



2024, Volume 24, October, Issue 06 AOGD BULLETIN

Shared Decision Making - Enhancing Women Emancipation



Theme Menopause: Understanding & Embracing Menopause

AOGD SECRETARIAT

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AOGD Bulletin

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Publisher/Printer/Editor

Dr. Renuka Malik on Behalf of Association of Obstetricians & Gynaecologists of Delhi

Designed and Printed by

Krishers Publishing House, Mumbai

Published from

Department of Obstetrics & Gynaecology Maternity Nursing Home

ABVIMS & RML Hospital, New Delhi - 110001

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Message from the President



President

Dear AOGDians,

Namaskar,

True to our endeavours, many informative activities were organized in the preceding month. The PG Fiesta was conducted for the postgraduates, which witnessed a large number of participants. The subcommittees organized an anaemia detection camp and a webinar on oncology. We thank you all for your continuous support during all the events and look forward to your unwavering support and participation in our forthcoming 46th Annual Conference in the month of November 2024.

October, the month of festivities, is also celebrated as the **"World Menopausal Awareness Month"** to break the taboo surrounding menopause and improve women's health and well-being. Therefore, this month's Bulletin focuses on this topic of great relevance to every woman, since, on an average, one-third of her life is spent in the phase of menopause.

This AOGD issue is designed to give you a glimpse into the scope of clinical practice in this area of women's health. The goal is to enhance every gynaecologist's understanding of the ongoing changes and advancements in menopause management, ensuring they can adapt to the rapidly evolving needs of our menopausal patients.

Wish you all a very Happy Diwali!

Dr. Ashok Kumar MD, PhD, FICMCH, FICOG, FAMS President, AOGD Vice Chairperson, Elect, ICOG, an Academic Wing of FOGSI National Corresponding Editor, Journal of Obstetrics & Gynaecology of India Director Professor & Head Department of Obstetrics & Gynecology, Atal Bihari Vajpayee Institute of Medical Sciences & Dr. Ram Manohar Lohia Hospital, New Delhi

Message from the Hon. Secretary



Hon. Secretary

Dear AOGD members,

Warm greetings to all from AOGD secretariat at ABVIMS & Dr RML Hospital.

As we proceed towards the second half of our annual tenure, we want to convey our gratitude to all AOGD members for constant support and encouragement. Our attention now is focussed on the annual conference. The details regarding workshops, free communication and competition papers is available on website. A quiz is also planned for the resident students. It will be a great academic bonanza for all. We hope to see all of you in large numbers.

Last month was another active month with lot of academic activities, public forums as well as online campaigns. The preceding issue of monthly bulletin saw an overwhelming response, thankful to all. Menopause is an important landmark in a woman's life. Concerns during this period are varied and we as gynaecologist need to be aware of the pathologies as well as developments in this field. The current issue attempts to raise awareness about menopause so that it can be embraced gracefully by all.

We also bid final adieu to one of the most precious jewels of the country Mr Ratan Naval Tata. Taking inspiration from his life lets strive to keep moving forward taking the entire fraternity along. You will be missed sir!

It is a sincere wish from all aogdians that the Abhaya case is solved and closed soon, the doctors are able to join their duties and work without fear.

October is the month of festivities and we pray to almighty for a healthy and peaceful world. Wishing everyone a month full of happiness and brightness! May the truth always prevail and the goodness inside us may always defeat the evils!!



Left to Right: Dr. Vandana Agarwal, Dr. Neha Pruthi Tandon, Dr. Kamna Dutta and Dr. Geetanjali Nabiyal

EVENTS HELD IN THE MONTH OF SEPTEMBER

1st September 2024

PG Academic Fiesta: ABVIMS & Dr RML Hospital, Mini Auditorium LHMC







9th September 2024 Three Health camps under Rashtriya Poshan Maah program - Community Health and public awareness Subcommittee

- Health talk on Anaemia conducted at Nulife Hospital
- Haemoglobin detection camp done at Sai Polyclinic, New Ashok Nagar
- Awareness talk on Anaemia, Nutrition & HPV Vaccine for students, Apex School, Burari



AOGD stood in solidarity with FOGSI in seeking justice for ABHAYA. One month and the doctors were still counting days for justice.

A meeting at AIIMS to highlight the same along with importance of a safe work environment for females was conducted.



14th September 2024 Basics to Breakthrough in Gynae Oncology: series 2 Endometrial Cancer- Max Institute Vaishali & AOGD



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14th September 2024 Awareness session on Preventing birth defects and cervical cancer- Community health and public awareness



15th September 2024

Silver Jubilee 25th Gynae Update - IMA Janakpuri under the aegis of AOGD







24th September 2024 SIMS Black Professorship 2024 - IRC RCOG in a/w AIIMS & AOGD



28th & 29th September 2024 Managing Committee Meeting at FOGSI Office, Mumbai



Dr Ashok Kumar, AOGD2024-25 President, spoke about AICOG 2026 preparation at the FOGSI MCM. Team Delhi was accompanied by next FOGSI President Dr Sunita Tandulwadkar (2025) and President Elect Dr Bhaskar Pal (2026).

Forthcoming Events "for the month of October"

- 8th Webinar on Role of MRI in Gynaecological Cancers by Oncology Subcommitee and Action Balaji Hospital
- 17th Quiz on menopause MENO-Q on the occasion of World menopause Day by ABVIMS & Dr RML Hospital
- 18th Video based CME & Hands on workshop (simulators) on Hysteroscopy at LHMC
- 22nd Visit to a government school- Community health and public awareness subcommittee
- 23rd Webinar by Infertility and Reproductive endocrinology committee
- 25th Monthly Meeting at DDU Hospital



AOGD IS PROUD OF YOU: DR NEERJA BHATLA

· Selected as Member of Indian delegation for launch of Quad Cancer Moonshot Program at Wilmington USA by PM Modi ji and Prez Biden for cancer control in Indo Pacific region with special focus on cervical cancer.

· Elected as Fellow of the Indian National Science Academy (INSA).



C N -	AWARDEES FROM	I DELHI
S.INO	Awards	Winners
L	Prize for the year 2024	Dr Jyotsna Snarma
2	FOGSI-Dr R D Pandit Research Prize 2024	Dr Aditi Agarwal 🛛 🤚
3	FOGSI-Dr D C Dutta prize 2024 for best	Text book on OSCE in Obstetrics &
	publication	Gynaecology
		Editors:
		Dr Hrishikesh D Pai,
-		Dr Laxmi Shrikhande,
10-		Dr Ashok Kumar,
		Dr Vandana Agarwal
1	FOGSI-Dr Kamini A. Rao orator for the year	North: Dr Neha Pruthi Tandon
	2024	21 7 1 1
5	FOGSI Movicol awards 2024	Senior: Winner: Dr Alpana Singh
		1st Runner up: Dr Neeta Singh
	51 4 1 4 1 1 1 4 F 1 4 1	19 N N N N N N N N N N N N N N N N N N N
		Junior :Winner: Dr. Kavita Khoiwal
5	FOGSI-Dr Shanti Yadav Award in Infertility	Winner :- Dr Vandana Agarwal
-	2024	2nd Runner Up :- Dr Akshita Jakhar
`	FOGSI - Dr Rajat Ray Award in Fetal Medicine 2024	1st Runner Up: Dr Avantika Gupta,
3	Winner of the best paper published in	(First Prize): Dr Arpita De
=6	FOGSI Journal during the year 2023 in Senior Category	(Second Prize): Dr Manisha Kumari
SP	RINGER AWARDS AND PRIZES - Journal of Ol	bstetrics and Gynaecology of India
	Best peer reviewer 2022	Dr Ashok Kumar
	congratul	otions
≿☆☆·	*****	***

From the Editors Desk



Chief Editor

Greetings from the Editorial desk!

As we go through the seasons of life, change is inevitable. Menopause is one such transition that marks a significant phase in a woman's journey. While it is a natural biological process, the symptoms—ranging from hot flashes and sleep disturbances to mood changes and bone health concerns—can sometimes feel overwhelming. Though often accompanied by physical and emotional challenges, it is essential to approach menopause with understanding, compassion, and empowerment. October being the menopause month we release the issue on menopause in this month. The theme this year of the international menopause society is

menopause hormonal therapy. We are aware of the effects of low levels of estrogen on the health of women as they age and the role of menopausal hormone therapy in the alleviation of menopausal symptoms and amelioration of the disease burden associated with prolonged hypoestrogenism. Hence, the issue for this month of the AOGD bulletin is directed specifically toward "Menopause: Understanding and Embracing Menopause".

