cancer in women aged 35 years and older without a prior history of breast cancer. The model was developed and validated using large U.S. cohorts, including the Women's Health Initiative, and has been evaluated across diverse populations. However, BCRAT is not suitable for women <35 years or those suspected of hereditary cancer syndromes. Hence, it should not be used for genetic risk assessment in women with strong family histories or known pathogenic variants. The tool is publicly available through the National Cancer Institute website (https://bcrisktool.cancer.gov).[56,57]

The CARE model: a modification of the Gail model, improves risk estimation for Black women and can be used alongside other clinical and genomic factors.[58]

The Breast Cancer Surveillance Consortium (BCSC) Risk Calculator is validated for women aged 35 to 74 years undergoing mammography and estimates 5- and 10-year risk of invasive breast cancer, and is particularly useful for screening and surveillance decisions. It was developed in over one million women undergoing mammography, incorporating age, breast density, family history, and benign breast disease.

The BRCAPRO (BRCA probability model): estimates the probability of carrying a BRCA1/2 pathogenic variant based on personal and first- and second-degree family history and is most useful in individuals with intermediate pretest probability, helping guide genetic testing decisions. The BRCAPRO model has no strict lower age cut-off and can be used in adult women of any age to estimate the probability of carrying pathogenic variants in BRCA1/2, particularly for genetic testing decisions.[59]

The Tyrer–Cuzick (International Breast Cancer Intervention Study [IBIS]) model: provides the most comprehensive assessment by estimating 10-year and lifetime breast cancer risk as well as the likelihood of BRCA mutations. It incorporates reproductive, hormonal, and anthropometric factors, benign breast disease, and detailed family history and is among the most consistently accurate models for identifying women eligible for MRI screening or chemoprevention. It can be applied from age 20 onward.[60,61] Based on 5-year risk estimates, women may be classified as low, intermediate, or high risk, with avoidance of menopausal hormone therapy recommended in high-risk individuals.

MIRAI (Mammography Risk Assessment using Artificial Intelligence) model: An artificial intelligence model is applicable only to women who have undergone mammography, typically aged 40 years and older, and estimates short- and long-term breast cancer risk based on mammographic images, with or without accompanying clinical risk factors. MIRAI then predicts annual breast cancer risk over multiple future time points, typically up to five years, using an additive hazard framework. Multinational validation studies have demonstrated consistent performance across diverse populations, with strong discriminatory accuracy for both 1-year and 5-year risk prediction. These findings suggest that MIRAI may complement traditional risk models by enabling image-based, individualised risk stratification, particularly in screening settings where clinical data may be incomplete.[62]

To summarise, Gail/BCRAT is used for population screening; BCSC estimates near-term breast cancer risk for screening; BRCAPRO estimates the probability of a BRCA mutation for genetic testing; Tyrer–Cuzick provides comprehensive genetic and lifetime risk assessment; and MIRAI uses AI on mammograms to predict individualised multi-year breast cancer risk.

Risk Assessment Tools For India

In the absence of an India-specific, validated breast cancer risk prediction model, the Gail/Breast Cancer Risk Assessment Tool (BCRAT) may be used for population-level risk estimation, while the Tyrer–Cuzick (IBIS) model is preferred for comprehensive assessment of genetic susceptibility and 10-year and lifetime breast cancer risk to inform surveillance and risk-reduction strategies. These tools are not calibrated for Indian women and often underestimate their risk.[13,55]

SCREENING FOR BREAST CANCER

The value of breast cancer screening remains a subject of ongoing debate universally, particularly in low and middle-income countries. At a population level, screening recommendations are intended for women above 40 years at average risk of breast cancer, and are defined as those without a personal history of breast cancer, without known high-risk genetic mutations, without prior therapeutic chest irradiation, and without a strong family history suggestive of hereditary breast cancer. Women perceived as low risk with risk assessment models are included in this group, as there are no validated thresholds below which screening can be safely omitted.

For women younger than 40 years at average risk for breast cancer, no randomised controlled trials have demonstrated a mortality benefit from routine screening. As a result, expert groups have not reached consensus on imaging-based screening in this age group. However, several organisations recommend breast awareness, defined as encouraging women to be familiar with the normal appearance and feel of their breasts and to promptly report any changes to a health care provider, beginning in early adulthood.

The National Comprehensive Cancer Network (NCCN) recommends that women at average risk for breast cancer undergo an initial clinical encounter by age 25 years, which should include breast cancer risk assessment and education on breast awareness. For asymptomatic women aged 25–39 years, NCCN advises periodic clinical encounters every 1–3 years, preferably incorporating clinical breast examination and risk-reduction counselling, until transition to imaging-based screening at age 40 years.[63] For women aged 40 years and older who are at average risk, both NCCN and the American College of Obstetricians and Gynaecologists (ACOG) support the use of annual clinical breast examination, when feasible, as part of routinepreventive care. [64,65]

Recommendations on discontinuing mammographic screening vary among professional organisations and are based on chronological age and life expectancy rather than age alone. Screening is commonly reconsidered after age 75, with continued mammography advised only for women with an anticipated life expectancy of at least 5–7 years, taking comorbidities into account.[64,66]

India currently lacks an organised, population-based, government-funded breast cancer screening programme. Consequently, screening in India is largely opportunistic, occurring when women access healthcare services for other reasons. At present, there are no nationally endorsed, evidence-based guidelines for systematic breast cancer screening in India, leading to regional variation in screening practices. Opportunistic screening is considered appropriate in low- and middle-income countries (LMICs) due to resource, infrastructure, and population coverage constraints, and is aimed at maximising early detection within existing healthcare encounters.

Evolution From Standard Age-Based Screening

Recent evidence supports a shift toward risk-based breast cancer screening. Modelling and clinical trial data show that tailoring screening intensity and preventive counselling to an individual's risk is noninferior to uniform annual screening for advanced cancer detection.[63]

Higher-risk women benefit from more frequent screening, with improved cancer detection and no increase in late-stage disease, while lower-risk women can safely undergo less intensive screening. Although overall biopsy rates are not reduced, screening intensity, cancer detection, and biopsy rates appropriately increase with rising risk. These findings indicate that risk-based screening is safe, acceptable, and represents a practical step toward precision medicine–based breast cancer screening.[67]

Screening Methods

Breast cancer screening includes three approaches to early detection: breast self-awareness (BSF), formerly breast self-examination (BSE), clinical breast examination (CBE), and imaging based screening.

Breast Self-Awareness

Routine, structured monthly BSE is no longer recommended as a screening tool in most developed countries. Instead, women are encouraged to develop breast self-awareness, which involves becoming familiar with the normal appearance and feel of their breasts and promptly reporting any persistent or unusual changes. BSF does not involve routine or systematic breast self-examination for the purpose of detecting breast cancer.[65] BSF includes observing the breasts and axillae for changes in size, shape, skin, or nipple appearance, as well as self-palpation. Initially, frequent self-examination helps women understand normal physiological variations of the menstrual cycle; after that, examination may be continued monthly, preferably around the 7th or 8th day of the cycle. Common physiological findings such as cyclical nodularity, premenstrual tenderness, and a lumpy breast texture should be explained to reduce unnecessary anxiety.[68]

Clinical Breast Examination

CBE is performed by the clinician or other health professional and involves a systematic examination of the breast skin and tissue.[69-72] CBE involves careful inspection followed by systematic palpation. With the patient seated, the breasts are inspected for symmetry, contour, skin changes, and nipple abnormalities at rest and during arm movements. Dimpling, redness, retraction, or nipple inversion should be noted. Axillary and supraclavicular lymph nodes are palpated to assess for enlarged, firm, or fixed nodes.

Palpation begins with the patient sitting upright, using the finger pads to examine all breast tissue from the clavicle to the inframammary fold in a vertical strip pattern, progressing from superficial to deep layers. The patient is then examined in the supine position with the arm raised to allow better assessment of all quadrants, including the areola and subareolar region, using a radial pattern. Nipple discharge is assessed only if discharge other than breast milk is reported. Findings are documented using the clock-face method, noting the distance from the nipple, depth, and characteristics of any lesion. A normal examination records breast symmetry and tissue consistency.

Fibroadenoma typically presents as a firm, freely mobile lump, often described as a "mouse in the breast," whereas breast malignancy commonly presents as an irregular, hard, painless mass. These features are not absolute, and variations may occur. Normal breasts may feel lumpy and tender before menstruation; therefore, palpation should be performed using a flat hand rather than fingertips.

Mammography

Mammography is an X-ray–based imaging technique of the breast that uses low-dose ionising radiation. Mammography remains the gold standard imaging modality for breast cancer screening and is the only screening technique proven to reduce breast cancer–specific mortality, with an estimated reduction of 15–25% in screened populations.[73] Reported performance characteristics of mammography show a sensitivity of approximately 74–81% and specificity of 89–91% for the detection of breast malignancy. The sensitivity of mammography is reduced in women with dense breast tissue, which is more common in younger women.[74]

Mammography carries a small potential risk to the patient. The average radiation dose for a standard mammogram with two views of each breast is approximately 0.4 mSv, which is equivalent to about seven weeks of natural background radiation exposure (average background radiation is more than 3 mSv per year). Despite this exposure, the overall benefits of mammography in early cancer detection and mortality reduction far outweigh the associated risks and inconvenience. Digital mammography has largely replaced conventional film–screen mammography and typically includes two standard views of each breast: craniocaudal (CC) and mediolateral oblique (MLO). The combined use of digital mammography (2D) with digital breast tomosynthesis (DBT) provides three-dimensional reconstruction of the breast and has been shown to improve cancer detection rates and reduce false-positive recalls, including in women with dense breasts.

False-positive mammography results occur when benign findings, such as harmless microcalcifications, tissue overlap, or well-circumscribed lesions with irregular margins, are mistaken for malignancy. These are most common during initial screening examinations and are significantly reduced when prior mammograms are available for

comparison. A substantial proportion of women undergoing repeated screening may experience at least one false-positive result, and a subset of these undergo unnecessary biopsies.[75,76] False-negative results occur when an existing breast cancer is not detected on mammography. Contributing factors include dense breast tissue, technical or positioning errors, perceptual or interpretive mistakes, subtle radiologic features, and slow-growing tumours. Awareness of these limitations is essential to ensure appropriate clinical correlation and follow-up.[75-77]

Breast Ultrasonography

Breast ultrasonography is a widely available and valuable adjunct to mammography, primarily used to further evaluate abnormalities detected on clinical examination or mammography.[78] It is particularly useful in women with dense breast tissue and in differentiating solid masses from cystic lesions, as well as for guiding biopsies and interventional procedures.[79,80] When combined with mammography for screening, ultrasonography increases sensitivity (approximately 85–97%) but reduces specificity (around 84–87%), [74] largely due to higher false-positive rates. As a standalone screening tool, ultrasound is limited by its inability to detect microcalcifications, operator dependence, and reduced specificity; therefore, routine population-based ultrasound screening is not recommended. Automated breast ultrasound systems (ABUS) have been developed to address operator dependence and are approved as an adjunct to mammography in asymptomatic women with dense breasts who have negative mammograms and no prior breast interventions. Ultrasound screening may also be considered in selected situations, such as in women with mammographically occult cancers, those unable to undergo MRI, or highly anxious patients requesting supplemental evaluation.

Breast Magnetic Resonance Imaging

Contrast-enhanced breast MRI is the most sensitive imaging modality for the detection of breast cancer and is recommended in addition to mammography for women at high risk, defined as a ≥20–25% lifetime risk based on validated risk models or the presence of specific genetic or clinical risk factors. MRI demonstrates higher sensitivity than mammography, particularly in dense breasts; however, its specificity is lower, resulting in a higher rate of false-positive findings and additional investigations.[81,82] International guidelines recommend annual breast MRI, combined with mammography, for high-risk women, including BRCA1/2 mutation carriers, untested first-degree relatives of mutation carriers, women with a lifetime breast cancer risk ≥20% based on models such as BRCAPRO, Tyrer–Cuzick, BOADICEA/CanRisk, or BCSC, those who received chest irradiation between ages 10 and 30 years, and individuals with Tp53 (Li-Fraumeni syndrome) or PTEN (Cowden syndrome) mutations. When indicated, screening is typically initiated by age 30 years or 10 years earlier than the youngest affected relative, whichever occurs first.[56,83,84]

In the Indian context, routine MRI screening is not recommended for the general population due to high cost, limited availability, and the need for specialised expertise. Its use should be restricted to selected high-risk individuals or specific diagnostic scenarios, such as inconclusive mammography or very dense breasts.[6] At present, India-specific evidence-based guidelines for MRI screening are lacking.[6]

Role of Positron Emission Tomography Imaging

Positron emission tomography (PET), particularly PET/CT using F-fluorodeoxyglucose (FDG), has a limited role in breast cancer and is not recommended for screening or routine evaluation, especially in early-stage disease, due to low sensitivity for small primary tumours and in situ lesions. Its principal clinical utility lies in assessing treatment response, as serial changes in FDG uptake during systemic therapy can help identify early metabolic response in locally advanced or metastatic breast cancer. PET/CT may also be useful in selected cases for staging or restaging when conventional imaging is inconclusive.[85]

HARMS OF MAMMOGRAPHIC SCREENING

Mammographic screening is associated with two principal harms: false-positive results and overdiagnosis.[73] False-positive results occur when a screening mammogram leads to additional imaging and/or biopsy for an abnormality that is ultimately benign. Among women undergoing biennial mammographic screening between the ages of 50 and 69 years, the cumulative risk of experiencing at least one false-positive result has been estimated at approximately 20% in European screening programmes. False-positive findings may result in psychological distress, anxiety, and a short-term reduction in quality of life.[73] Overdiagnosis refers to the detection, through screening, of breast cancers that would not have become clinically apparent during a woman's lifetime. Overdiagnosis may lead to overtreatment, including unnecessary surgery, radiation, or systemic therapy. Reported estimates of overdiagnosis vary widely,

ranging from 0% to 54%, reflecting differences in study design, populations, and assumptions.[73]

Despite these harms, the absence of screening is associated with later-stage diagnosis, requiring more extensive treatment and conferring a poorer prognosis. Population-level evidence demonstrates that mammographic screening is associated with a 15–25% reduction in breast cancer–specific mortality, suggesting that the benefits of screening outweigh its harms in appropriately selected populations.[73,78] The benefits and harms of breast cancer screening should be discussed with all women, particularly those aged 40–49 years, in whom the absolute mortality benefit is smaller and the false-positive rates are higher. Screening decisions should be based on shared decision-making, incorporating individual risk factors, values, and preferences, and the discussion should be documented in the medical record.[68,73,78]

Screening Suggestions For Women At Average Risk In India By The Indian Menopause Society

In 2016, the Government of India initiated a population-based screening programme for common cancers, including breast cancer, under the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS). This programme recommends clinical breast examination (CBE) performed by trained health-care workers every five years for women aged 30 years and above, alongside screening for cervical and oral cancers.[86,87] Given the absence of an organised, population-based mammography programme and the relatively younger age at presentation of breast cancer in India, CBE performed by trained frontline health workers represents a pragmatic, low-cost screening strategy for low-and middle-income settings.[68,70,71] Evidence from large Indian randomised controlled trials has demonstrated that CBE-based screening leads to earlier stage detection, a significant reduction in advanced-stage disease, and an approximately 30% reduction in breast cancer mortality among women aged ≥50 years, without evidence of increased overdiagnosis.[70-72,88,89]

The CBE-based opportunistic screening model is supported by global and regional evidence, particularly in low- and middle-income countries. Systematic reviews consistently demonstrate a significant stage shift toward earlier breast cancer detection with CBE, although evidence for a direct mortality benefit remains indirect and of moderate quality.[90-92] Hence, opportunistic screening through CBE, breast self-awareness, and prompt evaluation of breast symptoms remains the most feasible and cost-effective approach in India.[68,71] Training and standardisation of CBE techniques are critical to optimising their effectiveness and reproducibility, further supporting their role as a feasible and cost-effective screening approach in resource-constrained settings.[92] Women with screen-positive findings are referred for further evaluation and imaging at district or tertiary care centres.[86,87]

Screening with mammography: The WHO recommends mammographic screening every 1–2 years for women aged 50–69 years in settings with adequate resources and quality assurance systems.[68] Mammography remains the only screening modality shown to reduce breast cancer–specific mortality at the population level; however, its implementation requires substantial infrastructure, trained personnel, and follow-up capacity.[81],[82] In India, breast cancer demonstrates a younger age distribution, with a significant proportion of cases occurring before 50 years of age.6,7,9-12 Observational studies and reviews suggest that mammographic screening may confer benefit in women aged 40–49 years, although the absolute mortality reduction is lower and false-positive rates are higher in this age group compared with older women.[78] Additional challenges include economic constraints, limited access, inconsistent quality control, dense breast tissue in younger women, and lower screening uptake, which restrict the effectiveness of mammography as a mass screening tool.[6] Consequently, routine population-wide mammography is neither feasible nor recommended in India.

In this context, selective or opportunistic mammographic screening every 2–3 years, guided by individual risk assessment and shared decision-making, may be considered where facilities permit.[6] In the Indian context, routine MRI screening is not recommended for the general population due to high cost, limited availability, and the need for specialised expertise. Its use should be restricted to selected high-risk individuals or specific diagnostic scenarios, such as inconclusive mammography or very dense breasts.[6] At present, India-specific evidence-base guidelines for MRI screening are lacking.[6] Ultrasonography can be useful as an adjunct to screening mammography in the evaluation of females with dense breasts and in differentiating solid lesions from cystic lesions. However, the routine use of ultrasound as a screening test is not recommended.[78]

SCREENING RECOMMENDATIONS FOR WOMEN AT AVERAGE RISK BY GLOBAL AUTHORITIES:

Refer to Table 2

Table 2. Screening recommendations for women at average risk by global authorities

Organisation (year)	Clinical Breast Examination	Age to Start Screening Mammography or Begin Discussions of Screening	Screening Interval	Age to Stop Screening Mammography
American Cancer Society (2015)[93]	Not recommended	Discuss at 40-44Y	45-55:Annual > 55: Biennialvs annual is optional	Not specified; continue as long as a woman is in good health and has life expectancy of at least 10 y
American College of Obstetricians and Gynaecologists (2024)[94]	Consider every 1-3 y for women aged 25-39 y and annually for women ≥40 y	Recommended: 40 y	Annual or biennial	If ≥75 y, decision depends on comorbidities and estimate of lifespan
American College of Physicians (2019)[95]	Not recommended	Discuss at 40-44y Recommended: >50y	Biennial	75 y
American College of Radiology (2017)[96]	No recommendation	40 y	Annual	None
National Comprehensive Cancer Network (2024) [64]	Every 1-3 y for women aged 25-39 y and annually for women ≥40 y	40 y	Annual	No recommendation
U.S. Preventive Services Task Force (2024)[76]	No recommendation	40 y	Biennial	75 y
World Health Organisation (2014)[97]	Recommended only in low-resource settings	50 y	Biennial	75 y

Multiple international guidelines provide recommendations for breast cancer screening in women at average risk. Mammography is consistently endorsed as the primary screening modality across guidelines issued by the World

Health Organisation (WHO),[97] American Cancer Society (ACS),[93] the National Comprehensive Cancer Network (NCCN,[64] the European Society for Medical Oncology (ESMO),[98] the American College of Obstetrics and Gynaecology (ACOG),[94] and the U.S. Preventive Services Task Force (USPSTF).[76]

Clinical breast examination (CBE): CBE may be performed every 1–3 years in women aged 25–39 years and annually from age 40 years onward, particularly in settings where mammography access is limited. For optimal performance and reporting, standardised techniques should be employed.[68,69,86]

SCREENING RECOMMENDATIONS FOR HIGH-RISK WOMEN

Women are considered high risk if they have a personal history of breast cancer or high-risk precursor lesions (ductal carcinoma in situ [DCIS], lobular carcinoma in situ [LCIS], atypical hyperplasia), strong family history, known pathogenic genetic variants, prior chest irradiation between ages 10–30 years, or extremely dense breasts.[78] For high-risk women, most guidelines recommend earlier initiation and more intensive surveillance, including annual mammography (not before age 30 years) and/or annual breast MRI (not before age 25 years), depending on risk magnitude and resource availability.[78]

GENETIC TESTING FOR BREAST CANCER SUSCEPTIBILITY

The lifetime risk of breast cancer in developed countries is approximately 10–12% (about 1 in 8–9 women). While nearly 25–30% of women report a family history or genetic susceptibility, only about 3–5% carry high-penetrance pathogenic variants, such as BRCA1 or BRCA2 mutations, which are associated with a markedly increased lifetime breast cancer risk exceeding 50%.[99,100] An inherited cancer predisposition should be suspected in individuals with early-onset breast cancer, bilateral disease, multiple affected relatives, or clustering of breast and related cancers, such as ovarian, pancreatic, and prostate cancer, within a family. Pathogenic variants, particularly BRCA1 and BRCA2, are associated with a markedly increased risk of contralateral breast cancer (exceeding 50% by age 70) and a significantly elevated risk of ovarian cancer, with inheritance possible through either parent and variable expression due to incomplete penetrance.[99,100]

Advances in sequencing technologies allow accurate detection of BRCA and other high-penetrance gene mutations; testing an affected family member is preferred when feasible, though testing unaffected individuals is appropriate when no affected relative is available.[101] According to NCCN guidelines, multigene panel testing including BRCA1, BRCA2, PALB2 (DNA repair-associated partner of BRCA2), CDH1, PTEN, serine/threonine kinase 11 (STK11), and TP53 is recommended for individuals with specific personal or family cancer histories, such as early-onset breast cancer (≤50 years), male breast cancer, triple-negative disease, multiple primary tumours, or associated ovarian, pancreatic, or high-risk prostate cancers.[100] Genetic testing is also indicated at any age when results will influence systemic treatment decisions, including the use of poly (ADP-ribose) polymerase (PARP) inhibitors in metastatic disease or adjuvant olaparib in high-risk, HER2-negative breast cancer.[100,102-104]

GENETIC COUNSELLING: PRINCIPLES AND INDICATIONS

All major professional bodies, including the USPSTF, NCCN, ACOG, American Society of Clinical Oncology (ASCO), and ESMO, emphasise that genetic testing should be performed only in conjunction with genetic counselling.

Key principles include

- Testing should be offered only when personal or family history suggests inherited cancer susceptibility
- Testing of unaffected individuals should be considered only when an appropriate affected relative is unavailable
- Testing must be voluntary, with informed consent
- Pre-test counselling should address potential benefits, limitations, psychosocial implications, and possible outcomes
- Post-test counselling is essential for the interpretation of results and management planning
- Testing should be performed only if the results will influence clinical management of the patient or at-risk relatives
- Mutation carriers should be encouraged to facilitate cascade testing for family members

The USPSTF recommends that women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer undergo initial risk assessment using a brief familial risk assessment tool. The USPSTF reviewed tools such as the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, and 7-Question Family History Screening Tool and found insufficient evidence to favour any one over the others. In clinical practice, more comprehensive models are also commonly used, including BRCAPRO, which estimates the probability of carrying a BRCA mutation to guide genetic testing, and the Tyrer–Cuzick model, which integrates genetic, familial, and clinical factors to estimate both mutation probability and lifetime breast cancer risk.[105,106] Women with positive screening results should receive genetic counselling and, if indicated after counselling, genetic testing. General breast cancer risk models, such as Gail/BCRAT, are not appropriate for identifying candidates for genetic testing. The ACOG and Society of Gynaecologic Oncology recommend formal genetic risk assessment for women with a >20–25% probability of hereditary breast and ovarian cancer and consider it reasonable for those with a 5–10% probability, particularly when results would alter management.

Counselling for Associated Cancer Risk

For women with pathogenic variants such as BRCA1 or BRCA2, genetic counselling should address cancer risks beyond the breast. Counselling should include the substantially increased risk of ovarian and fallopian tube cancer, with discussion of risk-reducing salpingo-oophorectomy and its recommended timing. Women should also be informed of the elevated risk of pancreatic cancer, for which screening may be considered in the presence of a relevant family history. Routine intensified screening for colorectal or thyroid cancer is not recommended in BRCA mutation carriers unless there is additional family history suggestive of another hereditary cancer syndrome. Counselling should further include reproductive considerations, menopausal implications of risk-reducing surgery, and the importance of cascade testing for at-risk relatives.