World Menopause Day is marked each year on October 18th. The term "Menopause" was first coined in 1821 to describe the permanent cessation of menstruation, a phrase still used to define menopause today. It was another century before 'an ovarian hormone' was first described and, even then, remedies for the symptoms experienced by women during their transition from reproductive to post-reproductive life were based more on hope than on science. The age of hormone replacement therapy began just over 80 years ago with the initial goal being alleviation of associated symptoms. Large observational studies and randomized controlled trials [exploring the effects of menopause on wider aspects of midlife women's health, including mental, cardiovascular, musculoskeletal, and genitourinary health, and the effect of exogenous hormone therapy on those conditions followed and have led to the establishment of guidelines for the appropriate use of menopausal hormone therapy and the overall care of postmenopausal women.

The aim of this journal has always been to disseminate knowledge through comprehensive review articles. The current issue is no exception with review articles on varied aspects of menopause and MHT.

We would also like to thank all our respected authors for doing a wonderful job and some having submitted their articles so much in advance displaying terrific sincerity.

We stand in solidarity with the Bengal medical community following the tragic case of a female doctor's assault. Our thoughts are with the family and community as they seek justice. We support all efforts to ensure accountability and improve the safety and dignity of all healthcare professionals.

Happy reading! Dr (Prof) Renuka Malik Editor Professor and Senior Consultant ABVIMS & RML Hospital

Editorial Team- Dr PreetiSania, Dr KanikaKumari , Dr KavitaKumari, Dr Seema Sheokand, Dr NiharikaGuleria

THOUGHT FOR THE MONTH- Holding on to anger is like grasping a hot coal with the intent of throwing it at someone else; you are the one who gets burned.

""Healthy mother, healthy child, When the husband's role in planning is understood.""



For referral and facilitation, call any of these:

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Geriatric Care Special Needs Assessment - A Pandora's box

Ragini Agrawal

Director, A. A. Dermascience, Complete Clinic for Women Health, Gurugram

INTRODUCTION

Globally, the number of people aged 60 or over is set to rise from 841 million to more than 2 billion between 2013 and 2050; this equates to 21.1% of the world's population¹.

These demographic changes are largely due to the successful advances in public health and modern medicine but the challenge posed by cumulative demographic changes of such magnitude requires immediate action from multi-disciplinary teams to provide patient-centered and age-friendly health and social care.

COMPREHENSIVE GERIATRIC ASSESSMENT (CGA)

It is an iterative collaborative multidimensional framework and process of assessment used to assess people living with frailty. The goal of a CGA is to identify the geriatric person's needs and problems². CGA is considered the gold standard for managing frailty (Fig 1).



Figure 1: Comprehensive assessment of a gold standard for frailty

The main problems faced by middle-aged

1. Multimorbidity - These people often have complex, multiple, and interdependent problems which make their care more challenging than in younger people or those with just one medical problem.

2. Polypharmacy --Polypharmacy, defined as the concurrent use of at least 4–5 medications rises considerably as the number of health problems and healthcare service use increases.

Basic principles for Comprehensive geriatric assessment

CGA is considered the best way to evaluate the health status and care needs of older adults. The strength of the CGA lies in the fact it is a multidimensional holistic assessment of an older person that takes into consideration health and wellbeing.

As a result of the assessment

- 1. A problem list is created and a plan is created to address issues.
- 2. Emphasis on the plan improve quality of life and ability to cope for the individual. Particular importance is placed on what matters most to the patient

The CGA hallmarks (and differences from a standard evaluation) are:

- 1. Emphasizes:
- Quality Of Life
- Functional Status
- Prognosis
- Outcome entailing greater depth and breadth.
- 2. The employment of interdisciplinary teams and the use of any number of standardized instruments to evaluate aspects of patient functioning, impairments, and social support.

Geriatric assessment involves a comprehensive and coordinated approach to evaluating the physical, functional, and psychosocial aspects of elderly individuals, to develop an integrated care plan³ (Fig 2).



Figure 2: An integrated approach for formulating a plan

Various issues of Concern

Issues of concern in geriatric assessment are broadly divided into these four categories:

- 1. Functional Status
- 2. Physical Health
- Vision impairment
- Hearing loss
- Nutrition status
- Fall prevention
- Urinary Incontinence
- Osteoporosis and arthritis
- 3. Polypharmacy and Medication Reconciliation
- 4. Cognitive Assessment
- Dementia
- Sleep and insomnia
- Mood disorder

FUNCTIONAL STATUS

Assessing functional status involves evaluating an individual's capacity to perform activities necessary for independent living. It can be broadly divided into 2 levels (Fig: 3)⁴

- 1. Basic Activities of Daily Living (BADL)
- 2. Instrumental Activities of Daily Living (IADL)

Figure 3: Activities evaluating ability for independent work performance



instrumental activities of daily living (IADL)

 It includes activities to live independently such as taking medications, shopping, preparing meals, driving/using public transport, handling finances, doing household works, using telephone, etc.

Commonly used indices to assess such activities are the Katz index for BADL and the Lawton scale for IADL. Information about functional status can also be achieved by asking open-ended questions about their daily activities. Functional status is directly affected by physical health, so any change in functional status should prompt further evaluation.

Katz index for BADL

The Katz ADL Index (Katz, 1963) was first developed in an effort to find a way to assess function and how it changed over time in the elderly⁵.

It is an ordinal index designed to assess the physical functioning using a dichotomous rating (dependent/ independent) of six ADLs in hierarchical order of decreasing difficulty as listed:

- 1. Bathing
- 2. Dressing
- 3. Toileting
- 4. Transferring
- 5. Continence
- 6. Feeding

It is rated on a scale of independence. Scoring happens in two stages

- 1. First is translating the 3-point scale into a dichotomous scale using guidelines created by Katz.
- 2. Secondly the dichotomous scale is out of 6, where 6 is considered dependent in all ADLs and 0 is considered independent in all ADLs.

Most Katz ADL assessments combine the two stages by creating a guideline that gives specific descriptions.

Lawton Brody Instrumental Activities of Daily Living Scale (IADL)

The Lawton Instrumental Activities of Daily Living Scale (IADL) is an instrument developed to assess independent living skills (Lawton & Brody, 1969)⁶. These skills are considered more complex than the basic activities of daily living as assessed by the Katz Index of ADLs⁶. The instrument is considered useful for identifying how a person is functioning at present as well as detecting improvement or decline.

It differentiates among task performances including the amount of help and amount of time needed to accomplish each task. There are eight domains of function assessed with the Lawton IADL scale.

Women are scored on all areas of function, interestingly enough; historically men are assessed on five and exclude food preparation, housekeeping, and laundering

• There are eight domains of function assessed with the Lawton IADL scale.

• Women are scored on all areas of function, interestingly enough; historically men are assessed on five and exclude food preparation, housekeeping, and laundering

The Lawton IADL administration time is 10-15 minutes and is easy to administer.

 Table 1: Various levels of care evaluated to assess decline in functions

Basic Self Care	Intermediate Self Care	Complex Self Management
Toileting (ADL)	Bathing (ADL)	Handling Money (IADL)
Dressing (ADL)	Walking (ADL)	Phone USE (IADL)
Eating (ADL)	(House Work (IADL)	
Grooming (ADL)	Shopping (IADL)	
Transferring (IADL)	Meal Prep (IADL)	
	Walking Outside (IADL)	

"Complex Self Management" was indicative of decline in cognitive functioning

Various validated tools to measure functional ability:

- Vulnerable Elders Scale-13
- Clinical Frailty Scale
- Gait speed

As per one pooled analysis, the gait speed is associated with better survival for every 0.1 m/s increments.

CLINICAL FRAILTY SCALE

With the growing elderly population and the specific challenges associated with frailty, key questions for researchers include how to refine frailty measurement and effectively translate it into practical clinical tools and strategies. Clinical Frailty Scale is one popular tool.

A geriatric assessment should encompass a thorough medical history and physical examination, emphasizing elderly-specific concerns such as vision, hearing, nutrition, fall prevention, urinary incontinence, osteoporosis, and preventive health.

PREVENTATIVE HEALTH

It includes screening for diseases common in older age such as diabetes mellitus, hypertension, cancer, and other chronic conditions like COPD.

Early detection and treatment can be advantageous for conditions such as diabetes, hypertension, and certain malignancies. Since older patients often have multiple comorbidities that may reduce their lifespan, it is essential to consider the potential benefits of screening tests along with the patient's preferences for further evaluation and invasive procedures in case of a positive result before proceeding with screening. Vaccine-preventable infections such as influenza, pneumonia, herpes zoster, etc., represent major causes of morbidity and mortality in older patients (Table 2). Table 2: Vaccines routinely recommended for elderly patients.

Influenza Vaccine	Herpes Zoster Vaccine
Pneumococcal	Tetanus, Diptheria, & Acellular
Vaccine	Pertussis Vaccine

Depending on specific co-morbidities, an older patient may qualify for other vaccines as well.