BREAST CANCER PREVENTION

The risk of breast cancer can be modestly reduced through lifestyle modification and careful use of hormone therapy(HT). Evidence suggests that healthy behaviours, such as limiting alcohol consumption, maintaining a healthy body weight, and engaging in regular physical activity, are associated with a lower risk of breast cancer. Sustained weight loss, even of modest magnitude, is associated with a significantly lower risk of breast cancer among women aged 50 years and older, highlighting weight reduction as an important and motivating strategy for breast cancer prevention in overweight and obese women.[106]

Alcohol intake of two or more drinks per day is linked to an approximate 20% increase in risk compared with abstinence, while higher body mass index is associated with a relative risk ranging from 1.2 to 1.9. Regular leisure-time physical activity, particularly in postmenopausal women, has been shown to reduce breast cancer risk by 20–80%. Despite these preventive measures, early detection through appropriate screening remains the most effective strategy for reducing breast cancer–related morbidity and mortality.[107]

PRIMARY PREVENTION OF BREAST CANCER

Primary prevention strategies for breast cancer should be considered in individuals with a life expectancy of at least 10 years, no prior history of breast cancer, and an increased risk as determined by validated risk assessment models, as well as in those who received chest radiotherapy between the ages of 10 and 30 years. Current risk-reduction approaches include pharmacologic risk-reducing agents and risk-reducing surgery for individuals with hereditary genetic predisposition. Risk-reducing medications are recommended for women aged 35 years or older who meet high-risk criteria, including a 5-year breast cancer risk of ≥1.7% by the Gail model, a 10-year risk of ≥5% by the IBIS/Tyrer–Cuzick model, or a history of lobular carcinoma in situ.[104,105] For women whose personal or family history is associated with an increased likelihood of pathogenic BRCA1/2 mutations, the USPSTF concludes with moderate certainty that the net benefit of risk assessment and referral for genetic counselling followed by selective genetic testing, early detection, and preventive interventions outweighs the potential harms.[105]

Rationale

Based on analyses of the biology of occult tumours, the reductions in breast cancer incidence observed in the Women's Health Initiative (WHI), National Surgical Adjuvant Breast and Bowel Project Protocol P-1 (NSABP-P1), and Study of Tamoxifen and Raloxifene (STAR) trials likely reflect effects on a pre-existing reservoir of undiagnosed tumours rather

than true prevention of de novo disease. Accordingly, many breast cancer "prevention" strategies may function as early treatment. The biologic characteristics of these occult reservoir tumours further suggest that commonly used risk prediction models, including the Gail and Tyrer–Cuzick models, may estimate the prevalence of existing undiagnosed tumours rather than the risk of tumour initiation. Consequently, the development of more sensitive methods to identify individuals harbouring occult tumours and to determine their inherent aggressiveness should be a high research priority.[108]

Pharmacologic Risk Reduction (Chemoprevention)

Currently, selective estrogen receptor modulators (SERMs) tamoxifen and raloxifene are the principal agents approved for the primary prevention of breast cancer in women at increased risk. These agents exhibit both estrogen agonist and antagonist effects and primarily reduce the incidence of estrogen receptor–positive breast cancer.[109-111] Tamoxifen has been extensively studied for breast cancer prevention. The Breast Cancer Prevention Trial (P-1) demonstrated a 50% reduction in invasive and noninvasive estrogen receptor–positive breast cancers compared with placebo in high-risk women, defined by age > 60 years, history of lobular carcinoma in situ (LCIS), or a 5-year Gail risk ≥1.66%.[109] Long-term follow-up confirmed a sustained protective effect, with an approximate 43% reduction in invasive breast cancer incidence.[109] However, tamoxifen use is associated with increased risks of endometrial cancer and thromboembolic events, including stroke.[109-111] Consequently, the USPSTF does not recommend tamoxifen for women at average risk, and its use in high-risk women requires individualised risk–benefit assessment.[111]

Raloxifene, evaluated in the Study of Tamoxifen and Raloxifene (STAR) trial, demonstrated comparable efficacy to tamoxifen in reducing invasive breast cancer in postmenopausal women, with significantly lower risks of thromboembolic events and endometrial cancer. [112] Although noninvasive breast cancer rates were numerically higher with raloxifene, this difference was not statistically significant. The adverse-effect profile also differed: tamoxifen was associated with more gynaecologic and vasomotor symptoms, while raloxifene was linked to higher rates of musculoskeletal symptoms and weight gain.[112] Raloxifene is FDA-approved for breast cancer risk reduction in postmenopausal women but is not approved for premenopausal women, and data in BRCA mutation carriers remain limited.[111,112] Across randomised trials, both SERMs increase the risk of venous thromboembolism, with tamoxifen conferring a higher risk than raloxifene. Tamoxifen is also associated with an increased incidence of cataracts and endometrial cancer, whereas these risks are not observed with raloxifene.[111]

Surgical Prevention

For individuals at very high risk of cancer, such as those with hereditary genetic predisposition, surgical intervention provides another means of risk reduction. Main examples of surgical management of cancer risk include prophylactic mastectomy in BRCA mutation carriers, prophylactic salpingo-oophorectomy in BRCA carriers and mismatch repair gene mutation carriers, and prophylactic colectomy in individuals with familial adenomatous polyposis.

Risk-Reducing Mastectomy

Bilateral prophylactic mastectomy is a well-established risk-reduction strategy for individuals with BRCA1 or BRCA2 pathogenic variants, given their markedly elevated lifetime risk of breast cancer. Large cohort studies and long-term follow-up data demonstrate that bilateral prophylactic mastectomy reduces breast cancer risk by approximately 90–95% and is associated with a significant reduction in breast cancer–specific and overall mortality.[113,114] Contemporary surgical approaches favour skin-sparing and nipple-sparing mastectomy, which provide effective oncologic risk reduction while optimising cosmetic outcomes; subcutaneous mastectomy is discouraged due to the greater likelihood of residual breast tissue. Immediate breast reconstruction is a standard option and may improve quality of life. Despite its proven efficacy, uptake of prophylactic mastectomy remains limited. Barriers include the invasive and irreversible nature of surgery, potential surgical morbidity, concerns related to body image and psychosocial well-being, and the availability of alternative strategies such as intensified surveillance and pharmacologic risk reduction. Shared decision-making, incorporating individualised risk assessment and patient values, is therefore essential when considering this intervention.[113-116]

Prophylactic Salpingo-Oophorectomy

Risk-reducing salpingo-oophorectomy (RRSO) is a cornerstone preventive strategy for women with BRCA1 or BRCA2 pathogenic variants and is also indicated for women with Lynch syndrome and select other hereditary cancer

syndromes. In premenopausal BRCA mutation carriers, RRSO reduces the risk of ovarian and fallopian tube cancer by approximately 90–95% and breast cancer by about 50%, while in postmenopausal women, it primarily confers protection against ovarian cancer. A small residual risk of primary peritoneal carcinoma persists despite surgery. RRSO has been shown to significantly reduce cancer incidence and improve both cancer-specific and overall survival in this population.[117]

Risk-reducing salpingo-oophorectomy (RRSO) is generally recommended between 35–40 years of age for BRCA1 carriers and 40–45 years for BRCA2 carriers, or after completion of childbearing, reflecting differences in age of cancer onset. Bilateral salpingectomy alone is not currently recommended as a definitive ovarian cancer risk-reduction strategy in high-risk women, although clinical trials evaluating early salpingectomy with delayed oophorectomy is under investigation. For BRCA mutation carriers, removal of the fallopian tubes is recommended due to the recognised tubal origin of many high-grade serous cancers. Meticulous pathologic evaluation of the ovaries and fallopian tubes is essential, as occult malignancy is detected in approximately 4–8% of women undergoing this procedure. This thought is being questioned, since BSO induces irreversible menopause, associated with vasomotor symptoms, cardiovascular morbidity, bone loss, cognitive decline, and reduced quality of life. Hence, further studies are needed to define the role of BSO in hereditary breast cancer in terms of risks and benefits.[115] The role of concurrent hysterectomy remains individualised. It is routinely recommended for women with Lynch syndrome due to elevated endometrial cancer risk. In BRCA carriers, hysterectomy may be considered to facilitate complete salpingectomy, permit the use of unopposed estrogen therapy, or in women with prior or anticipated tamoxifen exposure.

However, bilateral salpingo-oophorectomy induces premature menopause, which is associated with vasomotor symptoms, bone loss, cardiovascular risk, cognitive decline, and reduced quality of life. Therefore, MHT plays a critical role in mitigating the adverse effects of early estrogen deprivation. Current evidence from observational studies, meta-analyses, and systematic reviews indicates that short-term MHT up to the age of natural menopause does not negate the breast cancer risk-reduction benefit of RRSO in BRCA mutation carriers.[120-123] The primary indication for MHT in this setting is the prevention of consequences of estrogen deficiency, including vasomotor symptoms, osteoporosis, cardiovascular disease, and impaired quality of life.[119,120] Accordingly, RRSO should not be delayed to avoid subsequent hormone therapy, and appropriately selected MHT should be offered following premenopausal surgery. Long-term use of systemic MHT beyond the natural age of menopause is generally discouraged due to limited safety data. MHT is contraindicated in women with a personal history of breast cancer or those with significant baseline breast cancer risk.[121,124] Emerging data remain reassuring regarding the short-term oncologic safety of hormone therapy, but individualised counselling regarding regimen, duration, and risk profile remains essential.

EFFECTS OF MENOPAUSE ON BREAST CANCER

Breast cancer risk is strongly influenced by the timing and type of menopause, reflecting cumulative lifetime exposure to endogenous estrogen. Later age at natural menopause is associated with an increased risk of breast cancer, with women experiencing menopause at age ≥55 years having approximately double the risk compared with those undergoing menopause before age 45 years. In contrast, early surgical menopause is associated with a significant reduction in breast cancer risk; oophorectomy before age 35 years reduces risk to approximately 60% of that observed in women with natural menopause, with protective effects extending up to age 50 years. These findings support the central role of ovarian hormone exposure in breast carcinogenesis and underpin risk-reduction strategies in high-risk populations.[124,125]

EFFECTS OF BREAST CANCER ON MENOPAUSE

Breast cancer treatment, particularly chemotherapy, frequently induces amenorrhoea or premature menopause, with the likelihood depending on patient age, treatment regimen, and baseline ovarian reserve. Treatment-induced menopause is commonly associated with vasomotor symptoms, sexual dysfunction,[126,127] bone loss, and adverse effects on quality of life. Hot flushes and night sweats are reported in approximately 65–85% of women following breast cancer therapy and are often more severe than in natural menopause. These symptoms may persist long term and are compounded by endocrine therapies, underscoring the need for proactive management of menopausal and survivorship-related complications.[128,129]

SYNOPSIS

- Breast cancer is the most common malignancy among women in urban India, accounting for approximately 25–32% of female cancers, whereas cervical cancer remains the leading cancer in rural women, with breast cancer ranking second.
- Non-modifiable risk factors include increasing age, family history, benign breast disease, BRCA1/2 mutations, early menarche, late menopause, high breast density, and prior chest irradiation.
- Modifiable risk factors include reproductive factors (age at first childbirth, parity, breastfeeding), obesity, alcohol use, physical inactivity, and appropriate use of hormone therapy in contraception and menopause.
- India lacks an organised, population-based breast cancer screening programme; screening is largely opportunistic, with no nationally uniform, evidence-based guidelines.
- Early detection methods include breast self-awareness, clinical breast examination, and mammography, with screening strategies adapted to age and risk profile.
- Lifestyle modification, weight control, physical activity, and judicious use of hormone therapy can modestly reduce breast cancer risk.
- Early detection remains the most effective strategy for reducing breast cancer mortality.
- In high-risk women, individualised prevention strategies including chemoprevention, intensified surveillance, and risk-reducing surgery (mastectomy and salpingo-oophorectomy) should be discussed within a multidisciplinary framework.

RESEARCH AGENDA

Development of a risk assessment model for India.

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BREAST CANCER -EFFECTS OF HORMONE THERAPY

29

Keywords: Breast, hormone therapy, breast cancer

INTRODUCTION

The breast is an important organ of the female reproductive system, whose development, structure, and function are intricately regulated by sex steroid hormones. From puberty through menopause, cyclical and lifelong hormonal influences govern breast growth, differentiation, and involution, rendering the breast particularly sensitive to changes in the endocrine environment.[1,2] Menopausal hormone therapy (MHT) is the most effective treatment for symptoms of estrogen deficiency, and is indicated to relieve symptoms of estrogen deprivation and to achieve the beneficial effects of estrogen on serum lipids, bone, and the cardiovascular system.[2]

A sound understanding of breast physiology and hormonal responsiveness is therefore essential for clinicians managing menopausal women. This will guide the clinician in advising women on the right choice of treatment for menopausal symptoms and in assessing the risk of developing breast cancer. Extra care is essential when treating women who have had breast cancer and need therapy for menopausal symptoms. Fear is rampant in both the lay public and the profession of an exaggerated possible increase in breast cancer, based on a few studies, which, in truth, is only marginally higher.[3] Research is ongoing to delineate the ideal MHT for those at higher risk of breast cancer and for those who have already suffered from breast cancer.

HORMONES AND BREAST DEVELOPMENT

Development and structural changes in the breast occur throughout a woman's life, beginning in utero and continuing throughout the lifespan. These changes are regulated by complex interactions among ovarian, pituitary, adrenal, and placental hormones.[1,4] At puberty, estrogen is the principal hormone responsible for initiating breast development. Estrogen stimulates ductal elongation and branching and influences the areola by increasing its size and pigmentation. A subareolar mass of glandular tissue develops, marking the onset of thelarche.[1,4] The human breast expresses both estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ), whose expression and maturation are dependent on prolactin.[4] Estrogen is also essential for the induction of progesterone receptors (PR) within breast tissue, thereby enabling progesterone-mediated effects.[1] Progesterone plays a synergistic role by promoting the growth and differentiation of the lobuloalveolar units of the breast. While estrogen primarily stimulates ductal proliferation, progesterone is responsible for alveolar development and secretory maturation.[1,5]

During the reproductive years, cyclical breast changes occur in response to the estrogen–progesterone sequence of the normal menstrual cycle. The breast reaches its maximal size during the late luteal phase, when progesterone levels are highest. Increased fluid retention, stromal oedema, and mitotic activity within glandular and nonglandular epithelium occur during this phase, often resulting in premenstrual breast tenderness and nodularity.[1,6] Estrogen receptor expression declines during the luteal phase, whereas progesterone receptor levels remain elevated throughout the cycle.[1] Pregnancy induces the most profound hormonal effects on the breast. Marked proliferation of ductal and lobular structures occurs early early in gestation under the influence of estrogen, progesterone, prolactin, and placental lactogen. Final differentiation into a fully secretory gland capable of lactation occurs progressively as pregnancy advances.[1,2]

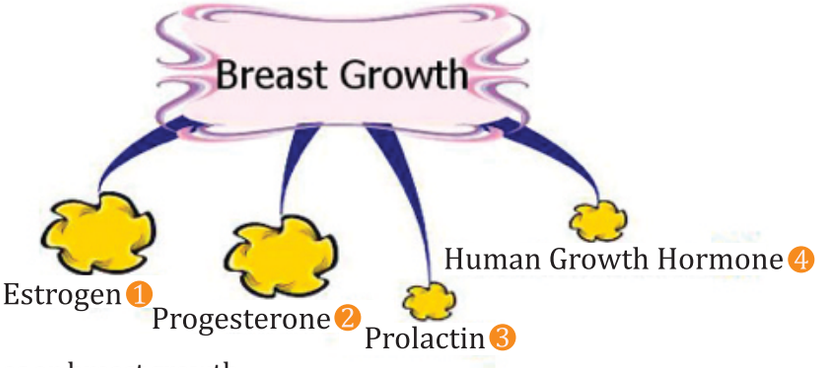

Figure 1 Effect of hormones on breast growth

BREAST CHANGES WITH MENOPAUSE

Following menopause, declining estrogen levels lead to involution of glandular tissue and an increase in adipose and fibrous components. The process accelerates so much that glandular tissue is mostly replaced by fat, altering breast density and responsiveness to exogenous hormones.[2,7] A gradual shrinking, or involution, typically begins around age 35. The connective tissue also becomes inelastic, leading to sagging.

BREAST CANCER

Risk Factors For Breast Cancer. Refer to Chapter 28.

BENIGN BREAST DISEASE AND RISK OF CANCER

A wide spectrum of benign breast lesions has been described, each with distinct histopathological features and varying degrees of associated breast cancer risk. These lesions are commonly classified according to their relative risk of subsequent breast cancer, aiding clinical management and patient counselling.[1,2] Based on epidemiologic and histologic evidence, benign breast lesions are broadly grouped into three risk categories.[6,8-11]

Lesions Associated with Minimal or No Increased Risk (<1.5%): This group includes non-proliferative breast lesions, such as fibrocystic changes, periductal fibrosis, hamartomas, lipomas, and neurofibromas.

Lesions Associated with Slightly Increased Risk (1.5%–2%): Proliferative breast lesions without atypia confer a modest increase in risk, including fibroadenomas, usual ductal hyperplasia without atypia, intraductal papillomas, papillomatosis, radial scars, blunt duct adenosis, and sclerosing adenosis. Careful follow-up is recommended, particularly when multiple lesions or additional risk factors are present.

Lesions Associated with Moderately Increased Risk (>2%): Proliferative lesions with atypia are associated with a substantially higher risk, such as atypical ductal hyperplasia (ADH) and atypical lobular Surgical excision for core biopsies that show ADH is considered the standard of care. However, ALH may hyperplasia (ALH). ADH is considered a pre-malignant, high-risk lesion, and ALH is only a high-risk lesion. be an incidental finding in small biopsies, and the standard surgical resection of these lesions remains controversial. In general, excision is usually recommended in high-risk patients. For ALH, in carefully selected lower-risk patients, surveillance and/or medical therapy, such as estrogen receptor modulators, are possible management options.[12]

ENDOGENOUS HORMONES AND BREAST CANCER

Lifetime Exposure to Circulating Estrogens and Breast Cancer Risk: The pathogenesis of breast cancer is closely linked to estrogen exposure. Extensive epidemiological, clinical, and experimental evidence supports a strong association between prolonged exposure to circulating estrogens and the development of breast cancer.[13,14] Breast cancer risk increases progressively from menarche through the reproductive years, reflecting cumulative hormonal exposure. Although the incidence continues to rise with advancing age, the slope of risk increase becomes less steep after menopause due to declining endogenous ovarian hormone production.[13] By the age of 70 years, the probability of developing breast cancer in the next 10 years is 4.31%.[15] By age 85, the cumulative lifetime risk of breast cancer in women in developed countries is approximately 11–12%.[16] Surgical reduction of estrogen exposure has demonstrated a significant protective effect; bilateral oophorectomy performed before the age of 35 years reduces breast cancer risk by approximately 40–75% compared with women undergoing natural menopause, underscoring the role of ovarian hormones in carcinogenesis.[17,18]

Reproductive Risk Factors: These include early age at menarche, late age at natural menopause, and postmenopausal obesity, the latter resulting from increased peripheral aromatisation of androgens to estrogens in adipose tissue.[13,14,19] Each additional year of ovarian function is associated with a small but significant increase in breast cancer risk, with a large individual-participant meta-analysis showing a 2.9% increase in risk for every year older at menopause (relative risk 1.029; 95% CI 1.025–1.032). High mammographic breast density, particularly in postmenopausal women, is one of the strongest independent risk factors for breast cancer and is associated with a four- to six-fold increased risk.[7] Breast density reflects cumulative hormonal exposure and breast tissue responsiveness to estrogenic stimulation.

Modifying and Cofactors: Several cofactors modify estrogen-related breast cancer risk. These include obesity, alcohol consumption, family history of breast cancer, nulliparity, delayed first full-term pregnancy, and smoking.[14,19] Women

have an approximately 100-fold higher risk of breast cancer than men, emphasising the fundamental role of female hormonal biology in disease development.[13]

Pregnancy: *Nature's Protection*: Early full-term pregnancy confers long-term protection against breast cancer. This protective effect is thought to result from the terminal differentiation of mammary epithelial cells and the predominance of estriol, a weaker estrogen, during pregnancy. This observation supports the concept that not only the duration but also the type and potency of estrogen exposure influence breast cancer risk.[14,20] The central role of estrogen in breast cancer biology is further supported by the effectiveness of endocrine therapies. Aromatase inhibitors, which profoundly reduce estrogen synthesis, are a cornerstone in the treatment of hormone receptor–positive breast cancer in postmenopausal women.[21]

EFFECT OF HORMONE THERAPY ON THE BREAST

MHT was initially established as an effective treatment for vasomotor symptoms and vaginal atrophy, and its role later expanded to include potential long-term preventive benefits, particularly for bone health and cardiovascular protection. However, publication of results from large observational and randomised studies, most notably the Women's Health Initiative (WHI), the Nurses' Health Study, and the Million Women Study (MWS), raised concerns about an increased risk of breast cancer associated with MHT, particularly combined estrogen–progestogen therapy.[22-24] These findings generated widespread anxiety among women and healthcare providers and led to a marked global decline in MHT use. The relationship between estrogen and breast cancer is biologically complex, with estrogen acting as both a tumour promoter and, under certain conditions, an apoptotic agent, underscoring the need for a careful interpretation of epidemiologic data and individualised risk–benefit assessment.

UNDERSTANDING THE MOLECULAR BIOLOGY OF ESTROGEN AND BREAST CANCER

Estrogens play a central and multifaceted role in breast carcinogenesis, acting through both genomic and non-genomic mechanisms mediated primarily by estrogen receptors ERα and ERβ.[25-27] Activation of estrogen signalling pathways regulates cellular proliferation, differentiation, and apoptosis within estrogen-sensitive tissues, including the breast, ovary, and fallopian tube, with effects that are highly dependent on the local tissue microenvironment.[25,26] ERα activation is strongly associated with enhanced cellular proliferation and inhibition of apoptosis, whereas ERβ generally exerts antiproliferative and pro-differentiation effects. Consequently, the relative expression and balance of ERα and ERβ are critical, and loss or downregulation of ERβ is postulated to contribute to tumorigenesis.[26,28] At the genomic level, nuclear binding of ERα leads to transcriptional activation of multiple proto-oncogenes and cell-cycle regulators, including c-fos, c-myc, cyclins, growth factors, and HER2/neu, thereby promoting tumour initiation and progression.[25,29]

Independent of receptor signalling, estrogen metabolism also contributes to carcinogenesis. Catechol estrogen metabolites, particularly estradiol-3,4-quinones, generate reactive oxygen species and DNA adducts that may act as direct mutagens, providing an estrogen receptor–independent pathway for DNA damage.[30] After menopause, local estrogen production becomes dominant, driven by aromatase (CYP19A1) activity in adipose tissue, breast stroma, and tumour cells. Aromatase converts adrenal androgens into estrone, the predominant postmenopausal estrogen.[31,32] Estrone excess may be pro-inflammatory and pro-oncogenic, particularly in the context of obesity, and promotes the expansion of stem-like cells in hormone-receptor–positive breast cancer.[33,34] This establishes a mechanistic link between obesity, inflammation, increased aromatase activity, estrone excess, and postmenopausal breast cancer progression.[34] The route of estrogen administration may further influence risk, as oral estrogen therapy increases circulating estrone levels, whereas transdermal estrogen does not increase the levels.[35,36]

HR-positive tumours account for more than 70% of invasive breast cancers, and reproductive and hormonal exposures are strongly associated with HR-positive but not HR-negative disease.[37]

PROTECTIVE EFFECTS OF ESTROGEN ON BREAST CANCER: THE TIMING AND GAP HYPOTHESIS

Paradoxically, under specific biological conditions, estrogen may exert protective effects against breast cancer, a phenomenon best explained by the timing or "gap" hypothesis. The Timing or "Gap" Hypothesis proposes that the effect of MHT on breast cancer risk is critically dependent on the interval between menopause and initiation of therapy. This hypothesis emerged from observations that breast cancer risk varies according to whether MHT is

started soon after menopause (short gap, <5 years) or after prolonged estrogen deprivation (long gap, ≥5 years).[24,39,40] Observational and randomised data indicate that breast cancer risk varies substantially according to this interval. In MHT-naïve women, combined estrogen–progestogen therapy initiated soon after menopause (short gap) is associated with an increased relative risk (RR 1.7–1.8), whereas initiation after a long gap is associated with little or no increase in risk.[24,39,40] The rise in risk typically becomes apparent within 3–5 years of initiation, a time frame inconsistent with de novo tumour formation and more suggestive of promotion of pre-existing occult lesions. In contrast, estrogen-alone therapy demonstrates a different pattern. In MHT-naïve women with a long gap, estrogen alone is associated with a reduction in breast cancer risk, whereas no such reduction is observed in women with a short gap or prior hormone exposure.[24,38-40]

This finding was most clearly demonstrated in the estrogen-only arm of the WHI, where women (mean age 63, approximately 12 years postmenopausal) showed no increase and a reduction in breast cancer incidence during both the intervention phase and long-term follow-up.[38] The proposed mechanism underlying this paradox is estrogen-induced apoptosis. Experimental and clinical data show that breast cancer cells deprived of estrogen for prolonged periods become sensitised to the pro-apoptotic effects of physiologic estrogen re-exposure.[40-42] Modelling studies suggest that estrogen alone may induce apoptosis in a significant proportion of ER-positive occult tumours in long-term estrogen-deprived women, effectively eliminating pre-existing malignant clones.[43]

This effect is not observed in women previously exposed to hormone therapy, supporting the importance of long-term estrogen deprivation in enabling this response. In contrast, observational studies and randomised trials in which estrogen or combined estrogen–progestogen therapy was initiated close to menopause consistently demonstrate either neutral or increased breast cancer risk, suggesting promotion of pre-existing occult tumours rather than initiation of new cancers. Importantly, studies evaluating estradiol-based MHT, including the Danish Osteoporosis Prevention Study (DOPS) and Finnish registry cohorts, were conducted predominantly in women who initiated therapy soon after menopause and therefore did not include women with a prolonged postmenopausal estrogen-deprivation interval. Thus, current evidence does not allow conclusions regarding whether estradiol would produce similar effects to conjugated equine estrogens when initiated after prolonged estrogen deprivation, as this clinical scenario has not been formally studied.[44]

PROGRESSION OF OCCULT TO OVERT BREAST CANCER AND IMPLICATIONS FOR MENOPAUSAL HORMONE THERAPY

Autopsy studies have consistently demonstrated a substantial reservoir of occult, undiagnosed breast cancers in otherwise healthy women. A synthesis of eight autopsy series involving women aged 40–80 years reported a mean prevalence of occult breast cancer of approximately 7%, comprising about 1% invasive disease and 6% in situ lesions, with some studies identifying occult lesions in up to 15.6% of women.[45,46] These findings suggest that many breast cancers exist in a subclinical state for prolonged periods before becoming clinically detectable.

The transition from occult to overt breast cancer depends largely on tumour growth kinetics, commonly expressed as tumour doubling time. Bailey and colleagues, reviewing published data in women over 40 years of age, estimated a median tumour doubling time of approximately 200 days, with an interquartile range of 100-400 days.[47] Based on biological modelling and computer simulations, only about 6% of breast cancers diagnosed over a 5–7-year period arise de novo, whereas the remaining 94% represent pre-existing occult tumours that have grown to exceed diagnostic thresholds. Using these growth estimates, it is calculated that breast cancer typically requires at least 10 years to progress from a single malignant cell to clinically evident disease.[48,49] Detection thresholds further influence the timing of diagnosis. Mammographic detection generally requires tumour diameters of approximately 1.4 cm in younger women with dense breasts and 0.9 cm in older women with predominantly fatty breasts, contributing to variability in apparent incidence across age groups. [48] These observations underscore the importance of early detection strategies and have critical implications for interpreting changes in breast cancer incidence following interventions such as MHT.

DURATION OF MENOPAUSAL HORMONE THERAPY,USE AND BREAST CANCER RISK

Across the epidemiologic literature, a recurring observation is that duration of MHT use, particularly combined estrogen–progestin therapy, is associated with increasing breast cancer risk, although the timing of risk emergence and magnitude vary by study design, formulation, and population. Early pooled observational evidence from the Collaborative Group on Hormonal Factors in Breast Cancer demonstrated that current MHT use was associated with

higher breast cancer risk, with risk increasing with longer duration of use and declining after cessation; women who were current users for approximately five years or longer had a commonly cited relative risk (RR) of about 1.3–1.4 compared with never-users.[50] Randomised evidence from the WHI estrogen–progestin trial (CEE+MPA) provided stronger causal support for a duration-related effect, showing an increased incidence of breast cancer during the intervention phase, with subsequent analyses indicating that risk became apparent earlier among women with prior hormone exposure, consistent with promotion of pre-existing occult tumours rather than de novo carcinogenesis.[22,51,52]

Observational data from the MWS similarly reported an association between combined MHT and breast cancer risk; however, the MWS observed increased risk even with relatively short reported durations of use, a finding that contrasts with WHI and many other cohorts and has been attributed to differences in exposure ascertainment, screening practices, and timing of initiation relative to menopause.[24,53] More recent analyses have reinforced the importance of duration. Jones and Schoemaker (2016) argued that many earlier cohort studies systematically underestimated duration-related risk because MHT exposure was not updated during follow-up, leading to misclassification of long-term users. By addressing this limitation, they demonstrated a progressive increase in breast cancer risk with longer duration of combined MHT use, extending beyond 10–15 years, thereby strengthening the case for a true duration–response relationship for combined therapy.[54]

Consistent with these findings, large contemporary "real-world" European and Nordic registry studies, including national cohorts from Scandinavia, have repeatedly shown higher breast cancer risk with combined MHT, particularly with longer duration and current or recent use, despite changes in prescribing practices over time.[39,55,56] In contrast, the evidence for long-duration estradiol (E2) therapy is more heterogeneous. The DOPS, which evaluated 17β-estradiol with norethisterone acetate initiated soon after menopause in young women, showed no increase in cancer after 16 years of follow-up.[44] In contrast, the evidence for unopposed estrogen therapy is less uniform. In the WHI estrogen-alone trial (CEE), no increase in breast cancer incidence was observed during the intervention, and extended follow-up demonstrated reductions in both incidence and mortality.[57]

However, long-term observational data from the Nurses' Health Study among women with hysterectomy showed that very long duration of unopposed estrogen use was associated with increased breast cancer risk, with current use beyond 20 years yielding an RR of 1.42 (95% CI 1.13–1.77) and statistically significant increases in ER+/PR+ tumours after approximately 15 years of use.[58] However, in a subgroup analysis of the DOPS, in which women with hysterectomy receiving unopposed 17β-estradiol experienced a significant reduction in the composite endpoint of mortality or breast cancer, similar to the WHI estrogen-alone results.[44]

UNDERSTANDING THE MOLECULAR BIOLOGY OF PROGESTERONE AND BREAST CANCER

The role of progestogens in mammary carcinogenesis is complex and less clearly defined than that of estrogens. Experiments performed in vitro, animal, and human studies demonstrate both proliferative and antiproliferative effects, depending on receptor isoform expression, the tissue microenvironment, the timing of exposure, and interactions with estrogen signalling pathways. These biological mechanisms support heterogeneous effects of progestogens rather than uniform carcinogenicity.

The PR exists as two major isoforms, PRA and PRB, which are typically expressed at approximately 1:1 in normal breast tissue; their relative expression is regulated, in part, by ER activation, reflecting the integrated nature of estrogen–progesterone signalling in the breast.[59,60] Alterations in this balance are biologically important, as PRB is the predominant transcriptionally active and proliferative isoform, essential for mammary gland development and ductal growth, whereas PRA may exert inhibitory or modulatory effects on PRB signalling.[59,61]

Through PR-mediated genomic mechanisms, progesterone induces transcription and secretion of mitogenic growth factors, including amphiregulin and receptor activator of nuclear factor-κB ligand (RANKL), thereby promoting epithelial proliferation and paracrine signalling within the breast microenvironment.[62,63] These pathways are strongly implicated in progestogen-associated mammary epithelial expansion and provide biologic plausibility for the increased breast cancer risk observed with certain combined estrogen–progestin regimens in clinical studies.[62,64] At the same time, progesterone signalling has been shown to exert context-dependent antiproliferative and pro-apoptotic effects, mediated in part through transforming growth factor-β (TGF-β)–related pathways, highlighting that PR signalling is not uniformly pro-oncogenic.[62,65,66]

Dysregulation of PR isoform expression, particularly the relative overexpression of PRB, has been associated with activation of signalling pathways implicated in breast carcinogenesis, altered stromal-epithelial interactions, and enhanced proliferative responses.[61,67] Importantly, the biological effects of progesterone differ by tissue. In contrast to its role in the breast, progesterone generally exerts inhibitory and differentiating effects in the ovary and endometrium, underscoring the tissue-specific nature of PR signalling.[68]

These mechanistic insights provide a biologic framework for understanding why combined estrogen–progestin therapy, but not estrogen alone, has been consistently associated with increased breast cancer risk in clinical studies, while also explaining heterogeneity among different progestogens and dosing regimens.[62,64]

OBSERVATIONAL STUDIES AND MENOPAUSAL HORMONE THERAPY (MHT)

Nurses' Health Study: An association between MHT and breast cancer risk has been demonstrated in the Nurses' Health Study. This large prospective cohort study, established in 1976, enrolled 121,700 female nurses aged 30–55 years at baseline and followed them through 1992. The analysis showed that menopausal hormone therapy was associated with an increased risk of breast cancer among users of estrogen alone (relative risk [RR] 1.32; 95% confidence interval [CI] 1.14–1.54) as well as among users of combined estrogen–progestin therapy (RR 1.41; 95% CI 1.15–1.75). The risk of breast cancer increased with advancing age and was highest among women aged 65–69 years (RR 1.69), followed by those aged 60–64 years (RR 1.42), 55–59 years (RR 1.41), and 50–54 years (RR 1.46). No increased risk was observed in women younger than 50 years (RR 1.0). These findings indicate a clear age-related increase in breast cancer risk associated with MHT.[23]

Collaborative Group on Hormonal Factors in Breast Cancer from the 1997 Meta-analysis: The Collaborative Group on Hormonal Factors in Breast Cancer conducted a large international individual-participant meta-analysis published in 1997, including data from 52,705 women with breast cancer and 108,411 women without breast cancer derived from 51 epidemiological studies across 21 countries. This analysis provided strong evidence supporting a causal association between MHT and breast cancer risk. The estimated cumulative excess number of breast cancer cases per 1,000 women who initiated MHT at age 50 was 2 (95% CI 1–3) after 5 years of use, 6 (95% CI 3–9) after 10 years, and 12 (95% CI 5–20) after 15 years of use. Short-term use of combined estrogen–progestin therapy for less than four years did not appear to significantly increase breast cancer risk, although it was associated with increased mammographic breast density, potentially impairing cancer detection. The effect of MHT on breast cancer mortality remained uncertain.[50] Among the various modifying factors examined, body mass index (BMI) had a substantial influence on risk: breast cancer risk increased linearly by approximately 2.3% per year among women using estrogen beyond ive years, with the highest relative risk observed in lean women (BMI <25).[69]

Collaborative Group on Hormonal Factors in Breast Cancer from the 2019 Meta-analysis: An updated individual-participant meta-analysis of pooled data from 58 prospective epidemiological studies. This analysis included 108,647 postmenopausal women who developed breast cancer, of whom 55,575 (51%) had used MHT. The study demonstrated that all forms of systemic MHT were associated with an increased risk of breast cancer, except for low-dose vaginal estrogen preparations used for local symptoms. Breast cancer risk was greater with estrogen–progestogen therapy than with estrogen-only therapy, although estrogen-only systemic MHT was also associated with a modestly increased risk. There was little or no increase in breast cancer risk with MHT use of less than one year; however, risk increased with longer duration of use and rose progressively with continued exposure beyond one year. Although risk declined after cessation of therapy, it remained elevated for more than ten years among former users compared with never-users.

For a given duration of use, the absolute number of MHT-associated breast cancers by age 69 was similar regardless of whether therapy was initiated in the 40s or 50s. Relative risks during years 5–14 of current use were substantially higher for estrogen receptor–positive tumours than for estrogen receptor–negative tumours. Risk estimates were simila r for women initiating MHT between ages 40 and 59, but were attenuated in women who started therapy after age 60 and in women with higher BMI. Notably, obese women using estrogen-only MHT had little or no excess risk. Consequently, both absolute and relative excess risks associated with MHT were greater among lean women than obese women. The analysis also highlighted that breast cancer risk varied according to the type of progestogen used, supporting the concept that not all MHT formulations carry equivalent risk. Subgroup analyses suggested that risk did not differ substantially between most progestogenic constituents, including micronised progesterone, although combinations containing dydrogesterone appeared to be associated with somewhat lower risks. As with earlier analyses, the effect of MHT on breast cancer mortality could not be determined.[69]

Strengths and limitations of this study include the use of very large sample sizes, often incorporating individual participant data, which enhance statistical power and the precision of risk estimates. The predominance of prospective cohort designs reduces recall bias and allows for temporal assessment of exposure and outcome. Additionally, many studies permit detailed evaluation of clinically relevant modifiers, including duration and timing of MHT, formulation, route of administration, and type of progestogen, with extensive subgroup analyses by age, body mass index, tumour receptor status, and MHT regimen. The inclusion of diverse international populations further improves the generalisability of findings. However, important limitations remain. The observational nature of most studies restricts causal inference and does not fully eliminate residual confounding. Information on exact hormone doses, changes in formulations over time, and treatment adherence is often limited. Increased mammographic density associated with MHT use may have influenced cancer detection, introducing potential detection bias. Furthermore, many studies lack sufficient power to reliably assess breast cancer–specific mortality, and exposure to vaginal estrogen has not been uniformly characterised, limiting definitive conclusions regarding its long-term safety.

Million Women Study: The Million Women Study (MWS) was a large prospective observational cohort conducted in the United Kingdom that evaluated the association between MHT and breast cancer risk. Between 1996 and 2001, a total of 1,084,110 women aged 50–64 years were recruited through the National Health Service breast screening programme and followed for cancer incidence and mortality. Approximately 50% of participants reported current or past use of MHT at baseline. Exposure data were collected via self-administered questionnaires completed before mammography, and outcomes were ascertained through national cancer and death registries.[24]

Current use of MHT was associated with an increased risk of breast cancer (relative risk [RR] 1.66;95% confidence interval [CI] 1.58–1.75) and breast cancer–specific mortality (RR 1.22;95% CI 1.00–1.48) compared with never-users. In contrast, women who reported past use of MHT did not demonstrate an increased risk. The initial MWS report indicated a higher relative risk with combined estrogen–progestin therapy (RR approximately 2.0) compared with estrogen-only therapy (RR approximately 1.3), with estimates exceeding those reported in randomised trials such as the Women's Health Initiative (WHI).[22]

Several methodological concerns have been raised regarding the MWS. The mean duration of follow-up was relatively short (approximately 2.6 years), and the average interval from study entry to breast cancer diagnosis was only 1.2 years, with a mean time to breast cancer death of 2.4 years. Given established estimates of breast tumour doubling time and the prolonged latency required for a malignant breast cell to reach clinically detectable size, these findings raise the possibility that many cancers detected shortly after recruitment were already present at baseline. This has led to concerns about detection bias, particularly in the context of differential mammographic surveillance and the self-selection of MHT users into breast screening clinics.[53,70,71]

Additional critiques include reliance on self-reported MHT exposure, a higher prevalence of MHT use and breast cancer incidence among study participants than in the general population, and potential residual confounding inherent to observational designs. Consequently, the magnitude of breast cancer risk reported in the MWS may have been overestimated.[70,71] Notably, the MWS findings differ from those of the WHI randomised controlled trial. In the MWS, estrogen therapy initiated within five years of menopause was associated with an absolute excess of approximately 13 additional breast cancer cases per 10,000 women per year, whereas WHI did not demonstrate an increased breast cancer risk with estrogen-only therapy during the intervention phase. These discrepancies may reflect differences in study design, timing of initiation relative to menopause, formulation and dose of estrogen, background breast cancer risk, and intensity of mammographic surveillance. When estrogen therapy was extended beyond 15 years in the Nurses' Health Study, however, an increased risk of breast cancer was observed, suggesting that duration of exposure remains an important determinant of risk.[23]

Evidence from Large Observational Database Studies: Nested case–control studies using the UK QResearch and Clinical Practice Research Datalink (CPRD) databases further evaluated the association between hormone therapy and breast cancer risk. Compared with never-users, long-term use of systemic hormone therapy (≥5 years) was associated with an increased risk of breast cancer, with an adjusted odds ratio (OR) of 1.15 (95% CI 1.09–1.21) for estrogen-only therapy and 1.79 (95% CI 1.73–1.85) for combined estrogen–progestogen therapy. Among combined regimens, risk varied by progestogen type, being highest with norethisterone (OR 1.88; 95% CI 1.79–1.99) and lowest with dydrogesterone (OR 1.24;95% CI 1.03–1.48).In absolute terms, these findings corresponded to approximately 3–8 additional breast cancer cases per 10,000 woman-years among estrogen-only users and 9–36 additional cases per 10,000 woman-years among estrogen–progestogen users, depending on age. These excess risks fall within the "rare"

category. No increased risk was associated with the use of low-dose vaginal estrogen preparations.[72]

European Prospective Investigation into Cancer and Nutrition Study: The European Prospective Investigation into Cancer and Nutrition (EPIC) study is a large multicenter prospective cohort study that evaluated the association between MHT and breast cancer risk among 133,744 postmenopausal women across several European countries. The study demonstrated an increased risk of breast cancer among users of estrogen-only therapy (relative risk [RR] 1.42; 95% confidence interval [CI] 1.23–1.64), with a slightly higher risk observed among users of combined estrogen–progestogen therapy (RR 1.77; 95% CI 1.40–2.24). Continuous combined regimens were associated with a greater risk than cyclic regimens (RR 1.43; 95% CI 1.19–1.72), supporting the importance of regimen type in modifying breast cancer risk.[73]

E3N French Cohort Study: The E3N cohort is a large prospective observational study conducted in France that has provided detailed insights into the differential effects of MHT formulations on breast cancer risk. Updated analyses reported between 1992 and 2008 identified 3,678 invasive breast cancers among 78,353 women. Short-term use (≤5 years) of estrogen combined with micronised progesterone or dydrogesterone was not associated with a statistically significant increase in breast cancer risk (hazard ratio [HR] 1.11; 95% CI 0.89–1.38). Long-term use (>5 years) of these combinations was associated with a modest increase in risk (HR 1.31; 95% CI 1.15–1.48).[74]

The E3N study was the first epidemiological investigation to specifically assess percutaneous estradiol combined with micronised progesterone or dydrogesterone. These regimens were associated with a lower risk of invasive breast cancer compared with combinations containing other synthetic progestogens. Within this cohort and the duration of follow-up, estrogen-only therapy was not associated with a statistically significant increase in breast cancer risk, nor was there evidence of a significant difference in risk between oral and transdermal estradiol administration. Additionally, regimens using the levonorgestrel-releasing intrauterine system for endometrial protection appear to confer a breast cancer risk similar to that observed with oral progestogens.[3]

Finnish Nationwide Registry Studies: A Finnish nationwide comparative study including nearly 489,105 women and 3.3 million cumulative exposure years between 1994 and 2009 reported a statistically significant reduction in breast cancer mortality among MHT users. Mortality risk was reduced among women using hormone therapy for 0–5 years (RR 0.56; 95% CI 0.52–0.60), 5–10 years (RR 0.46; 95% CI 0.41–0.51), and more than 10 years (RR 0.62; 95% CI 0.56–0.68). The greatest mortality reduction was observed in women aged 50–59 years (RR 0.33; 95% CI 0.29–0.37). Estrogen-only therapy was associated with a greater reduction in mortality than combined estrogen–progestogen therapy.[75] These findings suggest that while MHT may increase breast cancer incidence in some populations, earlier detection and improved prognosis may contribute to reduced mortality in certain subgroups.

Additional Observational and Meta-Analytic Evidence: A prospective cohort analysis from the Women's Health Study (1992–2004), reported no statistically significant increase in breast cancer risk among consistent current users of conjugated equine estrogen compared with never-users after a mean follow-up of 10 years (HR 1.13; 95% CI 0.77–1.64).[76] Women using unopposed estrogen replacement therapy (ERT) for 25 years or longer had no appreciable increase in risk of breast cancer from a population-based case–control study.

Similarly, a population-based case–control study found no increased risk among women who had used unopposed estrogen for up to 25 years.[77] The same study found that combined therapy is associated with an increased risk of breast cancer, particularly invasive lobular tumours, whether the progestin component was taken in a sequential or continuous manner.

A systematic review and meta-analysis evaluating estradiol therapy in peri- and postmenopausal women reported a small but significant increase in breast cancer risk with long-term use, consistent with findings from several observational cohorts.[77] Overall, estradiol-only therapy has not been consistently associated with an increased risk of breast cancer in randomised trials, whereas breast cancer risk varies substantially according to the type of progestogen used in combined therapy. In the prospective MISSION study, no increased breast cancer risk was observed among women using MHT containing progesterone or synthetic progestins over a mean follow-up of 8.3 years (relative risk [RR] 0.91, 95% CI 0.45–1.86), although the wide confidence interval limits definitive conclusions. Yet, the results reflect French gynaecologists' prescription strategy of avoiding prescribing HT to high-risk women.[78]

Women's Health Initiative Randomised Clinical Trials: In the WHI estrogen-alone trial, conjugated equine estrogen (CEE) was not associated with an increased risk of breast cancer during the randomised intervention phase.[41] After a median of 7.2 years of treatment, women assigned to CEE demonstrated a nonsignificant 21% reduction in breast

cancer incidence compared with placebo (hazard ratio [HR] 0.79; 95% confidence interval [CI] 0.61–1.02), corresponding to approximately seven fewer invasive breast cancer cases per 10,000 women per year.43 Among women who were highly adherent to therapy (≥80% compliance), breast cancer risk was significantly reduced by 32% (HR 0.67; 95% CI 0.47–0.97).[43]

Extended follow-up has provided the most robust evidence regarding long-term outcomes. After approximately 18–20 years of cumulative follow-up, prior randomised use of CEE alone was associated with a statistically significant reduction in breast cancer incidence (238 cases [annualised rate 0.30%] vs 296 cases [0.37%]; HR 0.78; 95% CI 0.65–0.93) and a 45% reduction in breast cancer–specific mortality (HR 0.60; 95% CI 0.37–0.97).[57]

Using WHI data, the Endocrine Society Clinical Practice Guideline estimated that treatment with unopposed CEE for five years in women in their 50s would result in approximately 2.5 fewer cases of breast cancer per 1,000 women.[79] The decrease in breast cancer–specific mortality among patients who received use of CEE alone prevented 4 breast cancer–related deaths per 10,000 person-years, on a population level, which will have an impact on the number of breast cancer deaths avoided. The greatest risk reduction was seen among women without a history of benign breast biopsy and those without a family history of breast cancer, two important factors in widely used risk scoring systems such as the Gail risk score and Tyrer-Cuzick model. These data help in counselling women at low risk of breast cancer on the safe use of estrogen therapy (ET). This sustained reduction in both incidence and mortality represents one of the most clinically important findings of the WHI estrogen-alone trial.[22,57]

BREAST CANCER OUTCOMES: ESTROGEN–PROGESTIN THERAPY

In contrast, the WHI CEE plus MPA trial was associated with a small but statistically significant increase in breast cancer incidence. After a median of 5.6 years of randomised treatment, this translated to approximately eight additional breast cancer cases per 10,000 women per year (0.8 per 1,000 women-years), representing a rare absolute risk comparable to or lower than that reported for several commonly used long-term medications.[22] The overall hazard ratio (HR) for breast cancer increased approximately 2.5–3 years after randomisation and persisted throughout the intervention period(HR1.24).[22,41,43]

Subgroup analyses demonstrated heterogeneity of risk according to prior hormone therapy exposure. Among hormone therapy–naïve women (approximately 75% of the cohort), breast cancer incidence was not significantly affected by CEE plus MPA during the intervention phase (HR 1.02; 95% CI 0.77–1.36) or after extended follow-up of approximately 11 years (HR 1.16; 95% CI 0.98–1.37). In contrast, the increased breast cancer risk was largely confined to women with prior hormone therapy use (25% of the cohort), in whom CEE plus MPA was associated with a substantially higher risk after 5.6 years of treatment (HR 1.96; 95% CI 1.17–3.27). These findings suggest that prior exposure and timing of initiation may influence breast cancer risk with combined therapy.[22,51]

With 18 years of cumulative follow-up, prior randomised use of CEE plus MPA remained significantly associated with higher breast cancer incidence compared with placebo (584 vs 447 cases; HR 1.28; 95% CI 1.13–1.45), although no statistically significant difference in breast cancer-specific mortality was observed (HR 1.35; 95% CI 0.94–1.95).[57] Breast cancers that developed in the combined therapy group included luminal, HER2-enriched, and basal-like subtypes.

Importantly, the increased relative risk was not driven by an excess incidence in the treatment group alone, but rather by a lower incidence among placebo-treated women with prior hormone exposure, supporting the hypothesis that combined hormone therapy may accelerate the growth and detection of pre-existing occult tumours rather than initiate new malignancies.

Breast cancer risk is known to decline during the first four years following menopause, likely reflecting decreasing endogenous estrogen and progesterone levels. Consequently, observational analyses must carefully account for time since menopause when comparing hormone therapy users and non-users. In combined analyses of the WHI clinical trial and observational study, initiation of estrogen–progestogen therapy soon after menopause was associated with a higher breast cancer risk with longer duration of use (HR 2.75 with >5 years of use), whereas initiation after a gap of five years or more was not associated with a comparable increase in risk.[24,38] Risk also appears to increase with use beyond 3–5 years and may be greater with continuous combined regimens, although whether this represents a class effect of progestogens or varies by specific agent remains incompletely defined.[22,41,57,80]

The WHI trials were not designed to evaluate the typical clinical use of hormone therapy initiated near menopause,

and only approximately 10% of participants were aged 50–54 years at randomisation. As such, extrapolation of WHI findings to younger, symptomatic women initiating therapy near menopause should be made with caution. Nonetheless, WHI remains the highest level of evidence for breast cancer outcomes with specific hormone formulations.

Wood et al. conducted a randomised crossover trial in a postmenopausal nonhuman primate model to compare the effects of estradiol combined with either medroxyprogesterone acetate (MPA) or micronised progesterone on breast cancer risk biomarkers. Compared with placebo, estradiol plus MPA produced significantly greater epithelial proliferation in both lobular and ductal breast tissue, as measured by Ki-67 expression, whereas estradiol combined with micronised progesterone did not increase proliferation above placebo levels.[81] These findings provide biologic plausibility for clinical observations that breast cancer risk differs according to the type of progestogen used and support the hypothesis that synthetic progestins such as MPA exert a more proliferative effect on breast tissue than micronised progesterone.

In the DOPS, women with prior hysterectomy who received unopposed 17β-estradiol demonstrated a significant reduction in the composite endpoint of all-cause mortality or breast cancer compared with controls. In DOPS, a nonsignificant increase in breast cancer incidence was observed after discontinuation of therapy, particularly among women older than 50 years; however, these differences were not statistically significant and did not persist consistently over time. Although a borderline interaction with age suggested a potential reduction or absence of harm among women younger than 50 years, the results were inconsistent, precluding firm conclusions. Overall, while the data do not support an increased breast cancer risk with early initiation of unopposed estrogen in this cohort, the study was not powered to definitively assess breast cancer outcomes, and further randomised evidence is required to clarify the roles of timing, estrogen formulation, and route of administration.[44]

Observational Studies vs Randomised Controlled Trial (RCT): The Women's Health Initiative

Differences between observational studies and the WHI largely explain the discordant estimates of breast cancer risk associated with MHT. The WHI enrolled an older population, with most women initiating therapy many years after menopause (approximately 45% aged 60–69 years and 24% aged ≥70 years), whereas observational cohorts such as the Nurses' Health Study and E3N predominantly included women who initiated MHT near menopause. Baseline risk profiles also differed substantially, with a higher prevalence of obesity in WHI (mean BMI ≈30 kg/m 2) compared with leaner women in observational studies; obesity modifies endogenous estrogen exposure and may attenuate the relative impact of exogenous hormones, with several studies demonstrating higher relative risks among lean women using MHT. Additionally, WHI evaluated conjugated equine estrogens, which contain multiple estrogenic compounds with mixed agonist and antagonist activity, whereas most observational data reflect estradiol-based therapies. Importantly, observational associations between MHT and breast cancer are generally modest, with relative risks rarely exceeding 1.5 and almost uniformly below 2.0.

DEBATE ON THE INTERPRETATION OF OBSERVATIONAL DATA

Several investigators have questioned whether associations between MHT and breast cancer observed in large observational studies satisfy accepted epidemiologic criteria for causality. Applying the Austin Bradford Hill framework, Bluming and Tavris concluded that the available evidence does not consistently fulfil key causal criteria, particularly with respect to strength and consistency of association, dose–response gradients, temporality, and biological plausibility.