Falls

Taking care of falls and fractures in the elderly are very important issue. Patients with a history of falls abnormal gait or difficult balance are at high risk and will benefit more from a multidisciplinary approach formulating individualized fall prevention strategies, that include the following:

- 1. Exercise Programs
- 2. Optimizing Medical Conditions
- 3. Discontinuing Medications Such as Benzodiazepine, Environmental Safety
- 4. Use Of Assistive Devices

URINARY INCONTINENCE (UI)

Many studies report the prevalence of urinary incontinence (UI) to be 25-45% and rises further with aging⁷. Older patients with urinary incontinence may withdraw from social activities, leading to isolation, a higher risk of depression, and functional disability. It can also increase the likelihood of falls and fractures, impact sexual health, and result in an overall decline in quality of life.

Primary evaluation of incontinence should include a noninvasive approach, mentioning the detailed medical history, fluid intake assessment, self-voiding diary, etc. Further complicated cases may require urodynamic studies.

Conservative treatments like behavioral adjustments, dietary changes, pelvic floor muscle exercises, scheduled voiding, and weight loss should be attempted initially. Additionally, several pharmacological therapies are available for managing urge incontinence. Devices like pessaries can be utilized for incontinence linked to pelvic organ prolapse, while surgical options, such as sling procedures and neuromodulation, may be considered for carefully selected patients with incontinence.

GSM is a chronic condition that can also lead to urinary symptoms. Can be treated with vaginal estrogen cream or laser rejuvenation.

OSTEOPOROSIS AND OSTEOPENIA

Osteoporosis and osteopenia are prevalent among the elderly, often resulting in fractures from minimal trauma. Age-related bone loss and menopause in women place older adults and postmenopausal women at a heightened risk for osteoporosis.

Preventive and screening measures for Osteoporosis

- Screening and diagnosis should be performed using dual-energy X-ray absorptiometry of the hip and/or spine. Given their higher risk, the USPSTF recommends routine osteoporosis screening for women over the age of 65.
- Calcium, vitamin D, and fall prevention are the major preventive measures in the elderly.

Osteoarthritis (OA) is a significant source of pain and disability among older adults. Approximately 50% of individuals will exhibit OA changes in their knees by age 65, and nearly everyone will have at least one joint affected by OA by age 75.

POLYPHARMACY

Polypharmacy in the elderly is because of multiple comorbidities, multiple hospitalizations and transition of care, self-medication, and cognitive decline in the elderly all contribute to polypharmacy.

Preventive strategies

- Conducting a comprehensive medication reconciliation at least once a year and following each transition of care is essential to determine whether the medications being used are truly necessary.
- Physicians can consult the American Geriatric Society's Beers Criteria, which identifies potentially inappropriate medications that should be avoided in the elderly.

Cognitive Assessment

- The prevalence of mild cognitive impairment (MCI) and dementia rises with age, with dementia affecting approximately 5% to 7% of older adults, while MCI is about four times more common than dementia⁸.
- Older patients are at a heightened risk of MCI and dementia due to their age, multiple comorbidities, and the factors mentioned above.
- Many of these older adults seek help from primary care providers due to concerns about memory issues.
- Early identification of these conditions can facilitate the determination of reversible causes, prompt appropriate pharmacological interventions, and assist patients and caregivers in planning for the future.

SCREENING OF DEMENTIA

Dementia and mild cognitive impairment (MCI) are underdiagnosed in community settings due to the lack of brief and suitable dementia screening tools available to general practitioners. Although routinely screening patients for cognitive impairment when they are over a certain age (e.g. 75 years) or with cognitive decline, is recommended. Validated tools to screen for cognitive declines.

- Mini-Mental State Exam (MMSE),
- Montreal Cognitive Assessment (MoCA) test
- Mini-Cog
- Clock Drawing Test (CDT)
- Ascertain Dementia 8 questionnaire (AD8)
- Characteristics of good tools
- Instruments that are simple and effective, with administration times of five minutes or less, appear to be the most suitable for dementia screening.
- An effective screening tool should not only be brief and unbiased but also demonstrate high sensitivity and specificity.

INSOMNIA (SLEEP DEBT)

Insomnia is commonly encountered presenting complaints in older patients. Quality of sleep decreases with aging. Poor sleep is associated with

- 1. Increased Fatigue
- 2. Falls
- 3. Nursing Home Placement
- 4. Poor Quality of Life

TYPES OF SLEEP DISORDERS

- A. Primary such as insomnia, restless leg syndrome, obstructive sleep apnea
- B. Secondary to comorbid medical, psychiatric, behavioral, environmental, or medication side effects.

Assessment of sleep disorder should include evaluation for secondary causes if any. Due to the increased side effects of hypnotics used, non-pharmacological interventions are the first line of treatment for insomnia. It includes:

- 1. Cognitive Behavioral Therapy
- 2. Education About Sleep Hygiene
- 3. Expected Changes in Aging
- 4. Stimulus Control
- 5. Decreased Daytime Sleep
- 6. Dietary Modifications

DEPRESSION

Nearly half of all depression cases begin at age 60 or above. Depression is linked to reduced cognitive abilities, impaired physical and social functioning, decreased self-care, and loss of independence. Older adults with depression have a higher mortality rate, partly due to the elevated suicide rate in this age group. When diagnosed early, treatment options include psychotherapy and antidepressant medications. The USPSTF recommends depression screening for all adults. The Patient Health Questionnaire (PHQ) 2 is a validated tool for initial depression screening; if the result is positive, it should be followed by PHQ 9 to confirm a diagnosis of depression in the elderly.

CONCLUSION

Global life expectancy has risen, leading to a growing population of older adults. The geriatric population has unique needs due to multiple comorbidities. This activity outlines the evaluation of different aspects of geriatric assessment and emphasizes the importance of the interprofessional team in managing older patients.

KEY POINTS

- 1) Due to the aging process, even a well-functioning older patient can deteriorate rapidly due to any one or combination of issues.
- 2) The emergence of new signs or symptoms in elderly patients may result from the adverse effects of medications. Therefore, medication reconciliation and the prevention of polypharmacy are crucial during every visit and at each transition of care.
- 3) Falls are a significant cause of disability and morbidity among older adults.
- 4) To avoid multi-morbidity complications specialized geriatric care clinics and specialists are a must. Physiotherapy plays a big role in the quality of life in the older population.
- 5) Proper nutrition, preventive health measures, safe medication practices, and surgical options such as knee replacement can greatly enhance the health of patients with osteoporosis and arthritis.
- 6) Urinary incontinence (UI), osteoporosis, and arthritis can all contribute to functional decline by restricting the mobility of older adults. Obtaining a detailed history is crucial for diagnosing the type of UI and delivering suitable treatment based on the specific UI type.

7) Utilizing various standardized tools can help reduce confusion and inconsistencies when assessing older patients. It is essential to address these issues on an ongoing basis during each clinic visit to enhance outcomes for this vulnerable population.

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AOGD Risk Management Support (ARMS) Group

One of the ways to ensure stress-free work environment and optimal patient care is mutual support among professional colleagues. An advisory group was set up last year so that they can be contacted if any of us is caught in a complex clinical dilemma/dealing with aggressive clients or is apprehensive about how to document or effectively troubleshoot a potential problem. The same group will continue to provide timely advice and is led by

Convener – Dr. Vijay Zutshi – 9818319110 Co-convener – Dr. Aruna Nigam – 9868656051

We invite suggestions from all members regarding functioning of this cell which will guide us forming the SOPs. Please mail to aogd.ucmsgtbh2023@gmail.com

Screening for Cancers in Menopause

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INTRODUCTION

Cancer and age have been found to be strongly interconnected in several studies. Menopause is a natural milestone in ageing and unless delayed beyond 55 years, does not increase the risk of gynecological cancers. With the rising incidence of cancers globally, newer and better methods of cancer screening have become the need of the hour, especially in our country, where we lack organized population-based cancer screening programs. In this article, we review the latest guidelines on screening for the two most common cancers affecting females, cervical cancer and breast cancer.

The World Cancer Day theme for 2024 is "Close the Care Gap". The theme aims to mobilize the necessary attention and resources to ensure that the rising burden of cancer can be addressed in an equal manner across the globe and that all people in the world have access to systematic testing, and early diagnosis and treatment.

Attempts at cancer screening should be directed to maximize cancer prevention and minimize harm from overtesting and overtreating. An ideal screening test should be sensitive, specific, acceptable, and cost-effective.

CHANGING LANDSCAPE OF CERVICAL CANCER

Availability of vaccination, public awareness campaigns regarding the same, socio-political will to include these vaccines in immunization programs, 90-70-90 target by the World Health Organisation (WHO)¹ have all played a big role in reducing the burden of cervical cancer globally.