A comprehensive causality reanalysis by Shapiro and colleagues evaluated three influential data sources: the Collaborative Reanalysis (1997), the MWS, and the WHI.[82-86] Using formal epidemiologic principles including assessment of bias, confounding, exposure misclassification, internal and external consistency, statistical stability, and biological plausibility, they concluded that none of these studies, individually or collectively, established that MHT initiates breast cancer. In particular, the Collaborative Reanalysis, which pooled data from 51 predominantly case–control studies, was found to be limited by recall bias, confounding, weak associations, and heterogeneous exposure definitions, precluding causal inference.[19,50] Shapiro and colleagues have argued that large observational cohorts may reflect detection bias, confounding by health-care utilisation, time-related biases, and acceleration of growth or earlier detection of pre-existing occult tumours rather than true causal initiation of breast cancer. Shapiro and colleagues further emphasised that relative risks observed in observational studies are generally modest, rarely exceeding 1.5, and almost uniformly below 2.0, and that effect sizes of this magnitude are particularly susceptible to bias and residual confounding in nonrandomised settings.[82-86]

Supporting this interpretation, population-level data from the United States demonstrated a rapid decline in breast cancer incidence following reductions in MHT use after publication of the Women's Health Initiative (WHI) results, a temporal pattern incompatible with de novo tumour development and more consistent with withdrawal of hormonal stimulation from existing subclinical disease.[22,87] Despite its size, the MWS was also judged to inadequately meet causal criteria because of self-selection of hormone users, short follow-up, implausibly rapid cancer detection after therapy initiation, and vulnerability to screening and detection bias.[24] In contrast, other investigators contend that observational studies may underestimate the true magnitude of risk if hormone exposure is misclassified. Jones and Schoemaker argue that failure to update duration of MHT use over time attenuates risk estimates, and that improved exposure assessment reveals a stronger association between long-term combined estrogen–progestogen therapy and breast cancer risk.[7] From this perspective, the increased risks observed with prolonged combined MHT use are considered causal and clinically meaningful.[54]

Causation, Detection Bias, and Interpretation of Evidence

In randomised data from the WHI estrogen–progestogen (CEE + MPA) trial, a small absolute increase in breast cancer incidence was observed, with divergence of hazard ratios beginning approximately 2.5–3 years after randomisation during a median treatment duration of 5.6 years. However, based on established estimates of breast cancer cell doubling time, progression from a single malignant cell to clinically detectable disease typically requires a decade or more, rendering de novo carcinogenesis within the trial's treatment window biologically implausible. This temporal pattern supports an alternative explanation consistent with the null hypothesis, namely, that hormone exposure accelerated the growth or earlier detection of pre-existing occult tumours rather than initiating new cancers.

This interpretation is further supported by subgroup analyses demonstrating that the increased overall hazard ratio in the CEE + MPA arm was largely attributable to a lower-than-expected incidence of breast cancer among placebo-treated women with prior hormone therapy use, potentially reflecting estrogen-induced apoptosis of occult disease. Importantly, breast cancer incidence did not differ materially between hormone-naïve women randomised to placebo and those randomised to active therapy, arguing against initiation of new malignancies during treatment. Detection bias is also highly relevant, particularly in observational studies, as MHT users typically undergo more frequent mammographic surveillance, leading to earlier diagnosis and inflation of observed risk over time. This bias increases with duration of use and may spuriously generate duration–response gradients.

From an absolute-risk perspective, the excess breast cancer incidence observed in the WHI CEE + MPA trial, approximately eight additional cases per 10,000 women per year, falls within the range of risk associated with common lifestyle factors such as obesity, alcohol consumption, and physical inactivity, and is far lower than the relative risks associated with established carcinogens such as smoking and lung cancer. At the same time, randomised evidence from WHI demonstrates a reproducible increase in breast cancer incidence with combined estrogen–progestin therapy, lending support to a causal interpretation for this specific regimen. Umbrella reviews and pooled analyses reinforce that combined MHT shows the most consistent and duration-dependent increase in breast cancer risk, particularly with longer use, whereas conclusions regarding estradiol-only therapy remain context-dependent, varying by population characteristics, timing since menopause, and duration of exposure.[88] Importantly, caution is warranted in extrapolating findings across different hormone formulations, populations, and patterns of use, as emphasised by methodological re-analyses of both randomised and observational data.

In totality, these considerations underscore that interpretation of MHT-related breast cancer risk must integrate study design, biological plausibility, exposure assessment, and absolute risk estimates from randomised trials, with individualised breast cancer risk assessment forming the foundation of informed clinical decision-making.

Tibolone and Breast Cancer

Tibolone reduced the incidence of invasive breast cancer in cancer-free older postmenopausal women,but carries an increased stroke risk. This finding does not apply to breast cancer survivors. In women with a prior history of breast cancer, tibolone has been shown to increase recurrence risk and is therefore contraindicated in this population.[89]

CLINICAL CONSIDERATIONS: DO HORMONES CAUSE BREAST CANCER?

Current evidence indicates that menopausal hormones do not initiate breast cancer by inducing oncogenic mutations. Rather, endogenous and exogenous sex steroids influence breast cancer risk indirectly by modulating cell proliferation and differentiation in hormonally responsive breast tissue. Estrogen increases mitotic activity primarily

in ductal epithelial cells and may accelerate the growth of cells that have already acquired oncogenic mutations, whereas progesterone predominantly affects lobular–alveolar units, inducing an initial proliferative stimulus followed by cellular differentiation and maturation. Importantly, there is no experimental or clinical evidence that progestogens directly cause oncogenic mutations, although they may increase mitotic activity in susceptible breast epithelium. These biological effects underscore the importance of baseline breast cancer risk assessment when considering MHT.[13,50,90]

Benign Breast Disease and Menopausal Hormone Therapy

Women with benign breast conditions such as fibroadenosis or fibroadenoma do not have a higher likelihood of malignant transformation attributable to MHT than women without such lesions. Hormone therapy does not induce oncogenic changes in these tissues. However, the presence of benign lesions may complicate clinical or radiologic detection of breast cancer; therefore, women with fibroadenomas should undergo age-appropriate breast surveillance with mammography and/or ultrasonography as indicated. If the aetiology of a breast lump is uncertain, core needle biopsy should be performed before initiating MHT. Continuous combined MHT may be safely prescribed in women with fibroadenomas following appropriate evaluation.[6,9]

Family History of Breast Cancer and Menopausal Hormone Therapy

Women with a family history of breast cancer can be broadly categorised into two groups. A small proportion (approximately 5%) have relatives with early-onset breast cancer, often associated with pathogenic variants in the BRCA1 or BRCA2 genes. These women have a substantially elevated lifetime risk of breast cancer independent of hormone exposure. Historically, MHT was discouraged in this group; however, emerging prospective data suggest that MHT, particularly estrogen-only therapy, does not meaningfully increase breast cancer risk in BRCA mutation carriers. In a prospective cohort of BRCA1 mutation carriers, combined estrogen–progestin therapy was associated with breast cancer risks similar to nonusers, while estrogen-only therapy after hysterectomy was associated with a nonsignificant trend toward reduced risk.[91]

The second, more common group comprises women with a single first-degree relativen diagnosed with breast cancer at a later age (typically after 50–60 years). These women have only a modest increase in lifetime breast cancer risk compared with the general population (approximately 12%), which doubles to about 24% when two such relatives are affected. This pattern is usually non-hereditary and sporadic. In the WHI, family history of breast cancer did not modify the association between MHT and breast cancer incidence and was not associated with increased breast cancer risk among hormone users. Notably, family history was associated with lower overall mortality in women using MHT. Similar conclusions were drawn from the Collaborative Reanalysis, suggesting that strong genetic determinants of breast cancer risk generally outweigh the small incremental effects of hormonal exposure.[50,92]

BREAST CANCER SURVIVORS

In India, many women with breast cancer present with locally advanced or advanced-stage disease, necessitating a multimodal treatment approach. Management of most patients requires a combination of treatments, including surgery, systemic therapies such as chemotherapy, targeted therapy, immunotherapy, hormonal treatment, and radiotherapy, tailored to tumour biology, disease stage, patient factors, and resource availability within the Indian healthcare setting.[93,94]

Follow-up: Is individualised based on age, comorbidities, tumour biology, prior therapies, genetic risk, and patient preferences. Specific to breast cancer, regular physical examinations and annual mammographic surveillance are recommended for women with remaining breast tissue. Those with a hereditary predisposition to breast cancer or a known pathogenic breast cancer, associated genetic mutation, should undergo annual breast MRI in conjunction with mammography to enhance early detection. Routine use of PET scans (positron emission tomography), including fluorodeoxyglucose (FDG) PET–CT, is not recommended for surveillance in asymptomatic breast cancer survivors after curative-intent treatment. The use of PET scanning should be restricted to clinically indicated situations, such as when there is a suspicion of recurrence or metastatic disease based on new symptoms, physical examination findings, abnormal conventional imaging, or other clinical concerns.[93,95,96]

ENDOCRINE THERAPY IN BREAST CANCER

Adjuvant endocrine therapy is a cornerstone of treatment for hormone receptor–positive breast cancer, significantly

reducing the risk of recurrence and breast cancer–related mortality. Treatment selection is guided primarily by menopausal status, disease risk, tumour biology, patient comorbidities, and tolerability.

Endocrine Therapy in Premenopausal Women

Tamoxifen: Refer to Chapter 40

Role of Ovarian Function Suppression (OFS) and Ablation: Gonadotropin-Releasing Hormone (GnRH) Suppression: In premenopausal women at higher risk of recurrence, particularly those with nodal involvement, larger tumours, high-grade disease, or those receiving adjuvant chemotherapy, ovarian function suppression in addition to endocrine therapy provides significant long-term benefit. Ovarian suppression reduces the 15-year risk of recurrence by 12.1%, breast cancer mortality by 8.0%, and all-cause mortality by 7.2%.[95] Gonadotropin-releasing hormone (GnRH) agonists, such as goserelin and leuprolide, are the most commonly used methods of ovarian suppression and are typically administered for a duration of five years. GnRH suppression is reversible and generally preferred over permanent ovarian ablation in most patients.

Surgical Ovarian Ablation (BSO): Refer to Chapter 28. In the absence of a genetic predisposition, BSO should not be routinely performed in breast cancer survivors.

Endocrine Therapy in Postmenopausal Women

Aromatase Inhibitors: In postmenopausal women with hormone receptor–positive disease, aromatase inhibitors (AIs), including anastrozole, letrozole, and exemestane, are preferred over tamoxifen. Comparative trials have not shown clinically meaningful differences in efficacy among individual Ais, allowing treatment selection based on toxicity profile, patient preference, and comorbidities.[97,98]

Patient-level meta-analyses demonstrate lower recurrence rates during the first four years of treatment and reduced 10-year breast cancer mortality compared with tamoxifen (12.1% vs 14.2%; RR 0.85, 95% CI 0.75–0.96).[99] Compared with tamoxifen, AIs are associated with a higher risk of adverse skeletal and metabolic outcomes, including osteoporosis, fragility fractures, cardiovascular disease, diabetes mellitus, and hypercholesterolaemia.[99,100] In contrast, AIs are associated with a lower risk of venous thromboembolism and endometrial cancer, reflecting the absence of estrogen agonist effects on hepatic coagulation pathways and the endometrium.[101] While AIs are generally well tolerated, musculoskeletal symptoms are common and occur in nearly half of treated patients, typically developing within the first few months of therapy. These symptoms most often manifest as morning stiffness and joint pain involving the hands, knees, hips, shoulders, and lower back. The underlying mechanism is thought to be related primarily to estrogen deprivation, although inflammatory pathways may also contribute. Symptoms may persist throughout treatment and are a frequent cause of reduced adherence or treatment discontinuation.[101]

Tamoxifen in Postmenopausal Women: Tamoxifen remains an appropriate alternative for postmenopausal women at low risk of recurrence or for those who are unable to tolerate aromatase inhibitors or have contraindications to their use. In postmenopausal women, tamoxifen is associated with a small but measurable increase in endometrial cancer risk due to its estrogen-agonist effect on the endometrium.[101,102]

MANAGEMENT OF MENOPAUSE IN BREAST CANCER SURVIVORS

Diagnosis of menopause: There is currently no universally agreed or published consensus for the diagnosis of menopause in younger women treated for breast cancer, particularly in those receiving endocrine therapies that may alter gonadotropin and estrogen levels. In the absence of standardised criteria, the following pragmatic approach is recommended.

In premenopausal women receiving adjuvant tamoxifen alone, a diagnosis of menopause may be made if the patient has experienced amenorrhoea for at least 12 months, in conjunction with biochemically elevated follicle-stimulating hormone (FSH) levels (FSH >30 IU/L) on two separate blood samples taken 4–6 weeks apart.[103]

Pretreatment serum anti-Mullerian hormone (AMH), FSH, antral follicle count, and age may predict late ovarian activity.[104] However, interpretation of serum FSH levels can be unreliable in the presence of tamoxifen, as tamoxifen may interfere with hypothalamic–pituitary feedback mechanisms. Therefore, tamoxifen should be discontinued for 6–8 weeks prior to hormonal assessment to allow accurate evaluation of menopausal status.[103,105]

This approach is particularly relevant for women being considered for extended adjuvant endocrine therapy beyond five years, in whom a switch to an aromatase inhibitor may be recommended if postmenopausal status is

confirmed.[103] In younger patients treated with a combination of a gonadotropin-releasing hormone agonist (GnRHa) and an AI, irrespective of prior chemotherapy exposure, assessment of menopausal status should be deferred until the suppressive effects of GnRHa on the hypothalamic–pituitary–ovarian axis have resolved. A washout period of at least 12 weeks following cessation of GnRHa therapy is recommended before performing serial FSH measurements to avoid misclassification of ovarian function.[103] Given the clinical implications of menopausal status on endocrine therapy selection, diagnosis should be made cautiously, integrating clinical history, menstrual pattern, and biochemical assessment, with repeated testing where uncertainty exists.

Counselling: All women should receive comprehensive counselling regarding menopause, including its short- and long-term sequelae, impact on quality of life, and available preventive and management strategies. Lifestyle counselling should emphasise a low-fat, calcium-rich, balanced diet, maintenance of an ideal body mass index, and adequate sunlight exposure (approximately 20 minutes daily). Measures to reduce vasomotor symptoms include avoiding overheating, wearing breathable natural fabrics, and minimising known triggers such as caffeine, tea, alcohol, tobacco, and spicy foods. Regular physical activity, paced breathing techniques, and stress-reduction strategies have demonstrated benefit in randomised controlled trials. Sexual counselling, ideally involving both partners, should also be considered to address intimacy concerns and relationship dynamics.

Vasomotor Symptoms: Women with breast cancer experience a higher burden of hot flushes due to abrupt estrogen deprivation from chemotherapy-induced ovarian failure or bilateral oophorectomy, and from tamoxifen therapy, which causes hot flushes in up to 80% of users, with severe symptoms in approximately 30%; tamoxifen used for chemoprevention has similar effects, and genetic variations in estrogen receptor pathways may further influence susceptibility and severity. AIs may also cause hot flushes, but they tend to be less frequent and less severe.

Cognitive behavioural therapy (CBT): CBT appears to be a modestly effective intervention for menopause-associated insomnia but less so for hot flushes.[106]

Role of complementary therapies is discussed in Chapter 41.

MHT and tibolone are contraindicated.

Non-hormonal pharmacologic therapies represent the first-line treatment for vasomotor symptoms in breast cancer survivors. Selective norepinephrine reuptake inhibitors (SNRIs), including venlafaxine (37.5–75 mg/day) and desvenlafaxine, have demonstrated efficacy. Gabapentin, a gamma-aminobutyric acid (GABA) analogue, at doses of approximately 900 mg/day, is effective in reducing the frequency and severity of hot flushes. Duloxetine and paroxetine have also shown benefit. Neurokinin B receptor antagonists, Fezolinetant and elinzanetant, are a novel class of drugs for hot flushes. Refer to Chapter 9. Findings from a recent systematic review and meta-analysis suggest that MHT may serve as an off-label treatment option for breast cancer (BC) survivors with menopausal symptoms.[107,108] This could be considered for selected HR-negative survivors experiencing severe, refractory symptoms, especially after nonhormonal therapies have failed, and only following explicit shared decision-making.[107,108] Further randomised trials are needed before reconsidering the current advice against offering MHT to BC survivors.

Genitourinary Syndrome: For vaginal symptoms, vaginal moisturisers and vaginal lubricants are effective in relieving mild symptoms. In the absence of randomised controlled trials, available data suggest that low-dose vaginal estrogen may be considered for the treatment of bothersome genitourinary syndrome of menopause (GSM) symptoms in breast cancer survivors, including those with estrogen receptor–positive disease, when non-hormonal measures fail. Use should be individualised and undertaken through shared decision-making involving the patient, oncologist, and gynaecologist. For more severe symptoms, vaginal estrogens, preferably low-potency estriol, can be used for a short duration, although safety and efficacy studies have not been performed.[109]

In women without a history of breast cancer, local estrogen therapy (LET) has been shown to be effective in reducing recurrent urinary tract infections (UTIs). A recent randomised study demonstrated a 51.9% reduction in recurrent UTIs among hypoestrogenic women treated with vaginal estrogen, supporting its efficacy for urogenital health.[110]

Bone loss: In premenopausal women receiving AIs, estrogen levels decline abruptly, resulting in a 6–8% reduction in bone mineral density (BMD) during the first 1–2 years of therapy. In contrast, postmenopausal women treated with AIs experience a more gradual annual BMD loss of approximately 2–3% per year.[111-113] Both groups have a significantly increased risk of osteoporotic fractures. All women receiving AIs should adopt proactive bone-protective strategies, including adequate calcium and vitamin D supplementation, lifestyle modifications, and regular

monitoring with dual-energy X-ray absorptiometry (DXA). Baseline assessment, prevention, and treatment of osteoporosis are integral components of survivorship care.[114] Early initiation of bone-modifying agents is recommended in women at intermediate or high fracture risk. Intravenous zoledronic acid 4 mg every 3–6 months for 2–5 years or denosumab is an effective option.[115-117] Sequential therapy with denosumab (60 mg subcutaneously every 6 months), followed by a bisphosphonate, is an accepted strategy for managing AI-associated bone loss. [117]

Endometrial Surveillance And Endometrial Cancer Risk

Women initiating tamoxifen should undergo a baseline gynaecological evaluation, including transvaginal ultrasound (TVS). However, current evidence does not support routine endometrial surveillance with TVS or biopsy in asymptomatic women receiving tamoxifen.[118,119] Endometrial cancer associated with tamoxifen typically presents early and is highly curable. Therefore, any woman presenting with abnormal uterine bleeding requires prompt evaluation, irrespective of ongoing estrogen therapy. Diagnostic assessment should include hysteroscopy-guided endometrial biopsy, or, where unavailable, saline infusion sonography with directed biopsy.[120-123] In asymptomatic postmenopausal women on tamoxifen, endometrial thickness alone is an unreliable predictor of malignancy and should always be interpreted in the context of clinical risk factors, such as obesity and duration of tamoxifen use, and detailed sonographic features, including irregular or cystic endometrial morphology and increased Doppler vascularity. Huang et al. propose a threshold of 9–10 mm for considering endometrial biopsy in asymptomatic women.[120,123]

SYNOPSIS

- The relationship between MHT and breast cancer risk is complex and multifactorial, influenced by baseline risk, type of hormone therapy, dose, duration, regimen, route of administration, and prior hormone exposure
- The absolute increase in breast cancer risk associated with MHT is small, estimated at fewer than one additional case per 1,000 women per year among women aged 50–59 years, comparable to or lower than common modifiable lifestyle factors such as obesity, alcohol intake, and physical inactivity
- With combined estrogen-progestin therapy (EPT), breast cancer risk increases with duration of use but declines after cessation, typically returning to baseline within 3–5 years, especially after short-term use; prolonged use beyond ive years or with certain synthetic progestins may be associated with residual risk
- Initiating estrogen-only therapy (ET) many years after menopause and for less than five years carries a low breast cancer risk
- Both ET and EPT increase mammographic density, potentially affecting screening interpretation; MHT does not appear to significantly alter the clinical behaviour of benign breast disease in postmenopausal women
- Estrogen-only therapy (ET) in women with prior hysterectomy is associated with a neutral or reduced risk of breast cancer, including lower incidence and sustained long-term benefit in randomised trial data
- Breast cancers diagnosed in women using MHT are more likely to be estrogen receptor–positive and of lobular histology, suggesting hormone-sensitive tumour biology
- Observational studies suggest a modest increase in breast cancer risk, particularly with combined therapy; however, these data are subject to confounding and selection bias, while randomised controlled trials provide more reliable estimates of absolute risk
- When counselling women, emphasis should be placed on absolute risk estimates from randomised trials, rather than relative risks from observational studies, to support informed, shared decision-making
- Use of systemic MHT in breast cancer survivors is contraindicated; studies are planned to understand the recurrence rate in the use of MHT in estrogen receptor-negative cancer and require highly individualised decision-making
- Local vaginal hormone therapy is preferred for severe GSM and is reserved as a second-line treatment

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Section 8

GENITAL CANCERS

CANCER CERVIX

30

Keywords: Prevalence, risk factors, prevention, screening, treatment, effect of hormone therapy

INTRODUCTION

Cervical cancer is an important public health problem. It is the fourth most common cancer among women globally, with over 660,000 new cases and approximately 350,000 deaths reported in 2022. More than 85% of new cases and 90% of deaths from cervical cancer occurred in women aged 40 years and older.[1]

CERVICAL CANCER BURDEN IN INDIA

Cervical cancer is the second most common cancer in women in India, with an age-standardised incidence rate of 18 and an age-standardised mortality rate of 11.4 per 100,000 woman-years. India contributes one fifth of the new cases and about one-fourth of the deaths to the global burden of cervical cancer.[2] According to GLOBOCAN 2022, 127,526 new cases of cervical cancer were reported, with 79,906 deaths.1 According to Population-Based Cancer Registries' data, there is a substantial variation in the incidence of cervical cancer across the different regions of India. The highest burden of cervical cancer was found in the northeast region (290.1 disability-adjusted life years [DALYs] per 100,000 women), followed by the central and northern regions (276.9 and 276.7 DALYs per 100,000 women, respectively). The eastern region had the lowest age-standardised DALYs per 100,000 women (156.1 DALYs).[3]

NATURAL HISTORY OF CERVICAL CANCER

The past two decades have witnessed substantial progress in our understanding of the natural history of cervical cancer. Human papillomavirus (HPV), one of the most frequent sexually transmitted infections (STDs), has been widely identified as a necessary (but not sufficient) cause in essentially all invasive cervical cancer cases. More than 99% of cervical squamous cell carcinomas are due to infection and subsequent transformation of squamous cells by oncogenic HPV genotypes, which are mostly asymptomatic.[4]

HPV is a double-stranded, non-enveloped DNA virus (55 nm in diameter with 8000 base pairs). Refer to Figure 1. Currently, more than 200 genotypes have been identified, of which 14 are considered high-risk. Of these, HPV 16 and 18 types are responsible for more than 70% of cervical cancers. Other high-risk types are 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.[5]

HPV is the most common sexually transmitted infection (STI) worldwide, affecting an estimated 50 to 80% of sexually active women at least once in their lifetime. Women are mostly infected with HPV in their teens, 20s, or early 30s. About 70-80% of women in the general population are estimated to harbour cervical HPV infection at a given time.[7]

HPV infections are transient due to an effective immune response that clears the infection or reduces viral load to undetectable levels, on average, within 8–24 months. However, in around 20% of women, HPV infection may persist. Only a small fraction of those infections that persist or progress to a preneoplastic lesion result in cancer. Persistence of HPV infection is needed to start the oncogenic process. Clearance of infection is common in young adults. Viral load and viral type are the main cofactors for progression from infection to cervical intraepithelial lesions (CIN) and cancer. Smoking, hormonal exposure, and human immunodeficiency virus (HIV) are additional exposures that increase the risk of progression to cancer.[8]

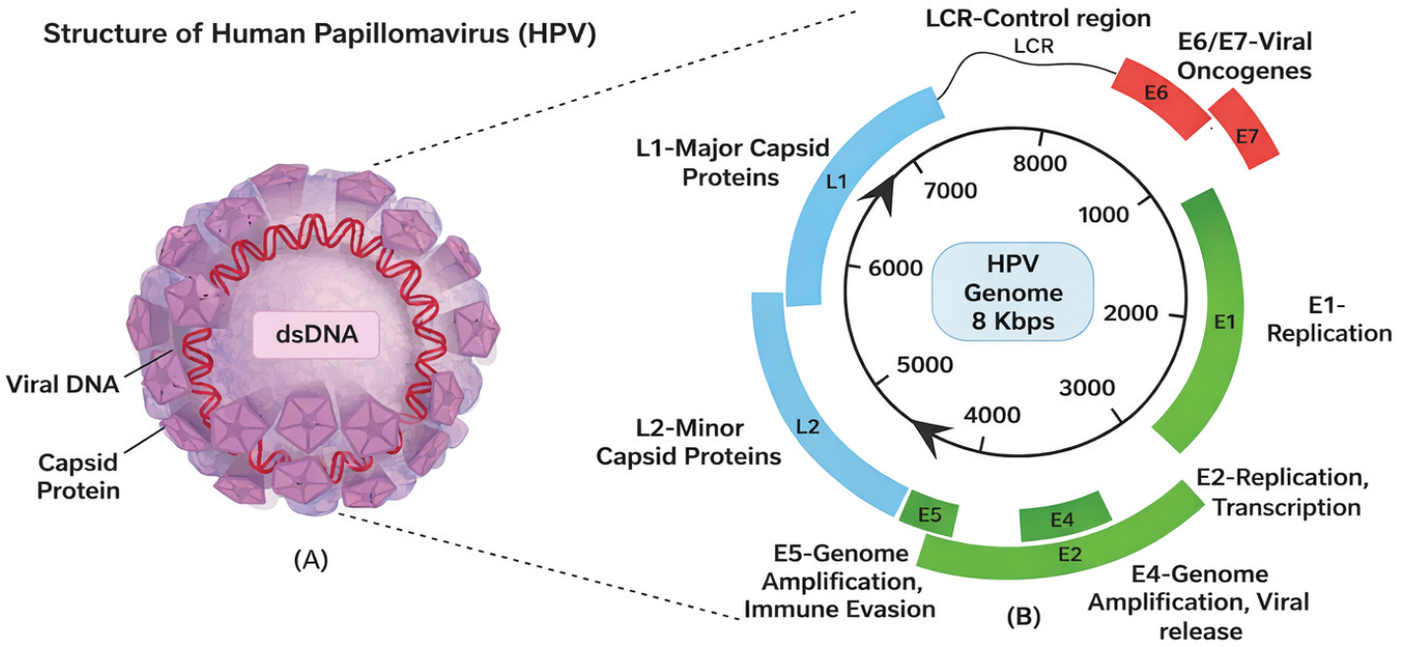


Figure 1: Structure of Human Papilloma Virus[6] (Reproduced with the permission of the author)

Preventing HPV transmission is very difficult. Barrier contraceptive methods are only partially effective because the virus can exist throughout most of the anogenital area (including areas not covered by male condoms) and can remain infectious for years. The level of sexual activity of a person will affect the risk of acquiring HPV infection. Early age of first intercourse, multiple sexual partners, unprotected sex and sex with uncircumcised men have been found to increase the risk of contracting HPV infection.[9] Cervical cancer is both a preventable and a curable disease, preventable by cervical screening, since it takes many years to develop from detectable precursor lesions and is treatable, especially if identified at an early stage.

CERVICAL CANCER SCREENING

The evolution of cervical cancer screening is one of the best examples of success in medical history, with the discovery of several screening tests that are aimed at the global elimination of cervical cancer as declared by the World Health Organisation (WHO) in 2020.[10] The National Cancer Control Programme (NCCP) was irst launched in India in 1975, with a priority on equipping the premier cancer hospitals/institutions. In 1984, emphasis was placed on primary prevention and early cancer detection. Cancer control is now a part of the National Programme for Prevention and Control of Cardiovascular Disease, Diabetes, Cancer and Stroke (NPCDCS), launched in 2010 to prevent and control major NCDs.[11]

In 2016, as part of the Ayushman Bharat Comprehensive Primary Health Care Programme and the NPCDCS, India proposed launching a national cancer screening programme.[12] Population-based screening for cervical, breast, and oral cancers is being implemented under the National Health Mission as part of comprehensive care, complementing the NPCDCS.

SCREENING MODALITIES FOR CERVICAL CANCER

Visual Inspection of Cervix with Acetic Acid (VIA)

The VIA technique was pioneered in India in the 1980s. It is a popular screening test to detect cervical pre-cancer and early cancer in asymptomatic women in several low- and middle-income countries. In India, VIA is the recommended population screening test by the Health and Family Welfare Department, Government of India. The recommendation is to screen women aged 30 to 65 with VIA every 5 years. It involves a naked-eye examination of the uterine cervix one minute after applying freshly prepared 3% to 5% acetic acid under good light.

Normal squamous epithelium appears pink and the columnar epithelium red, due to the reflection of light from the underlying stroma, which is rich in blood vessels. Acetic acid causes reversible coagulation or precipitation of cellular proteins. It also causes swelling of the epithelial tissue, columnar and any abnormal squamous epithelial areas and dehydration of cells. If the epithelium contains a lot of cellular proteins, acetic acid coagulates these proteins. This gives a distinct aceto-white appearance, visible to the naked eye. The degree of aceto-whiteness depends on the amount of nuclear content and the cells' DNA activity.[13]

Advantages of Visual Inspection with Acetic Acid

- VIA does not require laboratory infrastructure.
- VIA can be performed by various categories of health care personnel (general practitioners, nurses, midwives) after a brief period of training.
- The consumables are cheap and readily available.
- VIA is a truly point-of-care test; the test-negative women can be reassured and advised to follow up.
- Useful for community screening and for the single-visit screen-and-treat approach.
- The sensitivity of VIA ranges from 60% to 86%, which is higher than or similar to that of cytology, especially in resource-limited settings.
- Screening of women with VIA followed by appropriate management of screen-positive women can significantly reduce mortality from cervical cancer.[14]

Limitations

- The specificity of VIA is 64% to 94%. This may lead to unnecessary referrals, overtreatment and adverse psychological consequences to women.
- The interpretation of the test is subjective.
- VIA detects lesions limited to the ectocervix; it has limited accuracy in postmenopausal women and women older than 49 years, as the transformation zone (TZ) recedes into the cervical canal.
- Ensuring quality is difficult because cervical images are not documented in conventional VIA.

Cytological Screening

The Papanicolaou smear(PAP) test, a routine screening test for cancer of the uterine cervix, was described in 1928 by the Greek anatomist Georgios Papanikolaou. Its efficacy was proved by 1941. Since then, it has been used worldwide, especially in high-income countries, as a clinical tool for the early detection of cervical precancer and cancer. Exfoliated cells from the ectocervix and transformation zone are collected, stained, and examined on a glass slide under a microscope for any abnormalities that favour cervical precancer or cancer. A cervical cytology sample can be collected by two methods.

Conventional method: It involves using an Ayre's spatula and an endocervical brush. The cells are smeared onto a glass slide and fixed in 95% alcohol.

Liquid-based cytology(LBC): Invented in the 1990s, it involves transferring the cells collected by a cervical broom or brush into a liquid. The liquid is spun onto a glass slide as a uniform monolayer using a centrifuge, stained and studied under a microscope.

Reporting is done using the Bethesda System 2014 (TBS).[15] Several studies have compared both conventional and liquid-based cytology techniques. Unsatisfactory smears are more commonly reported in conventional cytology than in liquid-based cytology. There is no difference in the reporting of cytological abnormalities between the two methods.[16] The sensitivity and specificity of a single, quality-assured PAP smear for detecting CIN 2+ lesions are around 60% and 95%, respectively.[17] High-income countries have seen a reduction in cervical cancer incidence and mortality due to organised cytology screening programmes integrated into their medical and public health services. However, it is not possible in low- and middle-income countries due to a lack of resources, infrastructure, trained manpower and quality control.[18]

Human Papillomavirus Screening

With the recognition of persistent HPV infection with high-risk types as necessary for carcinogenesis, HPV-detection assays were introduced into practice. Initially, HPV testing was introduced as a triage for cytologic abnormalities (reflex testing), later as an adjunct to cytology (co-testing), and, more recently, as a standalone test for primary screening. HPV testing involves detecting HPV DNA or mRNA of two oncoproteins (E6 and E7) in cervical cell samples collected by health care workers or by self-sampling. Refer to Table 1 for WHO/FDA validated HPV tests.

Table 1: WHO /Food and Drug Administration (FDA)Validated Human Papillomavirus Tests[19]

Test Principle/Platform	Name of the test
HPV DNA Signal Amplification tests	Hybrid Capture 2Cervista HPV HRCare HPV
PCR Based Tests	Cobas HPV test, Abbott Real-time High-risk HPV test, Papillo Check HPV Assay,PreTec HPV proofer, Anyplex II HPV HR Detetction,Xpert HPV test
mRNA Based, E6/ E7 tests	Aptima HPV

HPV assays are further subdivided depending on their ability to detect different subsets of high-risk genotypes.[20]

Several indigenously made HPV DNA tests are being validated in India.

- No Genotyping: Detects all high-risk genotypes combined
- Limited Genotyping: Separate detection of HPV 16 and HPV 18 (sometimes HPV 45), and all other types are pooled
- Extended Genotyping: Detects individual types or groups of types beyond HPV 16, 18 and 45

Advantages[21]

- HPV testing is the most accurate and reproducible screening test
- Primary HPV testing is the most recommended screening test according to the WHO screening guidelines and several clinical studies
- Its sensitivity to detect CIN2+ lesions exceeds 90%, and CIN3+ exceeds 95%
- It has a high negative predictive value, which gives reassurance to the women who undergo screening
- Point-of-care HPV testing followed by ablative treatment is being used as a single-visit approach
- Screening interval can be delayed to 7 to 10 years in the general population with limited resources
- Self-collection of vaginal samples for HPV testing yields similar results compared to provider-collected samples
- HPV testing is more suitable for screening in HPV vaccinated women

Disadvantages

- HPV testing has low specificity compared to cytology
- The majority of HPV positive infections can be in the transient phase with no demonstrable colposcopy findings
- The test cost is more compared to VIA and cytology

Low-cost Indigenous Human Papillomavirus Tests in India

Several indigenously made HPV DNA tests are being validated in India.

- Truenat by Molbio: a chip-based real-time micro-PCR test. It is a point-of-care test. The machine is portable and battery-operated. Depending on the machine capacity, 1 to 16 samples can be processed at a time. The test duration is 60 minutes, and it detects 16 and 18, as well as 31, 33, 35, 45, 52, and 58 HPV types. It is being validated in field trials by ICMR-NICPR.
- Pathodetect: It is a cartridge-based, automated, point-of-care HPV test. At a time, 1 to 32 samples can be processed. This test detects HPV 16, 18 and 12 other high-risk types. The test duration is 120 minutes. It is being validated by CDSCO.
- TATA MD Check: It is a qualitative real-time PCR test. It is useful for batch testing of 20, 50 or 100 samples at a time. This test detects 15 high-risk HPV types. It is being evaluated at Tata Memorial Hospital, Mumbai
- Q-POC: It is a Real-time PCR, point-of-care HPV test. It detects 14 high-risk HPV types. The test lasts 60 to 90 minutes.

EFFECTIVENESS OF SCREENING MODALITIES

The performance of VIA as an alternative to conventional cytology has been evaluated in cross-sectional and randomised control trials in low- and middle-income countries (LMICs). VIA is a cost-effective technology that can be administered by a trained paramedical workforce in mass screening programmes with minimal logistical requirements, and can be undertaken in any modest health care setting. Since it provides instant results, adopting "See and Treat" approaches by initiating treatment in the same visit in socio-cultural and geographic settings with very low compliance for repeated visits becomes feasible. Pooled estimates of the sensitivity of VIA to detect high-grade lesions and invasive cervical cancer vary from 49-96%, and the specificity from 49-98%.[22-26] VIAM (Visual inspection with acetic acid plus magnification) showed results similar to VIA.

Visual inspection with Lugol's iodine (VILI) has been shown to be more sensitive than VIA, with pooled sensitivity and specificity estimates reported in large meta-analyses and IARC evaluations[27,28] The only cluster randomised trial of a single round of screening with VIA followed by treatment compared with no screening in Southern India demonstrated a reduction in cervical cancer incidence and mortality by 25% and 35%, respectively.[29] While another cluster randomised trial of cervical cancer screening in Mumbai, India, demonstrated 24% reduction in cervical cancer mortality after three rounds of VIA screening.[30]

Organised cytology-based screening programmes are known to reduce the cervical cancer incidence and mortality in programme settings with good quality control and adequate coverage done at optimal frequency. However, no significant reduction in incidence and mortality from cervical cancer has been observed in developing countries where cytology screening programmes exist.[31] Thus, it is important to recognise the limitations of cytology-based programmes in developing country settings.

In 2020, the WHO launched the global targets for eliminating cervical cancer. According to this, 70% of eligible women need to be screened twice in their lifetime at the ages of 35 and 45 by a high-precision screening test, which is HPV DNA screening. To support this strategy, the WHO published updated cervical screening guidelines in 2021, recommending that countries shift to primary HPV screening from VIA or cytology if resources are available.[21]

Several studies examined the effectiveness of primary HPV screening compared with conventional methods such as VIA and Cytology. Assuming 70% coverage, primary HPV screening approaches are the most effective and cost-effective, reducing cervical cancer age-standardised mortality rates by 63–67% when offered every 5 years. Screening with VIA or cytology every 3 years was less effective and less cost-effective than HPV screening every 5 years. Furthermore, VIA generated more than double the number of pre-cancer treatments compared to HPV. In conclusion, primary HPV screening is the most effective, cost-effective and efficient cervical screening option in LMICs.[32]

RECOMMENDATIONS ON SCREENING INTERVAL

Age to Start Screening

- The Ministry of Health and Family Welfare (MoHFW), Government of India, promotes population-based cervical cancer screening for women aged 30-65 years under the National Health Mission (NHM) through Ayushman Arogya Mandirs (AAMs), using VIA every 5 years.

- Screening should start from the age of 25 years for women living with HIV, other immune-compromised conditions and in a good resource setting for the general population. (Level 1)

Screening Interval

- For cytology-based screening, the interval is 3 years. (Level 1)
- For Primary HPV screening or Co-testing (Cytology and HPV), the recommended screening interval is 5 to 10 years for the general population and 3 to 5 years for immunocompromised women. (Level 1)
- Vaginal vault cytology and HPV testing are indicated for women following hysterectomy performed for high-grade cervical intraepithelial neoplasia (CIN 2/3) or cervical cancer, but are not required after hysterectomy for benign conditions.

Age to Stop Screening

At 65 years, with 3 consecutive negative cytology results, or 2 consecutive negative HPV tests within 10 years. The most recent test should have been performed within 5 years. (Level 1)

MANAGEMENT OF RESULTS WITH CYTOLOGY AND HUMAN PAPILLOMAVIRUS SCREENING TESTS

In 2019, the American Society of Colposcopy and Cervical Pathology (ASCCP) released risk-based guidelines for colposcopy and treatment of screen-positive women.[33] These guidelines take into account the age, past history, grade of cytological abnormality and HPV genotyping.

A recommendation to undergo immediate colposcopy or treatment like excision of the transformation zone of the cervix with a loop electrosurgical excision procedure [LEEP] versus surveillance is based on a statistically calculated risk of the patient harbouring CIN3 or worse at the time of the screening test. If that immediate risk is 4% or above, colposcopy and or treatment is recommended.[33] The 4% immediate CIN3+ risk threshold used in the ASCCP 2019 guidelines was derived from large population-based screening datasets and corresponds to the historical risk level at which colposcopy has traditionally been recommended.

The risk of CIN3+ for decision-making is given below based on the co-testing result:

High-risk HPV DNA positive with low-grade squamous intraepithelial lesion (LSIL). Cytology: 4-24% risk of CIN3+: Needs Colposcopy High-risk HPV DNA positive with high-grade squamous intraepithelial lesion (HSIL). Cytology: 25-59% risk of CIN3+: Colposcopy or excision

HPV 16 positive with HSIL Cytology: 60-100% risk of CIN3+: Excision

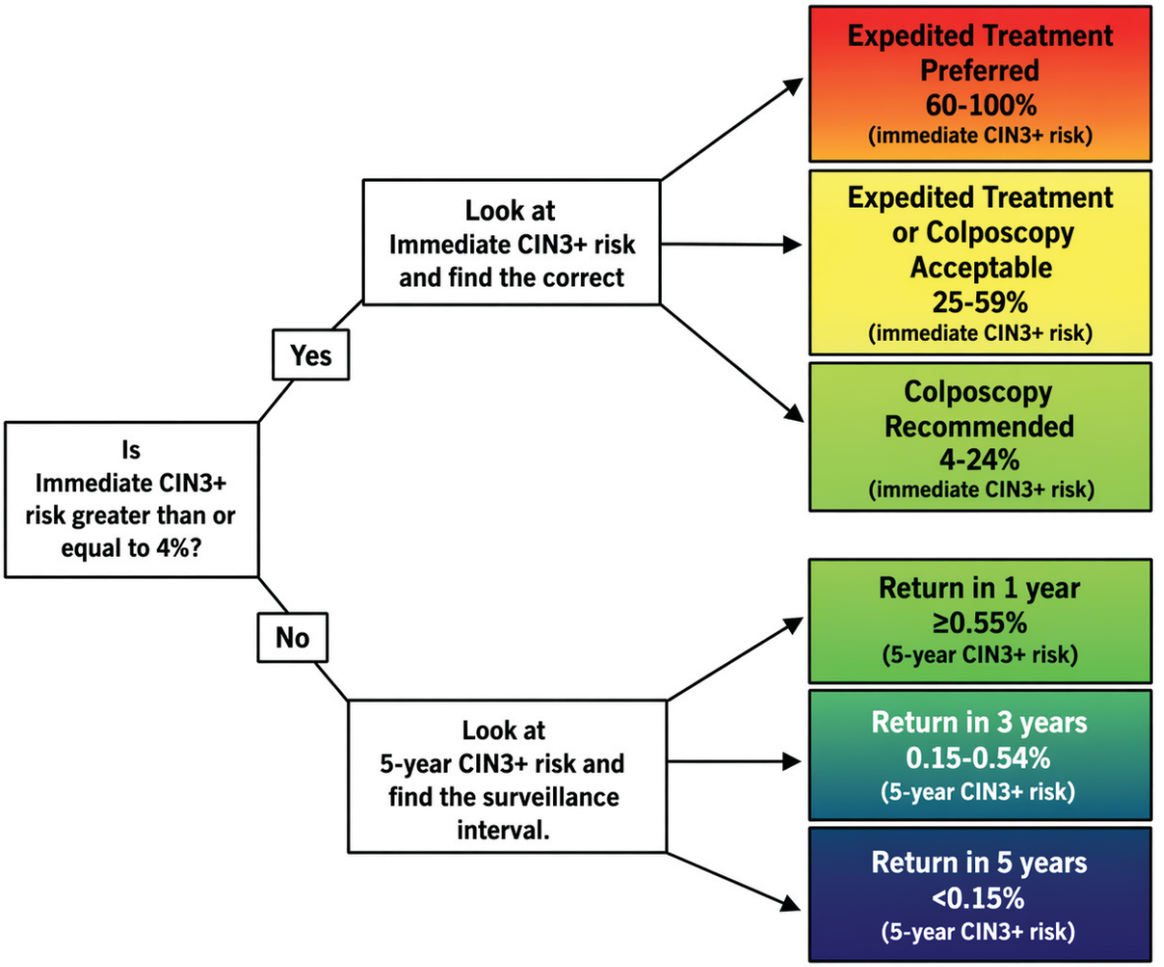
If the immediate risk of the patient harbouring CIN3+ or cancer is less than 4%, surveillance is recommended. Surveillance can be performed at 1, 3, or 5-year intervals, based on the statistically calculated risk of developing CIN3+ within 5 years.[33]

The numbers 0.55, 0.15–0.54, and <0.15 represent the estimated 5-year risk (probability) of developing CIN3+ (CIN3, adenocarcinoma in situ, or cervical cancer).

High-risk HPV DNA positive with ASC-US/LSIL cytology: Risk of CIN3+ is ≥0.55: Surveillance in 1 year with HPV based testing.

High-risk HPV DNA negative with ASC-US cytology: Risk of CIN3+ is 0.15-0.54: Surveillance in 3 years with HPV based testing.

High-risk HPV DNA negative or co-testing is negative: Risk of CIN3+ <0.15: Surveillance in 5 years with HPV based testing.



Flow chart 1: The diagram illustrates a decision-making flowchart for cervical intraepithelial neoplasia (CIN) treatment, categorising risk levels (immediate CIN3+, 25-59%, 4-24%) and recommending expedited treatment, colposcopy, or surveillance intervals based on the risk percentages.

Refer to Flowchart 1 for risk assessment for evaluation from the ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors[33]

In the year 2021, the WHO released new guidelines for the management of screen-positive women.[21] Subsequently, in 2023, the Federation of Obstetric and Gynaecological Societies of India (FOGSI) and the Indian College of Obstetricians and Gynaecologists (ICOG) released guidelines for the Indian context.[19]

Management of Women Aged ≥ 30 Years Who Undergo Primary Human Papillomavirus DNA Testing[19]

If the HPV DNA test is negative, these women return to screening after 5 -10 years

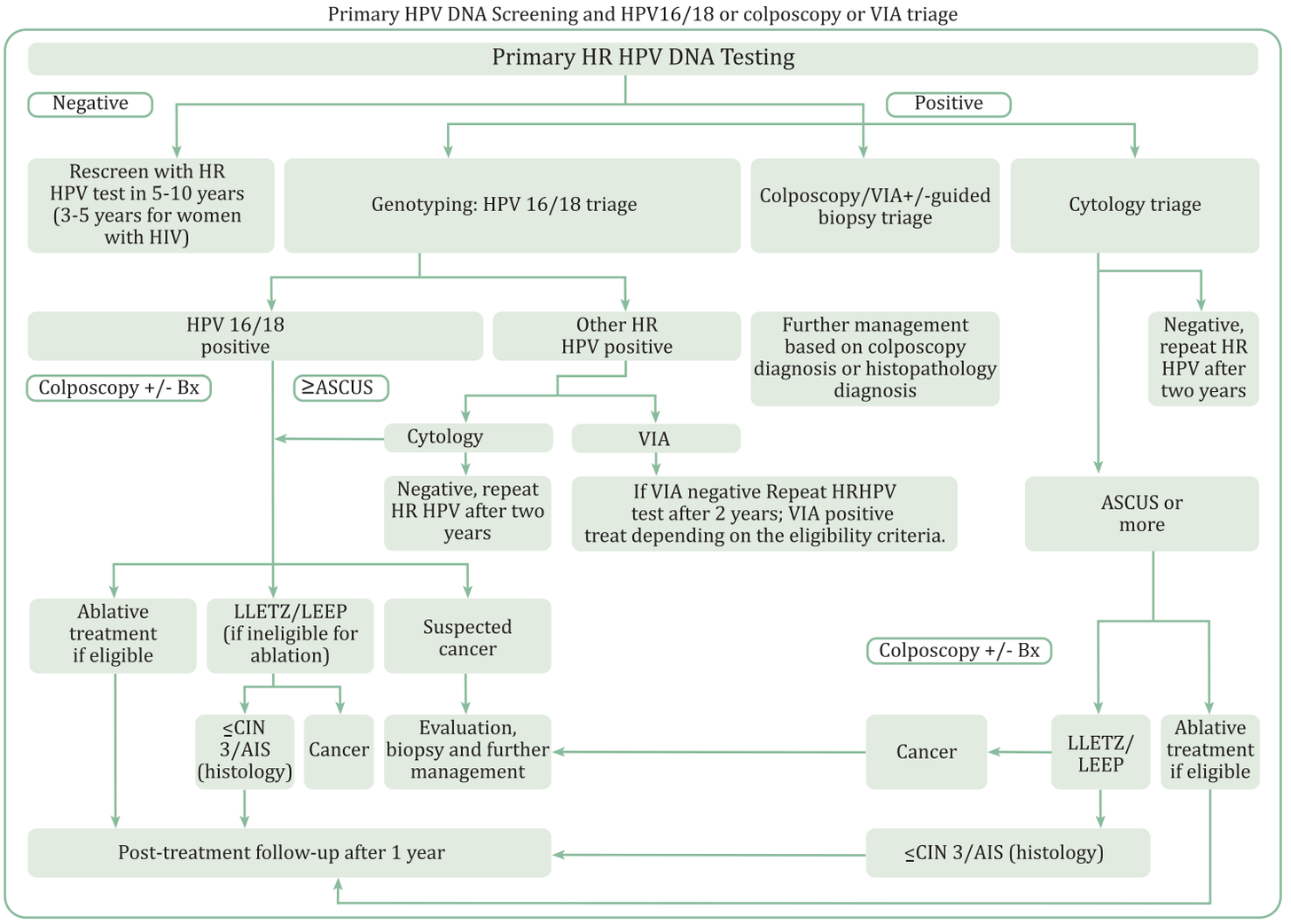
If the HPV DNA is positive, any of the following triage options can be considered:

A. VIA triage: If positive, for colposcopy; if negative, repeat HPV at 1 year

B. Cytology triage: If cytology is positive, colposcopy is recommended

C. HPV genotyping: If 16/18 is positive, immediate colposcopy is recommended. If other high-risk HPV types are positive, either VIA or cytology triage can be done; if these are positive, colposcopy is recommended.

Refer to Flow Chart 2: Management of HPV DNA-positive women[19]



Abbreviations: AIS, adenocarcinoma in situ; ASCUS, atypical squamous cells of undetermined significance; CIN, Cervical intraepithelial neoplasia; DNA, deoxyribonucleic acid; HIV, human immunodeficiency virus; HPV, human papillomavirus; LEEP, loop electrosurgical excision procedure; LLETZ, large loop excision of the transformation zone; VIA, visual inspection with acetic acid

Flow chart 2 The diagram illustrates a decision-making process for HPV screening and management, detailing various testing options, triage protocols, and treatment pathways based on HPV genotypes and cytology results.

Management of Women Aged ≥30 Years Who Undergo Cytological Screening[19]

If the cytology (Pap smear, either conventional or LBC) is negative, women are called for routine screening after 3 years.

If the cytology is positive, the triage options depend on the type of abnormality (squamous/glandular) and its grade.

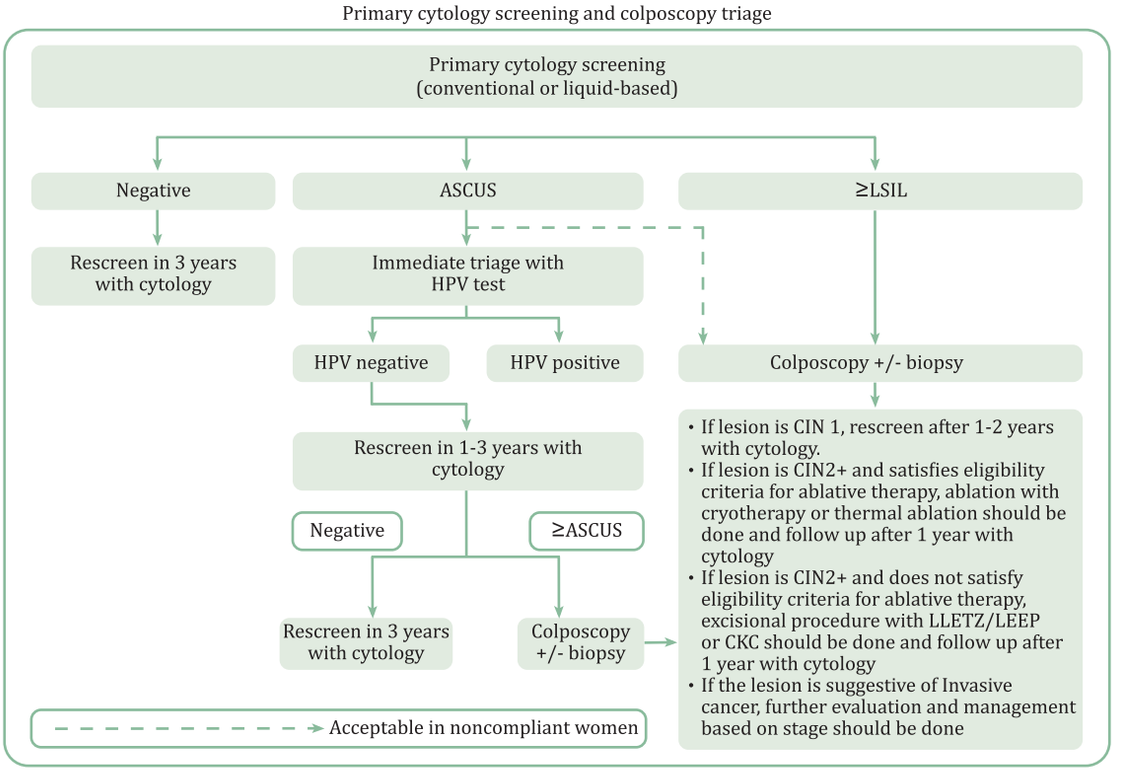
Squamous Abnormalities

ASCUS: Reflex HPV testing is recommended if facilities are available. If HPV DNA is positive, colposcopy is recommended. (Level A) If negative, repeat cytology is done in 1 to 3 years. If facilities are not available for HPV testing, either immediate colposcopy or cytology at one year is recommended.