One fifth of the global burden of cervical cancer is in India² (Globacon 2022). A multipronged approach towards cervical cancer has been advocated. This includes prevention strategies, screening algorithms (to detect precancerous stages), triage of screen positives (using a different test than the screening test), and in remote areas, see and treat policy in the same sitting.

PREVENTION STRATEGIES

The persistence of the high-risk genotype of Human papillomavirus (HPV) infection is causative of cervical cancer. The mainstay for the prevention of cervical cancer is vaccination against HPV high-risk strains. Vaccination has no role in menopausal women. This vaccine is most protective when given before the first sexual contact.

Primary HPV testing is a more rational approach to the screening of women after vaccination³.

SCREENING PROTOCOLS

The main goal of screening is the prevention of cervical cancer through detection and treatment at the precancer stage. In a good resource setting, primary HPV Deoxyribonucleic Acid (DNA) testing (every 5 years) cytology (every 3 years), or Co-testing with HPV DNA and cytology (every 5 years) can be used. Women aged 50–65 years, who have never been screened should be prioritized. Once a woman is 65 years old, screening can be stopped if she has consistently negative results in the last 15 years. If she has never been tested, she should be screened and can exit screening if tests are negative.⁴ One must be aware of the physiological changes of atrophic vaginitis in this age group which may preclude taking cervical smears.

Likewise, VIA (visual inspection with acetic acid) is recommended as a good option for low-resource settings.⁵ VIA test in menopausal women may, however, be unreliable and unsatisfactory because of mucosal atrophy and squamocolumnar junction receding into the endocervical canal. Screening by co-testing with cervical cytology and high-risk HPV DNA test, at least once, would be the minimum ideal in this age group.

AVAILABLE ALGORITHMS

In the "Screen-and-treat approach", the decision to treat is based on a positive primary screening test. Women can undergo treatment in the same sitting with ablative methods provided criteria for ablative techniques are met.⁶ "Screen-

see-and-treat" methodologies need a colposcope. "Screentriage-see-treat" helps to detect patients at the highest risk. The triage tools suggested by FOGSI are cytology or VIA (if HPV DNA was used as primary test) and if primary test is cytology, then HPV DNA test, HPV genotyping-16/18, colposcopy +/- biopsy, VIA +/- biopsy from any abnormal area or newer modalities (p16, Ki 67 testing, mRNA testing, E6/E7 protein testing) can be used. The choice of triage method depends on feasibility, training, program quality assurance, and resources.

Colposcopy and biopsy are indicated if primary and triage tests, both come positive which means HPV DNA positive along with either cytology > ASC-US (Atypical Cells of Unknown Significance), VIA positive, or HPV genotyping for high-risk types 16/18 is positive. Patients with persistent ASCUS or higher lesions beyond one year despite being HPV negative, poorly compliant patients, patients from remote areas, or unlikely to return for followup should also undergo colposcopy. Many women are likely to be on hormone therapy which raises the incidence of invasive cancers. Untargeted biopsies of the cervix are not recommended if colposcopy reveals no acetowhite area, metaplasia, or other visible abnormality, with a fully visualized squamocolumnar junction.

Figure 1: FOGSI GCPR (good clinical practice recommendations) screening of women >30 years with primary HPV testing



Figure 2: FOGSI GCPR (good clinical practice recommendations) screening of women >30 years with Co-testing



Unsatisfactory cytology is quite common in the postmenopausal age group due to the receding in of the

squamocolumnar junction. Two successive such reports qualify for colposcopy. However, for the same reason, colposcopy can also pose a problem. Estrogen treatment (Estrogen cream application intravaginally each evening for 4 weeks and stopped 1 week before repeat cytology) will cause enough ectropion of the endocervical cells to result in a satisfactory examination. It is therefore recommended to judiciously use screening tests and to use endocervical curettage at the time of colposcopy in such patients. Diagnostic conization may be an effective option.

THERAPEUTIC MEASURES

Based on the results of screening, the therapeutic measures used can be ablative (cryotherapy, laser ablation or thermoablation) or excisional procedures for high grade abnormalities; Loop Electrosurgical Excision Procedure (LEEP) /Large Loop Excision of the Transformation Zone (LLETZ), cold knife cone or laser cone biopsy). LEEP has the benefit of providing tissue for histologic examination. WHO has set down criteria for eligibility for Screen-andtreat (Ablative Procedures)⁶

- 1. The Transformation Zone is visible
- 2. Lesions should be entirely visible and occupy not more than two quadrants of the cervix.
- 3. Entire lesion should be located on the ectocervix without any vaginal and/or endocervical extension.
- 4. Lesion can be adequately covered by the largest cryotherapy probe available (Multiple overlapping applications with thermocoagulation).
- 5. There is no suspicion of invasive cancer or glandular disease (adenocarcinoma in situ).

Screen-and-treat by cryotherapy is contraindicated in cases of postcoital or postmenopausal bleeding, obvious cervical growth, irregular surface, or bleeds on touch.

N.B. Biopsy can be taken before ablation, if feasible, for posthoc correlation

PARADIGM SHIFT-EQUAL MANAGEMENT FOR EQUAL RISK

ASCCP (American Society of Colposcopy and Cervical Pathology) Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors, 2019⁷ have suggested that recommendations be based on risk (generated from screening tests), not results. Clinical Action Thresholds on which management recommendations are based have been defined. Similar risks are managed similarly. Risk assessment tables are available via smartphone app (for purchase) and web (no cost) through http://www.asccp.org. Surveillance at 1-5 years is recommended for patients whose risk of Cervical Intraepithelial Neoplasia (CIN 3) is intermediate. More frequent surveillance, colposcopy, and treatment are recommended for patients at progressively higher risk, whereas those with low risk can defer colposcopy, undergo

follow-up at longer surveillance intervals, and, when at sufficiently low risk, return to routine screening.

SCREENING FOR CERVICAL CANCER IN SPECIAL SITUATIONS

Immunocompromised women: Studies have shown that among women living with HIV, there is a higher incidence of HPV infection, HPV infection with multiple subtypes, persistent HPV infection with high-risk HPV types, higher incidence of CIN and High-Grade Squamous Intraepithelial Lesion (HSIL). WHO recommends HPV DNA detection in a screening, triage, and treatment approach starting at the age of 25 years (as compared to 30 years for the general population) with regular screening every 3 to 5 years (as compared to 5-10 years for the general population) till 50 years. After 50, screening can be stopped after two consecutive negative screening results. In immunocompromised patients of any age, colposcopy referral is recommended for all cytology results of HPVpositive/ ASC-US or higher. If HPV testing is not performed on ASC-US results, then repeat cytology in 6 to 12 months is recommended, with colposcopy referral for ASC-US or higher. If VIA or cytology is used as a primary screening test, then the screening interval is every 3 years.

Post hysterectomy (performed for treatment of preinvasive cancer cervix)

Three consecutive negative results in annual HPV testing should be ensured before entering long-term surveillance. Long-term surveillance after treatment of HSIL (CIN2 or CIN3) or Adenocarcinoma In Situ (AIS) involves HPV-based testing at 3-year intervals for 25 years.

Patients over the age of 65 years

If surveillance testing is recommended for either a history of abnormal screening results or treatment for precancer, discontinuation of surveillance is unacceptable if the patient is in good health and testing is feasible. Discontinuation of surveillance can be considered for patients with a limited life expectancy.

Follow-up after a negative triage test or treatment.

After a negative triage test, there are greater benefits with retesting at 12 months compared to 24 months. There is evidence that the HPV DNA test is more sensitive and less specific than cytology alone or Co-testing with HPV DNA and cytology in predicting recurrence or persistence after treatment in the general population. The test should be performed at 12 or 24 months after treatment.

SCREENING FOR BREAST CANCER

A lack of awareness, availability of only "opportunistic screening" and rising incidence of breast cancer among Indian women still call for attempts at increased breast awareness, self, and clinical breast examination at 1-3 year intervals in women aged 20-39. Findings suggest that screening mammography reduces the odds of mortality due to breast cancer and facilitates the use of early treatment. The American Cancer Society (ACS) systematic review and USPSTF (United States Preventive Services Task Force) reported that screening mammography was associated with a decreased risk of breast cancer mortality in randomized controlled trials (relative risk [RR], 0.80–0.82); in cohort studies (RR, 0.75; 95% CI, 0.69–0.81). Breast Imaging Society, India in 2022 also states that digital screening mammography is the investigation of choice for breast cancer screening.⁸

RISK ASSESSMENT

To determine the appropriate screening approach, the first step is risk assessment (average, moderate, high). It is important to determine if a woman is at average or increased risk of breast cancer to guide counseling regarding breast cancer surveillance, enhanced screening methods such as Magnetic Resonance Imaging (MRI) screening, risk reduction, and genetic testing. The risk categories are assigned according to the lifetime risk of being diagnosed with breast cancer (not the risk of dying due to breast cancer). These categories are average (less than 15 percent), moderate (approximately 15 to 20 percent), or high (greater than 20 percent) lifetime risk. The major risk factors include the following

- Personal history of breast, ovarian, tubal, or peritoneal cancer
- Family history of breast, ovarian, tubal, or peritoneal cancer
- Ancestry (eg. Ashkenazi Jewish) associated with breast cancer 1 or 2 mutations
- Known carrier of a pathogenic mutation for a hereditary breast and ovarian cancer syndrome in self or relative
- Mammographic breast density
- Previous breast biopsy indicating high-risk lesion (eg. atypical hyperplasia)
- Early menarche and delayed menopause (>55years)
- Radiotherapy of the chest between age 10 and 30 years

Risk assessment tools such as Gail⁹, and BRCA PRO are easily available.

MAMMOGRAPHY

Mammography should include mediolateral oblique (MLO) and craniocaudal (CC) views of each breast. The reporting room should have low ambient light not exceeding 20 lux. The reporting should be as per the American College of Radiology "Breast Imaging – Reporting and Data System" (BI-RADS)¹⁰

Table II: BI-RADS Classification Elements

Element				
Indication	Screening		Diagnostic	
Breast Density	A – mostly fatty	B - fibro glandular	C –Heterogeneously dense	D – Extremely dense
Location (L/R)	Upper - outer	Upper - inner	Lower - outer	Lower - inner
Description of Abnormality	Shape	Margins	Size	Cyst/Mass/ Calcification
Comparison to previous findings, if any				
Summary	The report concludes with a pertinent summary stating the most important findings, the final BI-RADS assessment category, and, if a suspicious abnormality is found, what type of management (eg, a biopsy) is indicated.			

Table II: BI-RADS Categories

Category	Interpretation	Explanation
BI-RADS 0	Incomplete	Needs additional imaging evaluation and/or prior mammograms for comparison — This category is used when there is not enough information from the views available to derive a conclusion. This is more commonly used in screening studies, which are interpreted as abnormal when the radiologist is not providing immediate reads.
BI-RADS 1	Negative	This is a completely negative examination. The woman should continue with screening mammography and clinical breast examination based on current screening guidelines.
BI-RADS 2	Benign	Benign masses such as fibroadenomas or cysts or benign vascular or parenchymal calcifications may be reported. There is no concern for malignancy and no further action needs to be taken. The rationale for reporting these findings is to document benignity and to prevent unnecessary evaluation. Routine follow- up is recommended.
BI-RADS 3	Probably Benign	This category is used when there is a finding that does not have characteristic benign features, but the likelihood of malignancy is less than 2%. Examples of lesions in this category would include a focal asymmetry, a group of round calcifications, or a circumscribed mass that is detected on a baseline screening examination.
BI-RADS 4	Suspicious	This category implies that there is a lesion with suspicious features for malignancy. The chance that the imaging finding is a cancer ranges between 2 and 94 %. The degree of suspicion or worry for malignancy varies both with the lesion and with the interpreter.
BI-RADS 5	Highly suggestive of malignancy	Lesions that have classic worrisome imaging features such as speculations (pleomorphic calcifications and skin retraction are placed in this category. The suspicion of malignancy is 95 to 100 %.
BI-RADS 6	Known, biopsy-proven malignancy	This includes patients with established biopsy-proven cancers that have yet to be surgically excised who present for further imaging to either evaluate the contralateral breast or assess response to neoadjuvant chemotherapy, or who present for a second opinion with interpretation of outside imaging studies.

BI-RADS Breast Imaging – Reporting and Data System

Screening mammograms should only be given BI-RADS assessments of 0, 1, or 2 BI-RADS categories 3 -6 are reserved for a diagnostic evaluation

Age at which screening should begin and frequency of screening

In India, opportunistic screening of women at average risk, on a 1-2 yearly basis, from the age of 40 years to the age of 70 years is deemed appropriate. Beyond 70 years, a decision is made based on the woman's comorbidities and life expectancy. It may be offered every 3 years for women greater than or equal to 50 yr. In the setting of a negative imaging evaluation (mammography plus ultrasound), the chance of malignancy ranges between 0 to 3 percent. Mammography may miss up to 20 percent of underlying breast cancers.

For those with a lifetime risk of breast cancer exceeding 20 percent, supplemental screening with Ultrasound or MRI in addition to mammography is consistent with guidelines from major groups¹¹. A common approach is to perform each modality annually, staggered by six months. Screening is recommended to begin at the age of 30 years or 10 years before the age of diagnosis of a first-degree relative with breast cancer, whichever is later. With a history of mantle radiotherapy, an annual mammogram (and annual MRI) should be started 8 years after radiotherapy. However, screening mammography is not to be started before the age of 25 years, irrespective of the cause of high risk.

NEWER MODALITIES

These include Digital Breast Tomosynthesis, Automated breast volume scanner, Gamma scan, Positron Emission Tomography(PET), Liquid biopsy, Elastography and Contrast Enhanced Mammography.

BREAST CANCER SCREENING IN SPECIAL SITUATIONS

Women with breast implants:

Standard imaging technique in females with breast implants involves four views, rather than the usual two views per breast.

Pregnancy and lactation - Screening mammography is not routinely performed in pregnant women, although the American College of Radiology (ACR) deems screening digital mammography, and screening digital breast tomosynthesis is more appropriate for both lactating and pregnant women. Upon getting a positive mammography report, all lesions higher than BI-RADS 0, 4, or 5 need biopsy. In the event of a benign pathology on biopsy in BI-RADS 4C/5, a rebiopsy should be done. With a negative mammography report, if there is a clinical suspicion of malignancy, a negative mammogram should not deter further evaluation.

Postmenopausal hormone therapy:

Menopausal Hormone Therapy (MHT) hampers mammographic accuracy with increasing age, due to an increase in breast density. Perhaps, MHT is associated with a marginal increased risk of breast cancer, when initiated near the time of menopause in women at low risk for breast cancer. In mammography reports, lesions higher than BI-RADS 0, 4, or 5 must be biopsied. In the event of a benign pathology on biopsy in BI-RADS 4C/5, a rebiopsy should be done. With a negative mammography report, if there is a clinical suspicion of malignancy, a negative mammogram should not deter further evaluation.

CONCLUSION

Together, breast and cervical cancers contribute to over 40% of cancer cases among Indian women. Menopause comprises a unique population group with its own set of physiological changes. Despite worldwide campaigns and initiatives by WHO to eliminate cancer cervix and the increasing acceptance of vaccination, consistent efforts are required to ensure access to screening and treatment, introduce economical yet robust methods of screening, and minimize reporting times. Breast cancer incidence has, in fact, overtaken its counterpart over the last few decades. Whether this is a consequence of environmental pollution with radiation, contamination of food with traces of estrogenic drugs, or urbanization, remains to be seen but it is certain that both these forms of cancer can be lethal and have good screening methods available. Hence the key to winning over the situation would be early detection and treatment which is associated with excellent survival rates.

KEY POINTS

- 1. Vaccination, public awareness campaigns, and the WHO 90-70-90 approach decreased the burden of cervix cancer globally.
- 2. In the "screen-and-treat-approach" the treatment can be done in the same sitting based on positive primary screening testing only.
- 3. Colposcopy and biopsy are indicated if primary and triage testing tests both are positive.
- 4. In menopausal women estrogen cream application intravaginally every evening for four weeks and stopped one week prior will help in satisfactory colposcopy.
- 5. Screening mammography reduces the odds of dying of breast cancer and facilitates early treatment.
- 6. As per the breast imaging society of India digital screening mammography is the investigation of choice for breast cancer screening.
- 7. Breast cancer screening should start at the age of 40 and should continue till 70 years.

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Vaccination in Menopause

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INTRODUCTION

Menopause, typically occurring between the ages of 45 and 55, marks a significant transition in a woman's life. While it brings new freedom and opportunities, it also increases the risk of certain health issues. As women age, their immune system weakens making them more susceptible to infections and vaccine-preventable diseases, and preventive healthcare can play a major role. However, lack of awareness and negligence towards recommendations about immunization leads to an increased rate of morbidity and mortality in women who are approaching menopause or are menopausal. In this review, we would like to discuss about the importance of immunization in menopausal women and what are the various checkpoints where we can give vaccines to these women to provide a better quality of life and maintain good health. We will also explore the impact of immunization on Women's Health.

WHAT IS MENOPAUSE?