LSIL: Colposcopy is recommended as the first option. (Level A) HPV triage is acceptable if colposcopy is not available. (Level B)

ASC-H and HSIL: All these women need immediate colposcopy referral. (Level A)

Refer to Flow Chart 3 for the management of cytology positive women[19]



Abbreviations: ASCUS, atypical squamous cells of undetermined significance; CIN, Cervical intraepithelial neoplasia; CKC, cold-knife conization; HPV, human papillomavirus; LEEP, loop electrosurgical excision procedure; LLETZ, large loop excision of the transformation zone; LSIL, low-grade squamous intraepithelial lesion

Glandular Abnormalities

Glandular abnormalities need to be managed aggressively due to a higher association with endocervical/endometrial cancers.

Abnormal Glandular cells: AGC NOS/Atypical Endocervical cells: These women need immediate colposcopy, ectocervical biopsy, endocervical curettage and endometrial biopsy

Management of Women Aged ≥30 Years Who Undergo Co-Testing

If the co-testing is negative, these women return to screening after 5 years

If the HPV DNA is positive and cytology is negative, any of the following options can be considered: Repeat co-testing after 1 year, and if negative, return to routine screening after 5 years. If any one of the tests is positive after one year, colposcopy is recommended

HPV genotyping: If 16/18 is positive, immediate colposcopy is recommended. If other high-risk types are positive, repeat co-testing is done after a year. If both are negative, women can return to routine screening after 5 years. If any one of the tests is positive, colposcopy is recommended. (Refer to Flow chart 1)

If HPV DNA is negative and cytology is positive, depending on the grade of cytological abnormality, a decision is made to refer for colposcopy. Refer to Flow Chart 3

TREATMENT OF CERVICAL PRE-CANCER

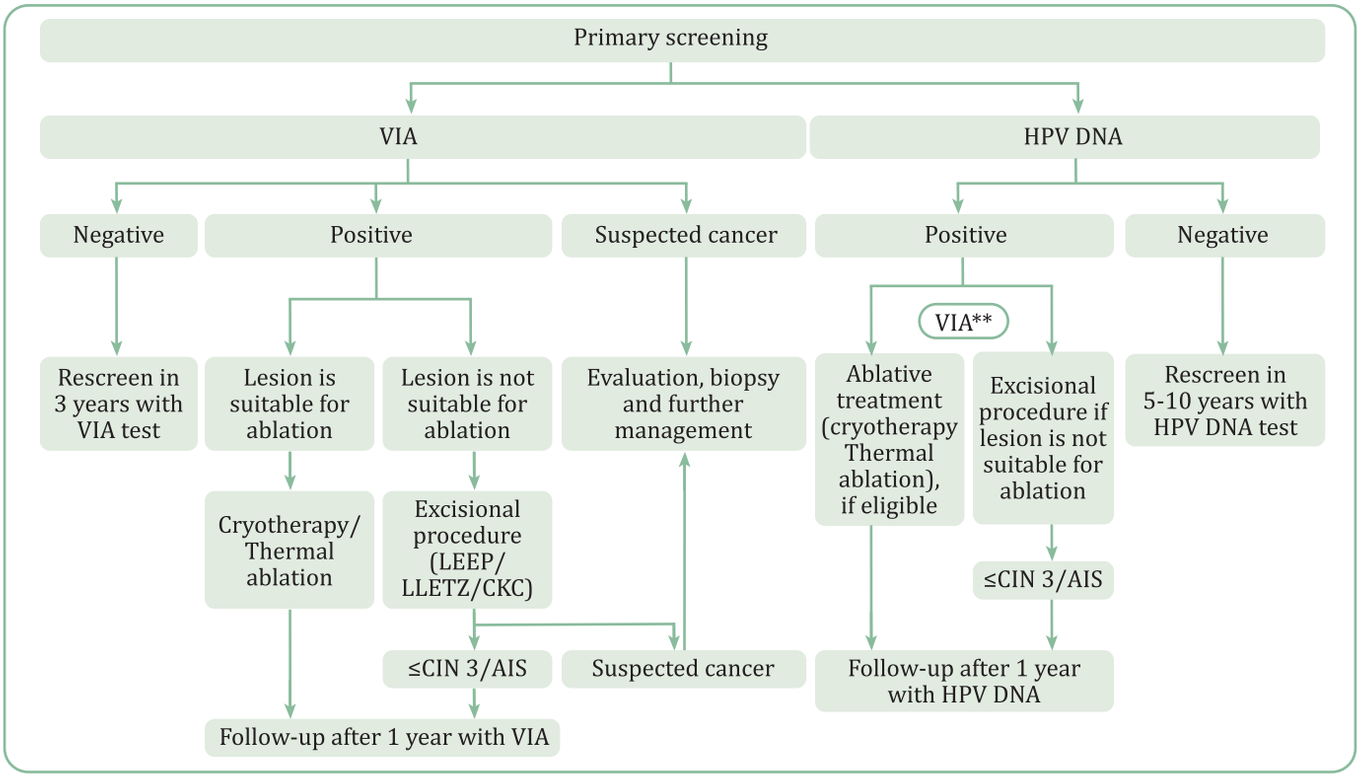
Screen and treat approach: It is a single-visit approach where women who test positive after VIA or Primary HPV DNA screening are treated by ablation if suitable, without a biopsy confirmation of cervical pre-cancer. This approach minimises the loss of follow-up and completes the treatment cycle. It is very useful in low and middle-income countries to reduce the burden of cervical cancer.[21] Refer to Flow chart 4 to Screen and Treat[19]

Flowchart 4: The image illustrates a flowchart detailing the diagnostic process for cervical lesions,

including primary screening, subsequent testing, and potential treatment options based on results, using terms like VIA, HPV DNA, and various treatment modalities.

Screen, Triage and Treat Approach: Following an abnormal cytology, except in ASCUS, where reflex HPV testing is recommended, women are triaged with colposcopy for identifying cervical lesions. Treatment is planned according to the grade of cervical pre-cancer. Following a positive HPV test, women can be triaged with HPV genotyping, VIA, Cytology or colposcopy before deciding the treatment plan. These triage options are shown in Flow Charts 2 and 3.

See-and-Treat Approach: This approach is used in good colposcopy centres. Following a colposcopic examination for screen-positive women, if the findings are suggestive of a high-grade lesion, electrosurgical excision is done both for diagnosis and treatment without any prior biopsy.



**VIA-Visual Inspection with Acetic Acid. VIA is used to identify new SCJ, type of TZ thereby to determine eligibility criteria for treatment Abbreviations: AIS, adenocarcinoma in situ; CIN, Cervical intraepithelial neoplasia; CKC, cold-knife conization; DNA, deoxyribonucleic acid; HPV, human papillomavirus; LEEP, loop electrosurgical excision procedure; LLETZ, large loop excision of the transformation zone; VIA, visual inspection with acetic acid

HUMAN PAPILLOMAVIRUS VACCINATION

HPV Vaccination as a primary prevention strategy is essential for cervical cancer elimination. The WHO's global strategy to accelerate cervical cancer elimination as a public health problem recommends including HPV vaccines in national programmes, reaching 90% of girls by age 15 years by 2030.[34] The first vaccine licenced was Gardasil (a quadrivalent HPV vaccine against HPV 6, 11, 16, and 18) in 2006, followed by Cervarix (a bivalent HPV vaccine against HPV 16 and 18) in 2009. Gardasil 9 was approved by the FDA in 2014. It offers protection against 9 HPV types: 6, 11, 16, 18, 31, 33, 45, 52 and 58. Cervavac, the Indian quadrivalent vaccine, was launched in January 2023. It is a gender-neutral vaccine approved for use in individuals aged 9 to 26.

As of April 2024, 137 WHO member states have included HPV vaccination in their national vaccination programmes, and 54 countries have adopted a gender-neutral vaccination strategy (vaccinating girls and boys).[35] In 2020, less than 30% of LMICs had introduced HPV vaccination in their national immunisation programmes, in contrast to more than 85% of high-income countries.[34]

The primary target population for HPV vaccination recommended by the WHO is girls aged 9–14 years, prior to their becoming sexually active, to undergo a two-dose schedule and girls ≥ 15 years of age, to undergo a three-dose

schedule. Adults aged 27–45 years who might be at risk of new HPV infection may benefit from vaccination. Several studies have investigated the efficacy and effectiveness of HPV vaccines. The efficacy has been remarkably high among young women who were HPV seronegative and who received the vaccine at the ages of 9 and 14 years.[36] Comparisons of the efficacy of bivalent, quadrivalent, and nonavalent HPV 16/18 vaccines showed they are similar. In a real-world setting, the notable decrease in HPV 6, 11, 16, and 18 among vaccinated women compared with unvaccinated women demonstrates the vaccine's high effectiveness.[37]

Vaccinating adult women who are sexually active needs a lot of counselling. According to the Centres for Disease Control and Prevention (CDC), vaccination is not recommended for everyone older than 26 years. Some adults aged 27 through 45 years might decide to get the HPV vaccine based on a discussion with their clinician, if they did not get adequately vaccinated when they were younger. HPV vaccination of people in this age range provides less benefit, for several reasons, including the fact that most women in this age range have already been exposed to HPV. For adults aged 27 to 45 years, clinicians can consider discussing HPV vaccination with those most likely to benefit. HPV vaccination does not need to be discussed with most adults aged 26 or older. Sexually active women need to be counselled for cervical screening.[36]

EFFECT OF MENOPAUSAL HORMONE THERAPY

Cervical Pre-Cancer

Menopausal hormone therapy (MHT) does not significantly raise overall cervical cancer (CC) risk. It may increase the risk for specific lesions, particularly adenocarcinomas.

A systematic review and meta-analysis of the results showed that MHT (current and past use) had a reduced risk for cervical cancer (CC) (OR=0.70, 95% CI [0.58, 0.85]), an increased risk for any cytological abnormality related to CC (OR=1.38, 95% CI [1.22, 1.55]), also an increased risk for adenocarcinoma of CC (OR=1.82, 95% CI [0.91,3.65]), but a decreased risk for squamous cell carcinoma of CC38 (OR=0.74, 95% CI [0.57, 0.96]). The relationship between menopause, MHT and HPV infection is complex to understand, with conflicting results.

Cervical Cancer

Cervical cancer treatment frequently leads to iatrogenic menopause, either due to hysterectomy with bilateral salpingo-oophorectomy or pelvic radiotherapy, resulting in premature ovarian insufficiency. Consequently, a substantial number of patients with cervical cancer may require MHT. The role of estrogen in HPV carcinogenesis is controversial.[39] This may need to be considered while discussing MHT in HPV positive cervical cancer patients. Although estrogen and progesterone receptors are expressed in 39% and 33% of patients, respectively, their expression does not influence recurrence or overall survival.[40] Information on the safety of MHT in other rare histological subtypes, such as neuroendocrine carcinoma, remains limited. A retrospective study conducted in Poland on stage I/II cervical cancer has reported no significant difference in recurrence or 5-year survival rates between MHT and non-MHT groups.[41] A few studies have investigated the use of MHT in women who had iatrogenic menopause following the treatment for cervical cancer. Fewer than half of all women received counselling and/or a prescription for MHT after diagnoses of iatrogenic menopause, and disparities were noted.[42]

CERVICAL CANCER SCREENING RECOMMENDATION

Primary Care Level: Urban & Rural

VIA: VIA can be performed by physicians and other health care workers, including Auxiliary Nurse-Midwives (ANMs) and Nurses. The VIA test is suitable only when the squamo-columnar junction is visible. At menopause due to low estrogens, the squamo-columnar junction recedes into the endocervix. The test results become unreliable and unsatisfactory.

HPV DNA testing: If low-cost, point-of-care HPV testing is available, primary HPV DNA screening should be performed every 5 years until age 65. Cytology or VIA testing can be used to triage and evaluate those with HPV-positive test results, helping plan appropriate treatment options.

Screen-and-Treat or Single-Visit Approach (Cryotherapy or Thermal Ablation)

VIA followed by Ablation: VIA screening followed by treating VIA-positive women immediately using ablation, where suitable, without further diagnostic confirmation, is the most efficient and effective strategy in low-resource settings.

HPV DNA followed by Ablation: If women test positive for HPV DNA, VIA is done to identify any visible cervical lesion. If the lesion is suitable for ablation, it is performed in the same sitting, with or without biopsy, to avoid loss to follow-up. If the lesion is not suitable for ablation, these women need referral to a higher centre. According to the International Agency for Research on Cancer (IARC) Evidence Summary, Brief No 7, Thermal Ablation is the best cost-effective and safe treatment option for all eligible women with cervical pre-cancer. With the availability of portable, rechargeable, battery-operated devices, the WHO recommends Thermal ablation over Cryotherapy.[43]

Secondary and Tertiary Care

Cytology: Conventional/LBC: Good-quality cytology needs to be ensured every 3 years until age 65.

VIA: The VIA test is not suitable for menopausal women.

HPV DNA testing: If resources are available, a validated Primary HPV DNA test is preferred over other screening tests.

Co-Testing (Cytology and HPV DNA): It is practised in some tertiary care centres because the results are complementary.

COLPOSCOPY

It is the preferred triage option for all screen-positive women in secondary and tertiary care centres to avoid over-treatment. Colposcopy should be performed by certified colposcopists to ensure careful evaluation of screen-positive women. Colposcopy in menopausal women is often challenging due to atrophic changes. It becomes unsatisfactory as the transformation zone recedes into the endocervical canal. Intravaginally, daily application of estrogen cream for 2 to 4 weeks, followed by colposcopy, will result in a satisfactory examination.

TREATMENT FACILITY

Secondary and tertiary care centres should be equipped with treatment facilities, like ablation, electrosurgical excision and conisation.

CERVICAL CANCER SCREENING FOR WOMEN AT MENOPAUSE TRANSITION AND POSTMENOPAUSE

- Regular cervical screening is recommended for women during the menopause transition (MT) and after menopause.[44]
- In India, since opportunistic screening is widespread, any woman in the specified groups should be advised to undergo screening if she has not had one in the past 3–5 years.[45,46]
- Women who have never undergone screening during their lifetime should be recommended to do so, even at age 65 or older, if they maintain a good quality of life (QOL).[46]
- VIA screening has limited accuracy because the TZ recedes into the cervical canal due to estrogen d iciency. VIA screening is generally not recommended for individuals over 50 years of age.[21]
- Cytological screening using conventional methods or LBC is recommended every 3 years. Transition to HPV DNA testing is recommended where feasible.[18,21,47]
- Primary HPV screening: Both provider-collected and self-HPV sampling are recommended.[48,49]
- For cervical intraepithelial neoplasia Grade 1 (CIN1) and certain CIN2 lesions that meet the WHO eligibility criteria, such as a fully visible TZ, no endocervical extension, and no suspicion of invasion, ablative treatments, such as thermal ablation, may be considered.[50]
- High-grade squamous intraepithelial lesion (CIN2/3) with endocervical extension or nonvisible squamo-columnar junction should be treated with excisional procedures (large loop excision of the TZ/loop electrosurgical excision procedure or cold-knife cone), not ablation.[50]
- In postmenopausal women, excisional treatment should ideally be performed by experienced colposcopists because cervical atrophy, stenosis, and Type 3 TZ increase the technical difficulty and the risk of complications.[49-53]

FOLLOW-UP AFTER TREATMENT OF PRECANCEROUS CERVICAL LESIONS

Post-treatment follow-up recommendations are similar to those for premenopausal women. An HPV-based test of cure is advised at 6, 18, and 30 months after treatment, followed by continued surveillance with HPV testing every 3 years for a minimum of 25 years.[33,49,51,52] After three consecutive negative HPV test results (with normal cytology if co-testing is used), long-term screening should continue at 3-year intervals, even beyond age 65, in otherwise healthy individuals. In cases where a hysterectomy is performed during the follow-up period, vaginal screening using HPV-based testing should be continued to complete the recommended 25-year surveillance duration.[54]

SYNOPSIS

- Cervical cancer is the leading cause of cancer death in women in both rural and urban areas.
- The cervical cancer death rate of 16/100,000 reported in the Million-Woman Death Study 2012 suggests that a 30-year-old Indian woman has about 0.7% risk of dying from cervical cancer before 70 years of age in the absence of other diseases. By contrast, the risk of dying during pregnancy for Indian women aged 15-49 years is about 0.6%.
- 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 1,27,000 new cases are diagnosed every year.
- Risk factors: HPV - Human Papilloma Virus, sexual intercourse at an early age, multiple sexual partners, sexual partners who have had multiple partners, HIV positive status, and smoking.
- Currently, only 1.9% of women aged 30-49 years have ever been screened. In urban areas, the coverage is 2.2%, and in rural areas, 1.7% (National Family Health Survey NFHS-5, 2019-2021).
- Screening tests available include visual inspection, VIA, VILI, conventional and liquid-based cytology, and HPV DNA testing.

RESEARCH AGENDA

Role of vaginal microbiome in HPV induced carcinogenesis

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CANCER ENDOMETRIUM

Keywords: Prevalence, risk factors, effect of hormone therapy, prevention, diagnosis.

INTRODUCTION

Endometrial cancer (EC) arises from the inner lining layer of the uterus. It is common in postmenopausal women and is often detected at an early stage because it frequently produces abnormal vaginal bleeding and has a good prognosis. If diagnosed early, a complete cure is feasible with regular follow-up. The treatment comprises surgical staging, adjuvant radiotherapy, with or without chemotherapy, depending on the final surgical-pathological stage.

PREVALENCE AND EPIDEMIOLOGY

EC is the most common female genital tract malignancy in most countries, affecting 2–3% of women. Worldwide, it ranks seventh among all female cancers.[1] The reported global incidence in 2020 was 417,367, which constituted about 2.2% of newly diagnosed cancer cases, and around 97,370 deaths attributed to EC, accounting for 1% of all cancer-related deaths. Overall age-standardised incidence was 8.7, with a mortality rate of 1.8/100,000 population. The incidence of EC is high in developed countries.[2] While the incidence and mortality rates of several other cancers have plateaued or decreased in the last decade, the incidence of EC has been rising throughout the developed regions. Overall, women have a 2.6% lifetime risk of developing this malignancy. EC has increased gradually by over 40% in the United Kingdom from 1993 to 2008, at the rate of 1.45% per year. The age-standardised incidence varies at least tenfold across countries, suggesting the strong influence of modifiable risk factors. In India, the incidence of EC is low compared to developed countries, with a reported incidence of 16,413 cases in 2020 and reported mortality of 6385 cases, with a cumulative risk of diagnosis of 0.75, but the current trend is rising due to changing lifestyles and reproductive patterns, particularly in urban areas. The age-standardised incidence rate is 2.3 per 100,000 women.[3] This increase has been attributed to increasing obesity, life expectancy, and adjuvant tamoxifen use for breast cancer.[4] EC occurs mostly after the menopause, with the peak incidence occurring between 55 and 65 years of age. It has an excellent prognosis with five-year survival of 96% when diagnosed while the disease is still localised, compared with 77% for regional disease and 44% for disease with distant metastasis. A majority of cases are diagnosed while still localised. Overall morbidity and mortality of EC is low because most patients present at an early stage because of abnormal bleeding or postmenopausal bleeding.

The exact aetiology of EC remains unknown, but prolonged exposure to estrogen is considered the main causative factor. Women having early menarche and delayed menopause are at high risk for developing endometrial cancer. The other risk factors include nulliparity, obesity, comorbidities such as hypertension and diabetes, estrogen-only hormone therapy (ERT), and genetic factors such as Lynch syndrome and Cowden syndrome. However, the available data is inconclusive, and the exact incidence in relation to the risk factors due to lack of estimates of endometrial hyperplasia(EH) and cancer risks and the evidence on secondary prevention via progestin-based hormonal treatments is insufficient. The incidence trends for EH could serve as harbingers of future cancer trends.[5] Hysterectomy eliminates a woman's future risk of EC and reduces the size of the at-risk population that provides the denominator for calculating incidence rates.[6]

There are two major histological types of EC: Type 1 or endometrioid endometrial cancer (EEC), accounting for > 75% of EC cases and Type 2, non-EEC. These type I tumours are mostly low-grade adenocarcinomas with a fairly good prognosis. In contrast, type II tumours, such as serous papillary carcinomas, clear cell adenocarcinomas or squamous carcinomas, originate from polyps or other non-hyperplastic endometrial lesions. They are more malignant and usually diagnosed at a more advanced stage. Rarely, mixed histology and undifferentiated histological types also occur.

Endometrial hyperplasia: EH most often results from prolonged, unopposed estrogenic stimulation of the endometrium. Hyperplasia may also result from excessive endogenous estrogen production or exogenous estrogen administration. It is known that approximately 80% of the EC are preceded by EH. Histologically, there is excessive proliferation of endometrial glands, with an increased gland-to-stroma ratio. EH can be further categorised into hyperplasia without cellular atypia and hyperplasia with cellular atypia (atypical hyperplasia). Hertig and Sommers proposed the theory of progression of endometrial hyperplasia to adenocarcinoma, going through a stage of atypical

changes. If left untreated, the incidence of progression to endometrial cancer ranges from 1% to 29% of cases, depending on the type of hyperplasia (simple vs complex) and the degree of cytological atypia. The malignant degeneration in EH without atypia is low. Atypical hyperplasia is often focal and may be found in the background of simple hyperplasia or in the normal endometrium. Adenomatous and atypical hyperplasia are reported to be the common precursors of endometrial carcinoma. It has been observed that a concurrent EC at the time of hysterectomy occurs in about 42% of women with a prior biopsy diagnosis of atypical endometrial hyperplasia.[7,8] On endo-vaginal sonography, EH presents as a thickened endometrial strip larger than 5 mm. The endometrium is echogenic with a well-defined margin. It has a similar appearance to EC confined to the endometrium. On hysterosalpingography (HSG), EH may present as focal or diffuse endometrial thickening without a localised mass. The localised EH may sometimes mimic a sessile polyp. Identifying the feeding vessel or stalk on colour Doppler ultrasound may help distinguish an endometrial polyp from localised EH. Colour Doppler findings of diffusely thickened endometrium with no vascularity are a consistent feature of EH.

ENDOMETRIAL CANCER PROTECTIVE AND RISK FACTORS

Increasing Parity and Lactation: Increased parity and lactation duration are associated with a decreased risk of EC.[9,10] Parous women have a 35% decreased risk of EC (hazard ratio = 0.65; 95% confidence interval [CI], 0.54–0.77) compared with nulliparous women. The duration of breastfeeding has also been associated with a decreased risk, with a 23% risk reduction noted with breastfeeding for more than 18 months.[10]

Factors Associated with Increased Risk of EC: The most significant risk factors for EC and its precursor, EH, include unopposed estrogenic exposure, sedentary lifestyle, a high-fat, low fibre diet, urbanisation, and shifts in reproductive patterns.[11]

Advancing age: EH primarily affects postmenopausal women, with a median age at diagnosis of 60 years.

Endogenous estrogens: Risk factors include obesity, a high-fat diet, polycystic ovarian syndrome, infertility or failure to ovulate, chronic anovulation, tamoxifen use, and reproductive factors such as nulliparity, early menarche, and late menopause.[11] Evidence suggests an increased risk of EC associated with postmenopausal levels of endogenous hormones, including estradiol, free estradiol, and estrone.

Late Menopause: Late menopause, defined as menopause occurring after age 55, increases the risk of EC two-fold, with a relative risk of 2.4.[11]

Nulliparity & Infertility: Overall, nulliparity appears to confer approximately a 2-fold risk of developing EC compared with parity of 1 or more. Several studies have shown a marked decrease in risk with increasing numbers of full-term pregnancies. The literature does not support a significant risk of endometrial cancer associated with infertility, although some studies have shown an elevated risk.[11]

Polycystic ovarian syndrome (PCOS): Women with PCOS have several risk factors for EC and may be at increased risk of developing EC. Some of the clinical, metabolic, and molecular risk factors include unopposed estrogen stimulation of the endometrium in anovulatory PCOS women, obesity, insulin resistance, insulin-like growth factors, diabetes, nulliparity, Cyclin D1, glutathione S-transferase, and progesterone resistance. Women with PCOS had an odds ratio (OR) of developing EC of 2.89 with a 95% CI of 1.52–5.48. This almost 3-fold risk of EC in women with PCOS translates into a lifetime risk of 9%, given the background lifetime risk of EC in the general population of 3%. Although most women with PCOS (91%) will not develop EC, evidence has shown that women with PCOS are at increased risk.[12]

Obesity: Obesity is known to increase endogenous estrogen because the presence of fat appears to be responsible for the conversion of androstenedione to estrogen compounds at a much higher rate than if fat is not present. Anovulation, which may be secondary to unopposed estrogen, also appears to contribute to this situation. Studies show that very obese women have a two-to-four-fold relative risk of EC. Relative risk of 3.0 in women 21–50 lb overweight and 10 in women more than 50 lb overweight.[13] The risk of endometrial cancer increases 1.59-fold per 5 kg/m2 change in body mass.[13]

Diabetes: Diabetes is an independent risk factor for EC and confers about a twofold relative risk after adjusting for obesity. There is no data on the relationship between the type or duration of diabetes and endometrial cancer risk. The risk was increased >6-fold among obese diabetic women compared with normal weight women without diabetes, whereas diabetics with low levels of physical activity had ~ 3-fold increased risk compared with women without diabetes and a high level of total physical activity.[14] Women with the most unfavourable combination of diabetes with

both high body mass index (BMI) and low physical activity had ~10-fold higher risk in comparison with nondiabetic women with normal weight who were highly physically active.[15]

Exogenous estrogens / Hormone therapy: Unopposed estrogen therapy in women with an intact uterus increases the risk of EC two- to 10-fold, and risk increases with duration of use.[16] Unopposed estrogen therapy is not recommended for women with an intact uterus for this reason.[17] The addition of progestin to estrogen, either cyclic or continuous, reduces the risk of EC to either the expected risk of women not taking hormone replacement therapy (HRT), or, in some studies, to lower than expected.[18] The length of cyclic progestin therapy appears important, with at least 10 days (preferably 14 days) necessary to decrease the risk associated with unopposed estrogen therapy.[19]

Role of Hormone therapy (HT): Combined menopausal hormone therapy (MHT), consisting of estrogen and progestin, was developed to reduce the risk of EC associated with unopposed estrogen use. However, its effect on EC risk depends on the regimen and duration of therapy. Evidence from observational studies in Finnish populations indicates that estradiol–progestin therapy, particularly when used in sequential regimens for prolonged durations, is associated with an increased risk of EC, whereas continuous combined regimens appear to have a protective effect.[20] The Women's Health Initiative (WHI) randomised trial demonstrated that continuous estrogen–progestin therapy does not increase EC risk and may reduce it.[21] The protective effect of combined therapy is influenced by the adequacy of progestin exposure, which is essential for converting the proliferative endometrium into a secretory state and preventing hyperplasia. Furthermore, current evidence suggests that neither the route of administration (oral versus transdermal) nor the type of progestin significantly alters endometrial safety.[22]

Selective estrogen receptor modifiers: Tamoxifen is widely used as part of adjuvant therapy for breast cancer and as chemoprevention for women at increased risk of breast cancer. While tamoxifen has beneficial anti-estrogenic effects on breast tissue, it exhibits partial estrogen agonist activity on the endometrium, thereby increasing the risk of endometrial pathology, including polyps, hyperplasia, and carcinoma.[23] The risk of EC is elevated in women receiving tamoxifen, especially among those with prior exposure to estrogen therapy.[24] Long-term use, particularly beyond two years, has been associated with a 2–7-fold increase in relative risk.[25] Evidence from the National Surgical Adjuvant Breast and Bowel Project (NSABP) trials demonstrated approximately a twofold increase in EC incidence among tamoxifen users compared to placebo, with the risk being more pronounced in postmenopausal women.[24] Despite this, the overall therapeutic benefits of tamoxifen outweigh the associated risks. Furthermore, EC arising in tamoxifen-treated patients do not appear to have a worse prognosis compared to those in non-users.[25] Early clinical studies demonstrated that adjuvant tamoxifen therapy in breast cancer was associated with an increased incidence of second primary malignancies, including EC.[26] In contrast, another SERM, raloxifene, has not been associated with an increased risk of EC.[27,28]

Genetic factors: Women with hereditary nonpolyposis colorectal cancer (HNPCC) syndrome have a markedly increased risk of EC compared with women in the general population. Among women who are HNPCC mutation carriers, the estimated cumulative incidence of EC ranges from 20% to 60%. Women with HNPCC account for only 2% to 10% of all female cases of colon cancer; however, about 5% of all EC occur in women with this risk factor. 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%. These cases are often diagnosed in the fifth decade, 10 to 20 years earlier than sporadic cases. Based on limited evidence, it appears that 5-year survival among HNPCC women diagnosed with endometrial cancer is similar to that of nonhereditary cases in the general population.[29,30]

Other Familial conditions with their lifetime risk of EC are:

- Lynch syndrome. Women with mismatch repair (MMR) gene mutations have various lifetime risks of developing EC depending on the specific gene mutation: 20%–54% for MLH1, 21%–49% for MSH2, 16%–71% for MSH6, 15% for PMS2, and 21%–57% for epithelial cell adhesion molecule (EPCAM).
- Cowden syndrome. Women with phosphatase and tensin homolog (PTEN) gene mutations have a 19%–28% risk of developing EC by the age of 70 years.
- Hereditary Breast and Ovarian Cancer Syndrome. Women with breast cancer susceptibility gene (BRCA) mutations (BRCA1/2) have a 2- to 3-fold increased risk of EC.

PREVENTION / RISK REDUCTION STRATEGIES

Interventions of Unproven/Disproven Effect on Risk

Weight reduction: The potential benefit of intentional weight loss was studied and found no association between EC incidence and intentional weight loss of at least 20 lbs (RR = 0.93; 95% CI, 0.60–1.44).[31]

Fruits, vegetables, and vitamins: The association between dietary factors, particularly fruit and vegetable intake, and EC has been evaluated primarily in case-control studies. No association between fruit intake and EC was observed. There is case-control evidence suggesting that regular consumption of soy products reduces the risk of EC. A consortium of seven prospective cohort studies examined the association between serum vitamin D levels and the development of EC. After controlling for BMI, there was no association between circulating vitamin D and EC risk. Multivitamin use has little or no influence on the risk of common cancers, including EC, or on total mortality in postmenopausal women.

Interventions Associated with Decreased Risk

Factors associated with a decreased incidence of EC include parity, lactation, use of combined oral contraceptives (COC), a diet low in fat and high in plant foods, and physical activity.

Oral contraceptives: The use of COCs is associated with a substantial reduction in the risk of endometrial cancer. Use for at least one year has been shown to reduce risk by approximately 40%, with evidence derived from both case–control and cohort studies.[32] This protective effect persists for many years after discontinuation, extending for at least 15 years. Longer duration of use confers greater benefit, with approximately 50–70% risk reduction observed with prolonged use.[21]

Physical activity: Consistently associated with a lower risk of endometrial cancer. Epidemiological studies suggest that regular exercise may reduce risk by approximately 30–40%, although a clear dose–response relationship with increasing intensity or duration has not been firmly established.[33,34]

RECOMMENDATIONS FOR SCREENING AND DIAGNOSIS OF ENDOMETRIAL CANCER

Screening: for evaluating asymptomatic patients. When abnormal bleeding occurs, evaluation becomes diagnostic rather than screening.EC is often diagnosed at an early stage, leading to a 5-year survival rate of 74–91.[35]. As a result, screening may not influence the mortality rates. Based on solid evidence, screening asymptomatic women will result in unnecessary additional biopsies, resulting in false-positive test results, leading to anxiety and procedural complications.

Currently, there is no evidence to support or recommend routine screening for EC in asymptomatic women with no or moderate risk factors, as it is not cost-effective.[36] Routine screening for EC is not recommended for the general population. On reaching menopause, all women should be informed about the risks and symptoms of EC and strongly encouraged to seek medical attention if they experience abnormal bleeding.

High-risk women, defined by a history of genetic mutations, may be offered annual screening with transvaginal ultrasonography (TVS) and endometrial biopsy starting at ages 30–35 or sooner before the age of onset of related cancer in a family member.[37] Physicians should adopt an individualised approach based on the patient's history and risk factors after counselling about the risks, benefits and limitations of screening.

Diagnosis: It is typically performed in an office setting, such as with an endometrial biopsy. Hysterectomy remains the cornerstone of primary treatment, with surgical approaches varying by hospital setting.

Endometrial Biopsy: Endometrial biopsy(EB) is easily performed as an office procedure and has good sensitivity. EB is the most common technique for obtaining endometrial tissue, and evaluation of endometrial histology has been the gold standard for assessing endometrial status. EB may result in discomfort, bleeding, infection, and rarely, uterine perforation.

Hysteroscopy-guided biopsy: Hysteroscopy is valuable and considered the gold standard for identifying endometrial lesions, such as polyps, particularly in patients with persistent or recurrent bleeding. Cooper and colleagues have recommended that hysteroscopy-directed biopsy is superior to EB for collecting endometrial tissue samples in

individuals trained to perform the procedure and equipped with the necessary equipment. An in-office EB without visual control is regarded as a reasonable approach for diagnostic sampling.[38] However, clinicians should be aware of the 10% false-negative rate.

Transvaginal ultrasound (TVU): Although TVU can be used to evaluate asymptomatic and occult endometrial pathology, it has not been evaluated as a screening method to reduce mortality in asymptomatic women. TVU, when used as a non-invasive screening test to evaluate the endometrium in postmenopausal women without vaginal bleeding, or in postmenopausal women whose endometrial thickness exceeds 4 mm, an EB should be performed during the same visit. The sensitivity of detecting endometrial pathology is 96%–98%, with a specificity of 42%–51% and a negative predictive value of 99%. False positives will be extremely high, resulting in a very low positive predictive value.[39] Endometrial thickness below 4 mm carries a very low risk (0.62%) of endometrial malignancy (EM).

TVU in women using tamoxifen: In a prospective, observational study of 304 women using tamoxifen for 6 years, women underwent annual endovaginal ultrasound screening; those with abnormal ultrasound findings or symptomatic bleeding underwent EB. Thirty-two per cent of the ultrasound examinations had associated significant uterine abnormalities identified that required further medical or surgical investigation and treatment. However, most abnormalities (80%) represented benign polyps for which no treatment was needed. Six cases of primary EC were identified, all presenting with irregular bleeding. The ultrasound sensitivity was 63.3%, the specificity was 60.4%, and the positive predictive value for cancer was 1%.[40] Routine ultrasound surveillance in asymptomatic women using tamoxifen is not useful because of its low specificity and low positive predictive value. Evaluation of the endometrium in women taking tamoxifen should be limited to women symptomatic with vaginal bleeding. Runowicz concluded that the current data do not warrant routine screening for EC in asymptomatic women on tamoxifen therapy.

The Pap test: EC detection is primarily incidental on the Pap smear. Evaluations of the potential of the Pap test to be a test for both cervical cancer and endometrial cancer have shown both sensitivity and positive predictive value to be too low for the Pap test to be a practical screening test for endometrial cancer. However, abnormal endometrial cells on the Pap test may indicate increased risk, especially when present in the secretory phase of the menstrual cycle or in postmenopausal patients. If atypical glandular cells are seen, further investigations are required to rule out neoplasia. All women with atypical endometrial cells on Pap tests need endometrial sampling irrespective of age/menstrual status.[41,42]

Imaging studies: should be performed to assess the extent of cancer spread and aid treatment planning. These imaging modalities may include magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET). MRI of the abdomen and pelvis is currently the most accurate method for assessing tumour invasion and disease spread, having 83% accuracy for evaluating the depth of myometrium invasion and 89% positive predictive value for detecting cancer spread to the cervix. CT scans of the chest, abdomen, and pelvis are indicated when there is suspicion of extra-uterine disease. Fluorodeoxyglucose (FDG)-PET scansmay be considered for patients at high risk of extra-pelvic disease.[43]

UPDATES ON STAGING OF DISEASE, ROLE OF IMMUNE-HISTOCHEMICAL STUDIES AND MOLECULAR TESTING

Surgical-pathological findings have been fundamental to staging by the International Federation of Gynaecology and Obstetrics (FIGO) since 1988, with significant revisions in 2009 and again in 2023. FIGO 2023 revised the staging system for EC to include important histopathological features, such as tumour type and grade, lymphovascular space invasion (LVSI), site of lymph node involvement as well as size of metastatic lesions, and incorporates molecular features with 4 subtypes that include: DNA polymerase epsilon (POLE) ultramutated, microsatellite instability hypermutated (MSI-H or MMR-deficient [dMMR]), copy number high (TP53-mutated/p53-abnormal), and copy number low (no specific molecular profile). The 2023 update plays a critical role in the staging of early-stage disease, influencing prognosis and guiding adjuvant treatment. Additionally, the growing importance of targeted therapies and immunotherapies in managing recurrent or advanced disease further underscores the value of molecular tests.[44]

MENOPAUSE HORMONE THERAPY FOR ENDOMETRIAL CANCER SURVIVORS

The overall five-year survival for all stages of EC is about 86%. The five-year survival rate may increase to 97% if the

disease is confined to the uterus. These women may have early physiological and psychological postmenopausal changes, either pre-existing or as a result of surgical removal of the ovaries along with the uterus, depending on age and menopausal status at the time of diagnosis. Lack of estrogen can cause hot flushes, night sweats, genital tract atrophy and longer-term adverse effects, such as osteoporosis and cardiovascular disease.[45] The use of MHT in survivors remains controversial due to concerns about stimulating cancer cells. There is a theoretical risk of promoting residual tumour cell growth and increasing cancer recurrence. Therefore, this is a potential survival disadvantage in a woman who has a potentially curable cancer.[45]

A retrospective cohort study analysed 176 women with histologically confirmed endometrial adenocarcinoma between August 2024 and May 2025. Participants were categorised into MHT users (n = 91) and non-users (n = 85), with a median age of 58 and 62 years, respectively. Demographic, clinical, and treatment data were compared. Survival analyses were conducted using the Kaplan-Meier method and Cox regression. Quality of life was assessed using the Menopause-Specific Quality of Life (MENQOL) questionnaire. Mean recurrence-free survival was longer in the MHT group (53.14 vs 46.28 months, $p < 0.001$). Improvement in menopausal symptom scores was sign icantly greater among MHT users (mean difference [MD] = -2.03) than in the control group (MD = -0.89). No sign icant increase in adverse cardiovascular or thromboembolic events was observed.[46]

Currently, there is insufficient high-quality evidence to inform women considering MHT after treatment for endometrial cancer. The available evidence does not suggest any significant harm. Postoperative MHT appears safe and beneficial for selected endometrial cancer survivors, especially those who were treated in the early stage. There is no information available regarding the use of MHT in higher-stage endometrial cancer (FIGO stage II and above). The use of MHT after endometrial cancer treatment should be individualised, taking account of the woman's symptoms and preferences, and the uncertainty of evidence for and against MHT use. Further prospective trials are needed to confirm these findings.[45,46]

SYNOPSIS

- EC commonly occurs in postmenopausal women.
- Overall morbidity and mortality from EC are low because most patients present at an early stage due to abnormal or postmenopausal bleeding.
- A strong influence of modifiable risk factors, such as increasing obesity, longer life expectancy, and adjuvant tamoxifen use for breast cancer, has been attributed. Adenomatous and atypical hyperplasias are common precursors of endometrial carcinoma.
- Factors that increase the risk of EC include those associated with higher endogenous estrogen levels or hormone therapy with estrogens.
- Unopposed estrogen therapy in women with an intact uterus increases the risk of endometrial cancer two- to tenfold, with risk escalating with the duration of use. Adding progestin to estrogen, either cyclically or continuously, reduces the risk of endometrial cancer to levels comparable to those of women not using MHT, or in some studies, even lower. The relative risk of EC with obesity is 3.0 in women who are 21–50 lb overweight and 10 in women exceeding 50 lb overweight.
- Women taking tamoxifen for more than two years face a 2.3- to 7.5-fold increased relative risk (RR) of EC.
- The lifetime risk of EC for women with hereditary nonpolyposis colorectal cancer (HNPCC) and those at high risk for HNPCC is as high as 60%.
- There is no evidence that screening through transvaginal ultrasound or EB reduces mortality from EC. Most cases (85%) are diagnosed at a low stage due to symptoms, and survival rates are high.
- Screening for EC is not recommended for women with no identified risk factors.
- It is advised that, at the time of menopause, women at average risk should be informed about the risks and symptoms of EC and encouraged to report any unexpected bleeding or spotting.
- Women with increased risk or in special situations, such as on MHT, genetic risk factors, or tamoxifen therapy, should undergo a complete diagnostic evaluation for abnormal bleeding.

RESEARCH AGENDA

Prevalence of endometrial hyperplasia and endometrial cancer in PCOS.

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CANCER OVARY, VULVA, AND VAGINA

Keywords: Prevalence, risk factors, screening, prevention, effect of hormone therapy

INTRODUCTION

Ovarian cancer is the eighth most common cancer in women globally. It causes more deaths than any other gynaecological malignancy combined. It is a very heterogeneous disease with distinct clinical and genetic types. There are no effective screening tests for early recognition of the disease. Women often present with vague symptoms, causing a delay in diagnosis and a poor response to the treatment.[1]

PREVALENCE AND EPIDEMIOLOGY

Ovarian cancer, being the eighth most common cancer in women, resulted in about 3.7% of cases and 4.5% of deaths in the year 2020.[2] Each year, worldwide, more than 225,000 women are diagnosed, and 140,000 die from this disease. According to the International Federation of Obstetrics and Gynaecology (FIGO), the number of women being diagnosed with ovarian cancer is likely to rise to 371,000 new cases a year by 2035. In India, it is the fifth most common cancer in women. The incidence is 4.9 per 100,000 women.[3] Commonly seen in the age groups of 35 to 64 years.

HISTOLOGY AND PATHOGENESIS OF OVARIAN CANCER

Ovarian cancer may be of germ cell, stromal or epithelial origin. Epithelial ovarian cancer (EOC), the most common type, is the focus of this summary. The term EOC encompasses a heterogeneous group of tumours. Classically, epithelial ovarian tumours were classified as serous, mucinous, endometrioid and clear cell. However, a dual classification system for type I and type II tumours has been proposed that incorporates molecular profiling, histology, and clinical behaviour.[4] Type I tumours include low-grade serous, low-grade endometrioid, clear cell and mucinous carcinomas. Type I tumours, usually present at a lower stage, are associated with an excellent clinical prognosis and encompass borderline malignant tumours. Type I tumours tend to be more stable genetically and do not exhibit tumour protein p53 (Tp53) mutations. They exhibit a shared lineage between benign cystic neoplasms and their corresponding carcinomas, often via an intermediate (borderline tumour) stage, supporting the morphologic continuum of tumour progression in these neoplasms.[5]

Type II tumours are highly aggressive and almost always present in the advanced stage. They account for approximately 75% of all epithelial ovarian carcinomas and have relatively similar morphologic features and a uniformly poor outcome. Type II tumours exhibit papillary, glandular, and solid patterns and are diagnosed as high-grade serous, high-grade endometrioid, or undifferentiated carcinomas depending on the dominant pattern. Type II tumours also have a high prevalence of TP53 mutations.[5]

Evidence also suggests that both types develop outside the ovary and then secondarily involve the ovary, with most type II tumours being of tubal origin. This is hypothesised to be the case for both genetic cancers (BRCA1/2-mutation associated cancers) and most non-inherited forms of ovarian cancer.[6] The heterogeneity of ovarian cancer and the suggestion of different molecular pathways of origin for cancer subtypes present challenges and opportunities for the conduct and interpretation of aetiologic factors associated with the development of ovarian cancer.[6]

RISK FACTORS

Numerous reproductive, environmental, and genetic risk factors have been associated with the development of ovarian cancer. Ten to fifteen per cent of ovarian cancers are hereditary. More than 90% of inherited ovarian cancers result from germ-line mutations in the breast cancer 1 (BRCA1) or BRCA2 genes.[7] For the other 90% of cases, no identifiable genetic link was found; most risk factors are related to uninterrupted ovulatory cycles during the reproductive years. Studies showed that women with early menarche (age <12 years) and late menopause (age > 50 years) were at higher risk for ovarian cancer due to a higher number of ovulatory cycles. Women with early menarche and late menopause are at a risk of 1.1 to 1.5 times and 1.4-4.6 times higher for ovarian cancer, respectively.[8] Long periods of repetitive stimulation of the ovarian surface epithelium are hypothesised to lead to malignant transformation. The nongenetic risk factors include obesity, nulliparity, postmenopausal hormone therapy, fertility

drugs, and perineal talc. Protective factors include use of oral contraceptives, multiple pregnancies, breastfeeding, tubal ligation and bilateral salpingectomy.[9]

GENETIC RISK FACTORS FOR OVARIAN CANCER

Three familial ovarian cancer syndromes have been described. The two most common hereditary cancer syndromes are: hereditary breast and ovarian cancer (HBOC), the most common and hereditary nonpolyposis colorectal cancer [Lynch syndrome or hereditary nonpolyposis colorectal cancer (HNPCC)]. The third least common is the hereditary site-specific ovarian cancer syndrome (HSSOC). All are inherited in an autosomal-dominant manner through either the maternal or paternal lineage, conferring a 50% transmission risk to offspring.[10]

Hereditary Breast and Ovarian Cancer

These account for 75–90% of all hereditary ovarian cancers. Women who carry disease-specific alleles for BRCA1 and BRCA2 are at significantly higher risk of EOC than women in the general population.[11] The BRCA1 mutations confer a higher ovarian cancer risk than BRCA2 gene mutations. Mutations of BRCA1 and BRCA2 are associated with the risk of ovarian cancer at 50% and 20%, respectively.[11] BRCA2 is also associated with breast cancer, prostate cancer, pancreatic cancer and male breast cancer. While no standard clinical definition of HBOC exists, several general characteristics are used to identify affected families.

- These familial characteristics include:
- Several cases of breast cancer were diagnosed before the age of 50.
- One or more blood relatives with ovarian cancer
- One or more relatives with both breast and ovarian cancer
- Presence of a BRCA1 or BRCA2 germ-line mutation.
- Personal history of breast cancer.[12]

Ovarian cancers associated with BRCA1/2 are typically high-grade serous carcinomas, but with a relatively favourable chemotherapy response

HNPCC/Lynch Syndrome

Hereditary nonpolyposis colorectal cancer/Lynch syndrome is an autosomal, dominant syndrome with a mean colorectal cancer onset of 45 years. This syndrome is characterised by germline mutations in one of the four DNA mismatch repair genes (MMR).[13] Lifetime risk of ovarian cancer in women with this gene is 8–12%. Families that exhibit HNPCC/Lynch include colorectal cancer and increased risk of endometrial, ovarian, gastric, pancreatic and biliary tract cancers. Unlike HBOC, HNPCC has a standardised clinical definition, termed the Amsterdam II criteria. These criteria include: three or more relatives with colorectal or other Lynch-associated cancer, one of whom is a first-degree relative to one of the other two; affected members in at least two generations; at least one Lynch-associated diagnosis in the family prior to age 50 and exclusion of a diagnosis of familial adenomatous polyposis.[14]

Factors with Adequate Evidence of Increased Risk

Menopause Hormone Therapy: Current postmenopausal HT is modestly linked to higher ovarian cancer risk, especially estrogen-only formulations. Continuous use of estrogen-progesterone therapy (EPRT) was associated with a risk comparable to that of sequential use. Subgroup analysis showed that both estrogen replacement treatment (ERT) and EPRT had minor risks; additionally, serous ovarian cancer appeared to be more susceptible than other pathological types.[15] The Million Women Study (relative risk -1.20) and meta-analysis of studies found increased risks with longer durations of use. Risk declines after stopping.[16] One large trial, the Women's Health Initiative (WHI), showed a non-significant increased risk (hazard ratio 1.58).