Changes to the female reproductive cycle occur as a normal part of reproductive aging.¹ The physiology of the female reproductive system is regulated by an interplay between hormones primarily from the hypothalamus, pituitary, and ovaries. ^{2,3} The hypothalamic-pituitary-ovarian (HPO) axis, otherwise known as the female reproductive axis, is the major regulator of the female reproductive hormones estrogen and progesterone. Gonadotropin-releasing hormone is released from the hypothalamus at the onset of puberty in young women and induces the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary. These two hormones bind to ovarian receptors and signal the release of estrogen and progesterone. Estrogen and progesterone are released in fluctuating concentrations throughout the menstrual cycle, resulting in the follicular (low estrogen) phase and the luteal (high estrogen) phase. These phases are separated by ovulation and end with either fertilization or menstruation.¹⁻³ The Follicular phase of the menstrual cycle decreases with aging.⁴

Menstrual cycles become irregular during early menopausal transition because of fluctuant anterior pituitary gonadotropins.⁴ Menopause is a normal, natural event, defined as the final menstrual period (FMP) in retrospect a year or more of no menstrual bleeding. It represents permanent cessation of menses resulting from loss of ovarian follicular function, usually due to aging. Estrogen deprivation in the body brings about changes in the immune system in postmenopausal women. Increased proinflammatory serum marker levels, decreased CD4, T, and B lymphocyte levels, cytokine responses in body cells, and natural killer cell cytotoxic activity are also observed during the postmenopausal period,⁵ which further lowers the immunity.

IMMUNIZATION AND ITS IMPORTANCE

Immunization is the way by which we can protect a person against a disease through vaccination. This term is often used interchangeably with vaccination or inoculation. Vaccines stimulate the body's immune response against diseases.⁶ Its need is crucial to protect from vaccine-preventable diseases. As individuals age, their immune system weakens, making them more susceptible to infections.⁷

The following vaccines are recommended for all postmenopausal women to prevent certain diseases to avoid morbidity.

COVID-19 VACCINE

According to CDC COVID-19 is a contagious viral infection of the nose, throat, or lungs; may feel like a cold or flu.⁸ Complications from COVID-19 include pneumonia, blood clots, liver, heart, or kidney damage, long COVID, and death.⁷ In adults it is recommended to give 1 or more doses of the current COVID-19 vaccine depending on age or health status.⁸

The vaccination dosage recommended for adults is 2 doses, at least 4 weeks apart. Additional booster doses are given for all older adults and adults with significant comorbidities or severe obesity (high priority-use group), at least 21 months after the previous dose.⁷

INFLUENZA VACCINE

WHO recommends annual vaccination for elderly individuals (≥65 years of age), especially individuals with chronic medical conditions (disorders of the cardiovascular or pulmonary systems, including asthma; chronic metabolic diseases, including diabetes mellitus; renal or hepatic dysfunction, hemoglobinopathies or immunocompromised. The CDC recommends annual influenza vaccine for all persons aged older than 6 months but is especially important for adults who are older or immunocompromised or who have chronic medical conditions. The vaccine components need to change regularly to reflect circulating strains of the influenza virus. Several vaccines are available, including inactivated quadrivalent and trivalent vaccines.9 Live attenuated influenza vaccine administered through intranasal route is contraindicated in individuals above the age of 50 years.⁷

PNEUMOCOCCAL VACCINE

About 500,000 cases of pneumococcal pneumonia are reported annually and Streptococcus pneumonia remains a leading infectious cause of serious illness in adults. The 23-valent pneumococcal polysaccharide vaccine (PPV23) is recommended by The Advisory Committee on Immunization Practices (ACIP) for all adults older than 65 years and younger immunocompromised adults. PCV13, a new 13-valent pneumococcal conjugate vaccine was approved by FDA in 2011 for adults aged 50 years and above. In 2014, ACIP recommended routine vaccination of all adults aged above 65 years and adults aged younger than 65 years at risk for invasive pneumococcal disease.^{9,10}

However, in 2019, ACIP stated that PCV13 vaccination is no longer routinely recommended for all adults aged 65 years and older. Instead, shared clinical decision-making for PCV13 use is recommended for persons aged 65 years and older who are not at high risk. Shared clinical decisionmaking considerations may include the risk of exposure to PCV13 serotypes and the risk of pneumococcal disease because of underlying medical conditions.^{9,11}

CDC recommends that for individuals who have not previously received a dose of PCV13, PCV15, or PCV20 or whose previous vaccination history is unknown, 1 dose of PCV15 OR 1 dose of PCV20 should be administered. If PCV15 is used, administer 1 dose PPV23 at least 1 year after the PCV15 dose (may use a minimum interval of 8 weeks for adults with an immune compromising condition).

HERPES ZOSTER VACCINE (SHINGLES)

There has been an increase in the incidence of herpes zoster (shingles) and postherpetic neuralgia with age, which leads to interference with daily activities, and increased hospitalizations as well. Two vaccines have been approved by the FDA and NACI to prevent herpes zoster in people aged 50. Years and above. These are a live attenuated virus vaccine (LZV), and the newer recombinant vaccine (RZV). The Advisory Committee on Immunization Practices, (ACIP) has advised that adults aged older than 50 years should be immunized with RZV regardless of shingles history and regardless of whether they were previously immunized with the LZV vaccine.^{8,11} The study of RZV conducted in older adults revealed efficacy of more than 97% in all age groups. The NACI, with the Canadian recommendations, states that both vaccines are acceptable; however, RZV has longer-lasting efficacy, is more cost-effective, and does not have the same contraindications as LZV, being a live virus.^{9,12,13} 2 doses of 0.5ml of the RZV vaccine are recommended, 2-6 months apart by the CDC in age groups above the age of 50 years (with a minimum gap of 4 weeks).

CONCLUSION

Menopause occurs at a critical juncture in a woman's life where emphasis on disease prevention can have a major impact. However, recommendations in this group are often neglected leading to an unnecessary increase in morbidity and mortality in women and is detrimental to the quality of life in an aging woman. Awareness and education of vaccination necessary for women in this age group would improve the lives of women and would be a boon in saving unnecessarily spent money in healthcare for elderly women.

KEY POINTS

Immunization in menopausal women is essential and should be actively recommended by the gynecologist as it reduces the risk of vaccine-preventable diseases and enhances immune function.

Covid 19, shingles, influenza, and pneumococcal vaccines should be recommended in menopausal women.

Vaccination helps in reducing the morbidity and mortality in postmenopausal women.

Travel vaccines like hepatitis A, Typhoid, etc should be taken based on travel plans.

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Sexual Health At Menopause

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INTRODUCTION

Sexual health is a "state of physical, emotional, mental and social well-being related to sexuality; not merely the absence of dysfunction or infirmity. Female sexuality has been recognized by the World Health Organization as a fundamental human health right.¹ Many assume that women lose interest in sex after menopause. Contrary to the past belief many women have good physical and sexual health until old age. Sexuality remains an extremely important element for many midlife women.

Sexual well-being is a type of coordination between the mind, senses (feelings), and body that can influence the social and intellectual aspects of human personal development². Menopause is a condition that causes many physical, biological, and psychological changes in women, affecting the quality of their sexual lives and sexual satisfaction resulting in **Female Sexual dysfunction FSD**. Individual variations in sexual life are caused by a woman's age, education, economic status, family structure, health status, good and poor behaviors, social relationships, sexual experiences, growth style, living conditions, and cultural influences during this period.³

2.0 IMPACT OF MENOPAUSE ON SEXUALITY

It is an accepted fact that sexual function worsens with advancing menopause status, independent of age. The main reason is decreasing in significant levels of estrogen in perimenopause and beyond, resulting in female sexual Dysfunction FSD.

2.1 Sexual response in Menopause

Masters and Johnson in the 1960s described four-phase patterns of female sexual response: excitement, plateau, orgasm, and resolution. With aging and inadequate estrogen

- 1. The excitement phase is prolonged due to inadequate vascularity.
- 2. The plateau phase is attenuated due to estrogen deficiency.

- 3. Vagnal dryness leads to dyspareunia.
- 4. During orgasm intensity and frequency of vaginal contractions decrease.

2.2 Physical changes

Thinning of the vagina and vaginal dryness are important recognized causes of dyspareunia. Menopause causes decreased blood flow to the clitoris and lower vagina with reduced sensation and pleasure during sex. Burning and itching due to dry vagina leads to discomfort. This makes penetrative sex difficult with a negative impact on sex.

2.3 Emotional shifts

Menopause is an emotional roller-coaster. Mood swings, irritability, stress, and fatigue can impact self-esteem and body image leading to decreased libido, and sexual desire.

2.4 **Insomnia and sleep problems** lead to irritability and decreased sex drive. 23% of women between the ages of 57 and 85 did not find sex pleasurable.

2.5 Sexual function

Sexual function worsens with advancing menopause status. Sexual activity reduces considerably with age. Women in their late teens and 20s engage in sexual activity 2.2 times per week as opposed to 1.3 per week in their 50.

2.6. Genitourinary Syndrome of Menopause (GSM)

GSM is a chronic, progressive condition that encompasses physiological and anatomical alterations that affect the labia majora/minora, vestibule/introitus, clitoris, vagina, and the lower urinary tract tissue, as a result of the decrease in sex hormones levels vaginal symptoms usually worsen and do not change without treatment. GSM affects approximately 50% of middle-aged and elderly women.⁴ It has detrimental effects on body image, sexual health, and overall quality of life. Many women are not aware that simple treatment prevents irreparable damage.

3.0 CLASSIFICATION OF FEMALE SEXUAL DYSFUNCTIONS – FSD

Many academic bodies like the International Association of Menopause, the American Association of Menopause, Urology Association have their own classification but all are pretty much the same.

3.1 Working classification of FSD

- a. Sexual desire disorders
- HSDD Hypoactive sexual desire disorder
- Sexual aversion disorder
 - b. Sexual arousal disorder
 - c. Orgasmic disorder
 - d. Sexual pain disorder Dyspareunia, vaginismus, other sexual pain disorders
 - e. anorgasmia. (delayed, infrequent, or absent orgasms)⁵

3.2 Frequency of Sexual Dysfunction

Low sexual desire- 40 % to 55 %

poor lubrication -25% to 30%,

dyspareunia- 10 to 15%6

3.3 Indian perspective

In a study from South India prevalence of female sexual dysfunction in postmenopausal women ranged from 68% to 86%. (Meeta et al). The major reason is urogenital atrophy.

However, only 1% of women discussed about sexual problems with healthcare professionals (HCP). Even HCPs did not give much attention while counseling due to a lack of time, knowledge, and ability to tackle.

4.0 DETERMINANTS OF SEXUAL HEALTH AT MENOPAUSE

4.1 Hormonal

estrogen deficiency - premature ovarian insufficiency - pelvic disorders - post-surgery, irradiation, and trauma.

4.1.1 Beyond Estrogen Deficiency

Decreased steroids (estrogen, progesterone & testosterone) result in lowered activation of the thalamus, amygdala, and anterior cingulate cortex following visual sexual stimulation. Estrogen loss has been suggested to exacerbate the effects of aging on cognitive functions, contributing to brain senescence and neurodegenerative processes⁷.

Estrogens and androgens work synergistically, in promoting sexual desire response. Androgen decline is age-related rather than menopause related. Though more testosterone is produced by postmenopausal ovaries, adrenal DHEA, prohormone of testosterone is decreased and not able to correct testosterone deficiency. The abrupt drop in testosterone levels is observed in young women undergoing surgical menopause leading to distressing SD.

4.2 Nonhormonal

- Relationship issues high education, misunderstandings, Bereavements, economic problems, retirement, children leaving home, diversity, lack of personal hygiene
- Past sexual abuse
- Biological aging
- Embarrassment and shyness with partner and HCW.
- Chronic disease cardiovascular disease risk: hypertension, peripheral vascular disease, smoking, diabetes; multiple sclerosis; renal failure
- Urinary incontinence
- Polypharmacy

Psychotropic medications: antidepressants (up to one-third of women on SSRIs) antipsychotics and mood stabilizers

Anti-hypertensives, adrenergic antagonists, diuretics, and Chemotherapeutic agents

Surgical issues – breast and pelvic surgery (Hysterectomy with or without oophorectomy) adversely affects female sexuality at any age.

4.3 Associated Morbidities: and sexual health in menopause

The genital sexual response in women is mainly a vasculardependent endothelial dysfunction. Due to cardiometabolic insults can lead to vascular insufficiency in female genital tissues⁸.

Prevalence of SD is higher in women with diabetes mellitus than in controls, Obesity and dyslipidemia have adverse effects on SD, The Study of Women's Health Across the Nation (SWAN) found that greater-than-expected weight loss was correlated with an increase in sexual desire at follow-up in midlife subjects. Doppler ultrasound of the genital vessels is currently being standardized and validated⁹.

5.0 DIAGNOSIS

5.1 History in detail about general and sexual history to decide the type of sexual dysfunction and to exclude other secondary causes like comorbidities, and medications.

5.2 General physical examination. Including breast exam

5.3 Pelvic examination to exclude skin lesions, STIs, other infections, vulvovaginal atrophy, urinary incontinence, prolapse uterus, and muscle tone 5.4 Laboratory investigations – Basic investigations(CBP, Blood sugar, TSH)are sufficient, Hormonal studies If indicated only,

6.0 MANAGEMENT

The management of sexual dysfunctions involves a multifaceted approach that addresses medical, psychological, and relationship issues.

6.1 Counseling

Psychosexual therapy or couples therapy can help identify and address relationship issues that contribute to sexual problems. Behavioral exercises can also help reduce anxiety.

6.2 Non-hormonal

- Lifestyle changes stop smoking. Limit alcohol intake, reduce caffeine, adequate water intake, appropriate diet for menopause, obesity control measures, and aerobic and weight-bearing exercises. Avoid a sedentary lifestyle.
- Vaginal lubricants and moisturizers for dry vagina and dyspareunia.
- Pelvic floor exercises.
- Probiotics
- Menopause is associated with dysbiosis.
- Vaginal probiotics may help to maintain a healthy vaginal microbiome by preventing the overgrowth of harmful bacteria and promoting the growth of beneficial bacteria.

Acidic medium prevents secondary infections in the vagina and recurrent culture-negative UTIs. This can contribute to vaginal health and alleviate symptoms of dryness and irritation.

• 6.2.4. Dilators and stimulators.

Dilators for narrowed vagina due to post-menopausal vulvo vaginal atrophy. Arousal may be enhanced with stimulation of the clitoris. The vibrator will provide clitoral stimulation.

6.3 Hormonal

6.3.1 Systemic hormone therapy is not particularly indicated for sexual dysfunction. Local estrogen therapy: For new-onset dyspareunia caused by the genitourinary syndrome of menopause and culture-negative recurrent UTI it is very much indicated. Some studies reported improved sexual desire, enjoyment, and orgasm with local estrogens. Options include vaginal estrogen creams, rings, tabs, and capsules. Uterine surveillance is not necessary while using vaginal estrogens for a short period, Additional progesterones are also not indicated in cases of intact uterus.MHT is not for primary prevention of sexual disorders during menopause.

- 6.3.2 vaginal dehydroepiandrosterone acts in low sexual desire problem
- 6.3.3. ospemifene. Only oral SERM for Dyspareunia.
- 6.3.4 Androgen therapy for sexual dysfunction is controversial.

6.4 pharmacological

6.4.1 Flibanserin (Addyi): The FDA has approved to treatment of low sexual desire in women before menopause. This medicine started as a treatment for depression. Originally developed as an antidepressant,

Potential side effects include low blood pressure, sleepiness, nausea, fatigue, dizziness, and fainting, particularly if the drug is mixed with alcohol. Stop alcohol while taking the drug, Stop the drug If no improvement in six weeks.

6.4.2 Bremelanotide (Vyleesi). Bremelanotide is another FDA-approved treatment for low sexual desire in premenopausal women. This medication is an injection you give yourself just under the skin in the belly or thigh before anticipated sexual activity.

7.0 POTENTIAL TREATMENTS THAT NEED MORE RESEARCH

More research is needed before these agents might be recommended for treatment of female sexual dysfunction:

1. Tibolone: It is a synthetic steroid with selective estrogenic, progestogenic, and androgenic effects. Improves mood and libido in postmenopausal women. Used in the UK and Australia.

Due to concerns over the increased risk of breast cancer and stroke in women taking tibolone, the drug isn't approved by the FDA for use in the U.S.

- 2. Phosphodiesterase inhibitors: Sildenafil (Revatio, Viagra), may prove beneficial for some women who have sexual dysfunction as a result of taking selective serotonin reuptake inhibitors (SSRIs), an antidepressant.
- 3. Lasers in FSD: Laser therapy may be a safe and effective treatment option for some women with genitourinary syndrome of menopause (GSM) and sexual dysfunction, but it is in the preliminary stage more evidence and research are needed.

Proposed Flowchartfor the management of SD in menopausal women

proposed flow chart for the management of SD in menopausal women.