Estimated excess risk: 1 extra case per 1,000 users after 5 years.[16]

Talc Exposure: In the 1960s, a link between talc and ovarian cancer was suggested by observations that some talc powders contained asbestos and that intraperitoneally administered asbestos in animals transformed the single layer of the ovarian surface into a multilayered one with abnormal cells.[17,18] Studies on talc exposure and ovarian cancer show mixed, often contradictory results. A large, pooled analysis showed a modest increased risk with perineal talc

use (odds ratio 1.24), but no dose-response was seen. The International Agency for Research on Cancer (IARC) classifies talc as a "possible carcinogen." Another retrospective study showed that risks for epithelial ovarian cancer from genital talc use vary by histologic subtype, menopausal status at diagnosis, hormone therapy use, weight, and smoking.[19]

Obesity, Weight Gain, and Height: Excess body weight may play a role in the aetiology of ovarian cancer. A recent meta-analysis reported a 16% increased risk of ovarian cancer for adult overweight (body mass index (BMI) 25–29.9 kg/m 2) and a 30% increased risk for adult obesity (BMI ≥30 kg/m 2) when compared with normal weight (18.5–24.9 kg/m 2).[20] It has been hypothesised that in postmenopausal women, adiposity enhances ovarian cancer risk partly through the mitogenic effects of excess endogenous estrogens synthesised in the adipose tissue via aromatisation of androgens.[21] According to this hypothesis, this association may be seen in women who do not use MHT.[21]

Smoking: Smoking, particularly current smoking, doubles the risk of developing mucinous ovarian cancer, a specific subtype of the disease. While overall risk for all types is only slightly increased, smoking is strongly associated with borderline and invasive mucinous ovarian tumours, though it may not increase risk for other types. Meta-analysis of several epidemiological studies has shown that overall ovarian cancer incidence was only slightly increased in current smokers compared with women who had never smoked (RR 1.06, 95% confidence interval [CI] 1.01–1.11, p = 0.01).22 A pooled analysis of 21 case-control studies has shown that current cigarette smoking increased the risk of invasive mucinous (OR = 1.31; 95% CI: 1.03–1.65) and borderline mucinous ovarian tumours (OR = 1.83; 95% CI: 1.39–2.41), while former smoking increased the risk of borderline serous ovarian tumours (OR = 1.30; 95% CI: 1.12–1.50).[23]

Factors with Adequate Evidence of Decreased Risk

Oral Contraceptives Pills: The protective effect of OC pills against ovarian cancer is inversely related. Women who have ever used OCPs have a 30% to 50% lower risk of ovarian cancer than women who have never used OCPs.[24] This protection has been found to increase with the length of time OCPs are used and to continue for up to 30 years after a woman stops using OCPs.[25] A reduction in ovarian cancer risk with the use of OCPs is also seen among women who carry a harmful mutation in the BRCA1 or BRCA2 gene.[26] A systematic review and meta-analysis of 67 studies has shown a statistically significant inverse relationship between duration of use, 61-120 months, 0.62 [95% CI: 0.48, 0.81] and more than 120 months, 0.51 [95% CI: 0.32, 0.80] and ovarian cancer. For the relationship between OCPs and histological subtype of epithelial ovarian cancer in the cohort studies, the pooled RR for invasive was 0.70 [95% CI: 0.56, 0.87], but no association between OCPs and borderline ovarian cancer, 0.64 [95% CI: 0.31, 1.31].[27]

Depot Medroxyprogesterone Acetate (DMPA): Ever use of DMPA was associated with a 35% decreased risk overall (OR = 0.65, 95% CI 0.50–0.85). There was a statistically significant trend of decreasing risk with increasing duration of use (p-trend < 0.001).[28] The results of a multicentre case control study showed that the use of DMPA was found to be associated with a 39% reduction in the risk of EOC with an OR of 0.61 and a 95% CI of 0.44-0.85 (P = 0.002). A significant risk reduction (83%) was observed with DMPA use for >3 years (OR 0.17; 95% CI 0.07-0.39; P < 0.001).[29]

Tubal Ligation: Meta-analyses of observational epidemiological studies have consistently found that tubal ligation (also known as sterilisation, in which the fallopian tubes are clipped, cut, or tied) is associated with an overall reduced risk of ovarian cancer.[30] A few studies investigated the relationship between tubal ligation and the histological subtype of EOC. The results of a Danish study showed that compared with serous ovarian cancer, the protective effect of tubal ligation was significantly larger for endometrioid ovarian cancer (p = 0.047) and epithelial ovarian cancer of "other" histology (p = 0.018), whereas the effect of tubal ligation for clear cell tumours did not differ significantly from that for serous tumours (p =0.880). Lastly, the overall risk of tubal ligation associated with the risk of mucinous ovarian cancer seemed to be larger compared with the OR associated with serous ovarian cancer (p = 0.052) (data not shown).[31]

Breastfeeding: Breastfeeding is found to be inversely associated with the risk of ovarian cancer, and long-term breastfeeding has demonstrated a stronger protective effect. The results of 5 prospective and 30 case-control studies showed that the pooled RR for ever compared with never breastfeeding was 0.76 (95% CI: 0.69, 0.83), with moderate heterogeneity (Q = 69.4, P < 0.001, I 2 = 55.3%). Risk of EOC decreased by 8% for every 5-month increase in the duration of breastfeeding (RR: 0.92; 95% CI: 0.90, 0.95). The risk reduction was similar for borderline and invasive EOC and was consistent within case-control and cohort studies.[32]

Risk-Reducing Surgery: Risk-reducing surgeries hav come into practice with the understanding of the tubal origin of ovarian cancers. Opportunistic salpingectomy at the time of hysterectomy in the general population can reduce the risk of ovarian cancer by 45% to 50%. Existing evidence demonstrates that opportunistic salpingectomy is

significantly associated with a lower risk of developing tubo-ovarian carcinoma. Clinicians should include this prevention intervention in preoperative counselling of eligible women.[33] Women who are at higher risk for ovarian cancer need risk-reducing bilateral salpingo-oophorectomy (BSO) over salpingectomy. Prophylactic BSO is recommended at ages 35-40, and once childbearing is complete, for all women with Hereditary Breast and/or Ovarian Cancer Syndrome. The benefits of prophylactic BSO for women at increased genetic risk are clear. A meta-analysis that included 10 studies demonstrates that prophylactic removal of the fallopian tubes and ovaries reduces the future risk of ovarian cancer in high-risk women by > 80%.[34]

Areas of Uncertainty

Fertility Treatments (In Vitro Fertilisation [IVF]/Ovarian Hyperstimulation):The evidence for increased risk of ovarian cancers with fertility treatments is inconclusive. Results from earlier studies indicated that women who remained nulligravid after fertility treatment may be at increased risk for ovarian cancer, and also that fertility drugs may preferentially increase the risk of borderline ovarian tumours.[35] Studies with a small sample size did not show any significant increased risk of ovarian cancer. However, other studies with a large sample size in this field clearly show the risk of developing ovarian cysts and ovarian cancer. The drugs used for ovulation induction can hyper-stimulate the ovary, increasing ovarian cyst formation and risk of ovarian cancer.[36]

SCREENING

Screening and primary prevention of ovarian cancer remain difficult because its aetiology is poorly understood, and symptoms appear late.

Low-Risk Group: There are no ovarian cancer screening recommendations for the general population. Screening in the general population is a challenge. A United Kingdom Collaborative trial on Ovarian Cancer screening in the General Population was done in postmenopausal women aged 50 to 74 years with intact ovaries and no history of ovarian cancer. Women had either multimodal screening (MMS) using a longitudinal cancer antigen 125 (CA 125) algorithm with repeat CA 125 testing and transvaginal scan (TVS) as a second-line test or using TVS alone with repeat scan to confirm any abnormality. The control (C) group had no screening. The results showed that in the MMS group, the incidence of stage I/II disease was 39.2% (95% CI 16.1 to 66.9) higher and stage III/IV 10.2% (95% CI -21.3 to 2.4) lower. There was no difference in stage in the USS group. There was no significant reduction in ovarian and tubal cancer deaths in either the MMS (p = 0.580) or USS (p = 0.360) groups compared to the C group. This study concluded that these strategies should not be used for screening in the general population.[37] The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomised Controlled Trial done in the United States also showed that simultaneous screening with CA 125 and TVS compared with usual care did not reduce ovarian cancer mortality. Diagnostic evaluation following a false-positive screening test result was associated with complications.[38]

High-Risk Group: Women with the following risk factors fall into the high-risk group

- *Genetic Mutations:* Inherited mutations in BRCA1 or BRCA2 genes are the most significant factor, with up to 50% of BRCA1 carriers developing breast or ovarian cancer by age 70. Lynch syndrome also increases risk.
- *Family History:* A first-degree relative (mother, daughter, sister) with ovarian cancer, especially if multiple relatives or multiple generations are affected.
- *Genetic Mutations:* Inherited mutations in BRCA1 or BRCA2 genes are the most significant factor, with up to 50% of BRCA1 carriers developing breast or ovarian cancer by age 70. Lynch syndrome also increases risk.
- *Family History:* A first-degree relative (mother, daughter, sister) with ovarian cancer, especially if multiple relatives or multiple generations are affected.
- *Ashkenazi Jewish Ancestry:* This population has a higher prevalence of mutations in BRCA1 and BRCA2.
- *Age:* Risk increases with age, particularly in women over 55-60.
- *Reproductive/Hormonal History:* Never having been pregnant, having children later in life, early menstruation (before age 12), late menopause (after age 55), or never having used oral contraceptives.
- *Medical Conditions:* Endometriosis is strongly associated with specific types of ovarian cancer (clear cell and endometrioid).
- *Lifestyle:* Being overweight or obese, especially post-menopause.

- *Hormone Therapy (HT):* Postmenopausal estrogen-only therapy

Genetic Testing

This is recommended to determine whether women carry BRCA1/2 mutations. The following groups of women can undergo genetic counselling followed by genetic testing. The first person tested in the family should be someone who has had breast, ovarian, or another BRCA-related cancer. If that person tests positive, all her first- and second-degree relatives are counselled regarding genetic testing.

- A strong family health history of breast and ovarian cancers.
- A moderate family health history of breast and ovarian cancers, and are of Ashkenazi or Eastern European Jewish ancestry.
- A personal history of breast cancer and meet certain criteria related to age of diagnosis, type of cancer, presence of certain other cancers or cancer in both breasts, ancestry, and family health history.
- A personal history of ovarian, fallopian tube, or primary peritoneal cancer.
- A known mutation in the breast cancer (BRCA) genes in someone in your family.

Screening for High-Risk Groups: The following three screening strategies are being evaluated in various studies.[39]

- An ultrasound approach based on primary screening with TVS ,with repeat testing after a fixed time interval if an abnormality is detected.
- Multimodal screening, which incorporates primary screening with a tumour marker, usually CA 125, with repeat marker assessment and TVS as second-line tests.
- CA 125 results are interpreted using the Risk of Cancer algorithm. This third combined approach uses both serum CA 125 and TVS as girst-line tests to maximise the detection rate, and its use is limited to screening the high-risk population.

Normal Risk Ovarian Cancer Screening Study (NROSS): Development of Risk of Ovarian Cancer Algorithm (ROCA) and ROCA screening trials: Serial CA 125 levels estimation in the previous trials showed that each woman has her own baseline level, and in ovarian cancer cases, CA 125 rose rapidly from her baseline following a change-point. Improved early detection of ovarian cancer may result if each woman were tested for the presence of a change-point CA 125 profile. Using the serial CA 125 from the completed trials, a statistical method was developed to measure the probability that a change-point had occurred. Subsequent screening trials implemented the risk of ovarian cancer algorithm (ROCA), in which screening decisions are made based on the risk of having a change-point. Serum CA 125 was analysed with the Risk of Ovarian Cancer Algorithm (ROCA) each year. If risk was unchanged and < 1:2,000, women returned in a year. If the risk exceeded 1:500, TVS was undertaken immediately; if the risk was intermediate, CA 125 was repeated in 3 months; and if the risk exceeded 1:500, referral for TVS was prompted. An average of 2% of participants were referred to TVS annually.

Thirty-four patients were referred for operations, detecting 15 ovarian cancers and two borderline tumours, with 12 in the early stage (stage I/II). As four ovarian cancers and two borderline tumours were diagnosed with a normal ROCA, the sensitivity for detecting ovarian and borderline cancer was 74% (17 of 23), and 70% of ROCA-detected cases (12 of 17) were in stage I/II. NROSS screening reduced late-stage (stage III/IV) disease by 34% compared with United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) controls and by 30% compared with US Surveillance, Epidemiology, and End Results (SEER) values. The positive predictive value (PPV) was 50% (17 of 34) for detecting ovarian cancer.[40]

Tumour Markers and Proteomics for Screening

Serum CA 125: It is a glycoprotein, and it is found to be elevated in 80% of advanced ovarian cancer cases, especially serous tumours.[41] Serum CA 125 levels correlate with both disease stage and response to chemotherapy, suggesting that CA 125 may be useful as a marker of disease progression and a prognostic biomarker. Because it is elevated in many benign conditions, CA 125 alone is not useful for screening.

Human Epididymis Protein 4 (He4): It is also a tumour marker used in the management of EOCs. Compared with CA 125, HE4 has a similar sensitivity for detecting late-stage OC but a higher specificity for distinguishing malignant from

benign tumours.[42] As with CA 125, elevated serum HE4 levels are not unique to women with ovarian tumours and are found in individuals with tumours of gynaecological and pulmonary origin.[43]

Proteomics: Proteomics help identify protein patterns and biomarkers in blood or cervicovaginal fluids,

offering higher sensitivity than CA 125 alone for ovarian cancer screening. Artificial Intelligence (AI)-powered, mass spectrometry-based blood tests show > 90% accuracy in early detection. Proteomic approaches are now widely employed across multiple areas of ovarian cancer research: characterising disease mechanisms, screening for disease markers in tumour tissue and body fluids, and identifying causes of chemotherapy resistance.[44] Currently, no biomarker-based strategy is available for screening high-risk women.

WOMEN WITH ADNEXAL MASS ON ROUTINE SCAN

Tumour Markers and Proteomics for Screening

RMI combines age, ultrasound examination score, menopausal status, and serum CA 125 level to discriminate between benign and malignant masses. It combines serum CA 125 levels, TVS findings,(U) and menopausal status (M) to determine a score. These three criteria are combined into RMI risk. RMI = U × M × serum CA 125, where U = Ultrasound of 1 for imaging score 0–1 and U = 3 for an imaging score of 2–5; M = Menopausal status, M = 1 if pre-M and M = 3 if post-M. The cut-off point is 200. [45] This index was found to be statistically effective to discriminate between cancer and benign lesions. Using an RMI cut-off level of 200, the sensitivity was 85%, and the specificity was 97%. Patients with an RMI score above 200 had, on average, 42 times the baseline risk of cancer and those with a lower value 0.15 times the baseline risk.[46]

International Ovarian Tumor Analysis (IOTA) Adnexal Mass Classification

In 2008, the IOTA group proposed simple ultrasound rules for the diagnosis of ovarian cancer. These rules are based on demonstration of certain sonographic findings, indicative of benignity (B features) and some of which are suggestive of malignancy (M features).[47]

Classifications	Maligation Characteristics
M1	Irregular solid tumor
M2	Presence of ascites
M3	At least 4 papillary st solidructures tumor with largest diameter ≥100 mm
M4	Regular multilocular
M5	High Doppler blood flow (color score 4)
	Benign Characteristics
B1	Unilocular
B2	Presence of solid components with largest component < 7 mm
B3	Presence of acoustic shadows
B4	Smooth multilocular tumor with largest diameter < 100 mm
B5	No Doppler blood flow (color score 1)

IOTA Simple Rules Model

Several studies looked into the usefulness of the IOTA model for evaluating adnexal masses. Indian studies showed that IOTA's simple rules provide excellent discrimination between benign and malignant adnexal masses.[48,49]

ADNEX Model

The IOTA group proposed the Assessment of Different NEoplasias in the adneXa (ADNEX) model. This is the first risk model to differentiate between benign, borderline tumours, stage I invasive, stage II/IV invasive ovarian cancer and secondary metastatic cancer. The ADNEX model was developed and validated using data from the IOTA phase 1-3 datasets, consisting of prospectively collected patients who were referred for an ultrasound examination to one of the participating centres for a known or a suspected adnexal mass. The ADNEX model consists of three clinical predictors and six ultrasound predictors. The clinical predictors are age (years), serum CA 125 (U/mL) and type of centre to which the patient has been referred for ultrasound examination. Type of centre has been divided into oncology centres versus other hospitals and is further discussed in the next section. The ultrasound predictors are the maximal diameter of the lesion (mm), proportion of solid tissue (%), number of papillary projections (0, 1, 2, 3, > 3), presence of more than 10 cyst locules (yes/no), acoustic shadows (yes/no), and presence of ascites (yes/no). The proportion of solid tissue is defined as the ratio of the maximal diameter of the largest solid component and the maximal diameter of the lesion. There is no single fixed approach to use this model, and the risk estimates need to be individualised to the patient care.[50]

OVA1 and OVERA Tests

The OVA1 test is approved by the FDA (Food and Drug Administration). It is a qualitative serum test that combines the results of five immunoassays (CA 125 and apolipoprotein A1, transthyretin, transferrin, and β2-microglobulin) into a single numerical score for women with an ovarian adnexal mass who are undergoing surgery. It helps assess the likelihood of malignancy further when an independent clinical and radiological assessment does not indicate malignancy.[51] In 2016, the FDA approved the Ova1 (OVERA) test, which includes CA 125-II, HE4, apolipoprotein A-1, follicle-stimulating hormone (FSH), and transferrin (sensitivity 91% and specificity 69%), as a reference or screening test for patients presenting with ovarian masses.[52]

SYMPTOMATIC WOMEN

Symptoms: Ovarian cancer is not entirely "silent." Studies show 75% of early-stage patients reported symptoms, often misattributed to ageing or menopause. The key symptoms attributed to ovarian cancer are:

- Persistent bloating or distension
- Early satiety/loss of appetite
- Abdominal/pelvic pain
- Urinary urgency/frequency
- Fatigue, bowel habit changes, unexplained weight loss

Awareness may aid earlier detection, though its impact on mortality is unproven. Persistent abdominal/pelvic pain, bloating, early satiety, urinary frequency, fatigue, weight loss, or bowel changes should raise suspicion.

Investigations: Good history and clinical examination are essential. The investigations are tailored according to the clinical situation. In addition to regular haematological and biochemical tests, tumour markers like serum CA 125, carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (β-hCG), lactate dehydrogenase (LDH), and inhibin can be done according to the clinical indication. A good ultrasound examination with IOTA or RMI will help to differentiate between benign and malignant masses. When indicated, other imaging modalities can be used. The presence of free fluid or extra-ovarian deposits warrants cytology and biopsy to establish the diagnosis.

PREVENTION

Chemoprevention: Oral contraceptive use is associated with a 30% to 50% decreased risk of developing ovarian cancer. However, there is a short-term increased risk of developing breast cancer and cervical cancer that should be considered when counselling patients.[25-27]

Prophylactic Surgery: Risk-reducing surgeries have come into practice with the understanding of the tubal origin of ovarian cancers. Opportunistic salpingectomy at the time of hysterectomy in the general population can reduce the risk of ovarian cancer by 45% to 50%. Women who are at higher risk for ovarian cancer need risk-reducing BSO over salpingectomy. The benefits of prophylactic BSO for women at increased genetic risk are clear. A meta-analysis that included 10 studies demonstrates that prophylactic removal of the fallopian tubes and ovaries reduces the future risk of ovarian cancer in high-risk women by > 80%.32 Prophylactic BSO is recommended at ages 35-40, and once childbearing is complete, for all women with Hereditary Breast and/or Ovarian Cancer Syndrome.[33]

Effect of Menopausal Hormone Therapy on Ovarian Cancer

MHT has been associated with an increased risk of endometrial, breast, and ovarian cancers, with the magnitude of risk influenced by the type of hormones used and the duration of therapy.[53] Evidence from a large meta-analysis indicates a small but statistically significant increase in ovarian cancer risk among MHT users, including those receiving both estrogen-only therapy (ET) and combined estrogen–progestin therapy (EPT).[54] An elevated risk has been observed even among current users with less than 5 years of use.[55] Earlier evidence suggested that ovarian cancer risk was primarily associated with estrogen-only therapy, and that continuous progestin use might mitigate estrogen-induced carcinogenic effects.[56] However, findings from the Women's Health Initiative reported a possible increase in ovarian cancer risk with combined estrogen–progestin therapy (hazard ratio 1.58; 95% CI 0.77–3.24), although this estimate was not statistically significant.[57] In contrast, several retrospective studies have not demonstrated a significant association.

The absolute increase in ovarian cancer risk with MHT remains small. For women initiating MHT at around 50 years of age, the estimated excess risk is approximately 1 additional case per 1000 users after 5 years of therapy.[58] Because baseline ovarian cancer risk increases with age, the absolute excess is slightly higher in older women, with an estimated increase of approximately 0.44 per 1000 women over 5 years in those aged 50–54 years, and about 0.78 per 1000 women over 5 years in those aged 55–59 years.[58] Women with BRCA1/2 may also be considered for short-term MHT use, as case–control data have not shown a significant increase in ovarian cancer risk in this population (odds ratio 0.93; 95% CI 0.56–1.56; P = 0.79).[59]

By analysing data from all prospective and retrospective studies, the following conclusions can be drawn about the use of MHT and ovarian cancer risk.[58]

- The link between MHT and ovarian cancer remains unproven.
- The principal indication for MHT use is alleviation of menopausal symptoms.
- Each woman should discuss her own individual risk factors before commencing or continuing MHT.
- Current evidence regarding MHT and ovarian cancer risk does not suggest a need for any change in clinical practice.

Role of Hormone Therapy in Ovarian Cancer Survivors

There is an increasing understanding of the nuances of tumour behaviour across tumour histological subtypes, so advice regarding HT use following cancer treatment has become more targeted.[60] A few prospective studies showed no difference in overall survival between patients with borderline tumours and those with epithelial cancers who used HT before diagnosis. The data also suggested improved survival in epithelial ovarian cancer patients who used HT after diagnosis.[61] A meta-analysis by Li et al. of two randomised controlled trials and four cohort studies also suggested that HT has a favourable impact on overall survival in patients with epithelial ovarian cancer and was not associated with an increased risk of recurrence.[62] Another meta-analysis of 6 studies has shown similar results.[63]

A recent prospective cohort study in Australia found that pre-diagnosis HT use was associated with improved survival, particularly in high-grade serous carcinomas (HGSC). Among women ≤ 55 years, use of MHT following treatment was not associated with poorer survival for HGSC.[64] HT can be offered to ovarian cancer survivors if they are troubled by menopausal symptoms.

SYNOPSIS

- Ovarian cancer remains the deadliest gynaecological malignancy in developed nations, and the poor prognosis is largely attributable to the late stage at diagnosis for the majority of patients.
- There are no guidelines to screen asymptomatic women at average risk for the disease. For high-risk women, several screening protocols are being evaluated.
- Advances in the analysis of known serum tumour markers, as well as in techniques for discovering novel markers, will surely impact future screening strategies.
- Peri- and post-menopausal women presenting with vague symptoms mentioned above need to be evaluated without any delay. A thorough clinical examination followed by an ultrasound examination of the abdomen and pelvis, along with tumour markers, are the minimum investigations.
- With the available evidence, MHT can be prescribed to women as an increase in ovarian cancer risk is not significant in low-risk women.
- MHT usage does not have any adverse effects on ovarian cancer survivors.

VULVAR CANCER

INTRODUCTION

Vulvar cancer is a rare malignancy accounting for only 4% of all gynaecological malignancies. It is commonly seen in postmenopausal women.

Incidence: According to cancer registries' data, globally, in 2020, about 45,000 cases of vulvar cancer were diagnosed. 65 In India, carcinoma of the vulva ranks 33rd in number, accounting for 0.26% of new cases and 0.02% of deaths from all sites.[66]

Risk Factors: Major Indian risk factors include HPV infection, chronic vulvar dermatoses (particularly lichen sclerosus), diabetes, obesity, poor genital hygiene, and tobacco use (Grade B).[67]

MHT and Vulval Cancer: The majority of vulval cancers are squamous cell carcinomas and are not hormone dependent. Although data are limited, MHT use does not appear to alter prognosis in vulval cancer and can be used if required. Paget's disease of the vulva is a rare form of neoplasm in the vulval skin. It is most commonly diagnosed in postmenopausal women, and the primary treatment is usually surgery. MHT should be avoided in this cohort, as extramammary Paget's disease is associated with other malignancies and adenocarcinoma of the vulva.[68]

SYNOPSIS

- Vulvar cancer is a rare malignancy
- Major Indian risk factors include HPV infection, lichen sclerosus, diabetes, obesity, poor genital
- hygiene, and tobacco use
- MHT should be avoided in Paget's disease.

VULVAR CANCER

INTRODUCTION

Primary vaginal cancer is a rare cancer seen in only 1-2% of all female reproductive tract cancers. Primary vaginal cancer is strictly drgined as a disease of the vagina without evidence of cervical or vulvar cancer or a history of either within the past five years.[69]

Incidence: Globally, about 18,000 new cases were reported in 2020, and 8000 women died from the disease.[70] In India, it is a relatively rare cancer with an estimated crude incidence rate of 0.83/100,000 women. The incidence increases

with age, with approximately 50% of patients presenting at age 70 years or older and 20% at age 80 years or older.[71] Of these cancers, squamous cell carcinoma (SCC) is by far the most common.[72] The average age of diagnosis is 67 years.

Risk Factors: Invasive vaginal cancer has many risk factors similar to those of cervical cancer. These include early marriage, younger age at first intercourse, multiparity, persistent high-risk HPV infection, multiple sexual partners and use of tobacco.[73]

Pathogenesis and Pathology: Understanding the natural history of vaginal cancer is extrapolated from studies on vulval and cervical carcinomas. The pathogenesis of vaginal carcinoma is broadly divided into HPV-dependent and HPV-independent pathways.74 The HPV-dependent pathway is initiated by infection with high-risk HPV. HPV 16 is the commonest type seen in 70% of vaginal cancers.[75] It progresses from a low-grade squamous intraepithelial lesion (LSIL) to a high-grade squamous intraepithelial lesion (HSIL), and finally to HPV-dependent SCC. This pathway also shows an increased risk of vaginal carcinoma due to cigarette smoking and immunosuppression, like in human immunodeficiency virus (HIV).[76]

Prevention

HPV Vaccination: HPV vaccination, used as a primary prevention strategy against cervical cancer, has also been associated with a reduction in HPV-related non-cervical premalignant lesions, including vulvovaginal high-grade lesions among vaccinated women.[77] A Danish real-world effectiveness study demonstrated a reduced incidence of vaginal high-grade squamous intraepithelial lesions (HSIL) among vaccinated women aged 17–26 years compared with unvaccinated women (HR 0.30, 95% CI 0.13–0.68).[77] Long-term registry-based analyses have similarly shown declining trends in HPV-related cancers following the introduction of vaccination programs.[78]

Screening

There are no separate screening guidelines for vaginal cancer. Vaginal examination is typically performed alongside cervical evaluation, and cytology and HPV testing as part of cervical screening may aid in identifying vaginal disease. If either test is abnormal, careful evaluation of the vagina is undertaken during colposcopy.

There is no evidence to support routine vaginal vault cytology in women who have undergone hysterectomy for benign disease.[79,80] However, women who undergo hysterectomy for high-grade cervical precancer may require long-term vaginal vault surveillance based on risk-stratified follow-up recommendations.[31]

Treatment of Vaginal Pre-cancer

Biopsy-proven low-grade lesions (LSIL) can be followed up with regular screening and colposcopy. High-grade lesions, depending on their location and number, can be treated medically with Imiquimod or surgically with laser ablation or local excision.

Menopause Hormone Therapy and Vaginal Cancer

MHT does not increase the risk of vaginal cancer as it is not estrogen-dependent. It is considered safe to use in the setting of vaginal cancer, although it is not commonly required as most patients are diagnosed when postmenopausal.[81]

SYNOPSIS

- Primary vaginal cancer is a very rare malignancy of the female reproductive system.
- The crude incidence rate is 0.83/100,000 women
- The majority of vaginal cancers are HPV-dependent squamous cell carcinomas
- There are no screening recommendations for primary vaginal cancer
- Usually, the vagina is evaluated along with the cervix if cervical cytology or HPV test becomes positive

RESEARCH AGENDA

Comparative study of cervical, vulvar, and vaginal HSIL trends post HPV vaccination.

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