Medicina (Kaunas). 2019 Sep; 55(9): 559. Published online 2019 Sep 2. doi: 10.3390/medicina55090559

KEY POINTS

Sexual health is a fundamental human health right.Sexual dysfunction in menopausal women can be categorized as disorders involving desire, arousal, pain, and orgasm. These categories often overlap. The treatment of sexual dysfunctions involves a multifaceted approach that addresses medical, psychological, and relationship issues. Indian women hesitate to talk about sex and present with depression somatic symptoms. Counseling the couple is the first approach to management. Physical and local examination is essential. Vaginal atrophy is a common cause of sexual pain in menopausal women. Modification of reversible causes includes sex therapy with lubricants, alteration of medications, lifestyle, and physical therapy for pelvic floor disorders. First-line therapy should be based on the diagnosis, needs, and expectations of the patient, risks, and benefits of medications like hormones. Route. Vasoactive agents, topical steroids, antimicrobials,

and analgesics. Surgery is always the second line. Women with premature ovarian insufficiency (POI) and surgical menopause need HRT/ MHT and special counseling.

CONCLUSION

Issues surrounding female sexual dysfunction are usually complex, so even the best medications aren't likely to work if other emotional or social factors remain unresolved.

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Date	H ospital
26th April, 2024	LHMC & Smt. Sucheta Kriplani Hospital
31st May, 2024	B L Kapoor Hospital
28th June, 2024	Apollo Hospital
26th July, 2024	Army Hospital (Research & Referral)
30th August, 2024	AllMS Delhi
27th September, 2024	ESI, Basaidarapur Delhi
25th October, 2024	DDU Hospital
29th November, 2024	MAMC & LNJP Hospital
27th December, 2024	Sir Gangaram Hospital
31st January, 2025	VMMC & Safdarjung Hospital
28th February, 2025	UCMS & GTB Hospital
28th March, 2025	RML Hospital
25th April, 2025	LHMC & Smt Sucheta Kriplani Hospital

Monthly Clinical Meetings AOGD Calendar 2024-25

Osteosarcopenia in Menopause: A Silent Epidemic Screening, Diagnosis, and Management

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INTRODUCTION

Bone and muscle function are integral for movement, and the interactions between them are increasingly being recognized and studied^{1,2}. Osteopenia/osteoporosis and sarcopenia are age-related musculoskeletal diseases that have adverse effects on health, cause dependency, and lead to poor quality of life³ and increase mortality. Taken together, they come under the larger bracket of "Osteosarcopenia" – a silent disease that slowly and gradually weakens the bone-muscle unit, especially in the postmenopausal age group, and gets recognized only when fragility fracture develops.

Through this article, we wish to make health professionals aware of this entity and empower them to focus on early detection, timely management, and ultimately, prevention of the development of osteosarcopenia in elderly women to improve the quality of their lives.

TERMINOLOGY

It was in 2009 that Binkley and Buehring, introduced the term, Osteosarcopenia⁴. The need for this new terminology arose because:

- Osteopenia/osteoporosis and sarcopenia are both older age-associated conditions.
- Osteopenia and sarcopenia do occur simultaneously as the bone and muscle work together and are called the "BONE-MUSCLE UNIT"
- This is further corroborated by the study where it was found that in post-menopausal women, those with sarcopenia had a 12.9 times higher risk of having osteoporosis vs. those without sarcopenia.⁵
- Several therapeutic interventions are common to both bone and muscle and thus are effective in treating osteo-sarcopenia.
- Compared to osteoporosis or sarcopenia alone, patients with osteosarcopenia have:

- 1. Poor physical activity and increased mortality
- 2. Significantly increased rate of falls of approximately three-fold and fractures by four-fold.
- 3. In the presence of sarcopenia, the classification of fracture increases from low risk to high risk to very high risk of fractures.

PREVALENCE

It is much more common in elderly people and the prevalence is higher in women and increases with age (Table 1).

 Table 1: The prevalence of osteosarcopenia in various age groups

	Men	Women
60-65 years	14.3%	20.3%
> 75 years	59.4 %	48.3 %
Overall	16.4 – 32 %	23.3 - 82.8%

Yoo et al. reported that in the older age group with hip fracture, the prevalence of osteo-sarcopenia was found to be 28.7% and the mortality rate was 1.8 times higher than in its absence⁶.

RISK FACTORS

It is important to identify the risk factors for Osteosarcopenia, especially in the elderly population. A detailed history should not just be taken from the patient but as well as from the kin/caretakers and other treating health professionals. The aim is to determine the risk factors, causes, and implications of osteo-sarcopenia (Table 2).

Disease	Causes
Aging	Age-related muscle loss – Primary Sarcopenia
Diseases	• Endocrine
	Malignancies
	• Organ failure
	Inflammatory disease
Inactivity	Sedentary behavior – Bedrest, limited mobility
	Physical inactivity
Malnutrition	Undernutrition or malabsorption
	 Alcohol excess, smoking, cachexia
	Over nutrition/obesity
	Medication-related anorexia

There are no precise screening or risk calculation tools for osteosarcopenia per se. However, numerous tools are available for the individual modalities, osteoporosis and sarcopenia.

SCREENING FOR OSTEO-SARCOPENIA

Sarcopenia

Sarcopenia is a widespread and worsening disorder of skeletal muscles, linked to a higher risk of negative outcomes such as falls, fractures, and physical disabilities.

There have been several guidelines published in the last decade for Sarcopenia. In 2018 the European Working Group on Sarcopenia in Older People (EWGSOP 2)⁷ was published and then the SWAG SARCO (South Asian Working Action Group on SARCOpenia) guidelines in 2021 especially for the South Asian population⁸.

According to the EWGSOP2, it is defined as a loss of muscle strength that is linked to a decline in muscle quality (Table 3).

 Table 3: Clinical tools for measurement of muscle strength, mass, and physical performance⁷

Test	Cut-Off Points For Men	Cut-Off Points For Women	
EWGSOP2 cut-off points for low muscle strength by grip test and chair stand test			
Grip Strength Chair Stand test	<27 kg > 15 sec for 5 rises	< 16 kg	
EWGSOP2 sarcopenia cut-off points for low muscle quantity			
ASM (DXA) MRI or CT– Gold standard BIA	< 20 kg	< 15 kg	

EWGSOP2 sarcopenia cut-off points for low physical performance		
GAIT Speed	<0.8 m/o	
4-m usual walking speed test	≤0.0 m/s	
SPPB		
Gait speed, a balance test, and a chair stand test		
	≤ 8 points indicat	tes poor physical
	perfori	mance
TUG		
Rise from a standard chair, walk to a marker 3 m away, turn around, walk back, and sit down again		
400 M WALK Noncompletion of	or > 6 m for completion	on
400 M WALK Noncompletion of Complete 20 laps of 20 m	or > 6 m for completion	on

DXA, dual-energy X-ray absorptiometry; ASM, appendicular skeletal muscle mass; BIA, bioelectrical impedance analysis; CT, computed tomography; MRI, Magnetic resonance imaging; SPPB, Short Physical Performance Battery; TUG, timed up and go.

EWGSOP2 has given an algorithm for case finding, making a diagnosis, and quantifying severity in daily clinical practice (Fig: 1).

Figure 1: Chart showing diagnostic and grades of sarcopenia



According to this algorithm, every elderly person sitting in the OPD, in the community, or old age homes should be screened for Sarcopenia by using the simple SARC F questionnaire (Table 4).

• SARC F has a low-to-moderate sensitivity and a very high specificity to predict low muscle strength.

- Is an inexpensive and convenient method for sarcopenia risk screening.
- SARC-F is a questionnaire from the patient, hence the results point toward outcomes that are relevant to the patient.
- A total score of 4 or higher predicts sarcopenia and poor outcomes⁹.

Component	Question	Scoring
	How much difficulty	None = 0
Strength	and carrying 10	Some = 1
	pounds?	A lot or unable = 2
Assistance in	How much difficulty	None = 0
walking	do you have walking	Some = 1
hanning		A lot, use of aids, or unable = 2
	How much difficulty	None = 0
Rise from a chair	do you have	Some = 1
	chair or bed?	A lot or unable without help = 2
	How much difficulty	None = 0
Climb stairs	do you have climbing	Some = 1
	a hight of 10 stairs?	A lot or unable = 2
	How many times	None = 0
Falls	have you fallen in the	1–3 falls = 1
	pasi year?	≥4 falls = 2

Table 4: SARC-F screen for sarcopenia⁹

In Clinical practice, if the SARC F score is more than 4, tests for evaluating muscle strength should be conducted.

While the EWGSOP 2 guidelines are acceptable around the globe, the need for the South Asian guidelines (SWAG SARCO) arose because:

- South Asians generally have lower muscle mass and strength compared to Caucasians.
- The region is experiencing rapid development, resulting in a dual challenge of both overnutrition and undernutrition.
- The characteristic pattern of obesity in South Asians is termed 'thin-fat obesity' or 'sarcopenic obesity', also referred to as normal weight obesity, which carries comparable cardio-metabolic risks to traditional obesity.
- Most South Asian nations are categorized as low to middle-income countries, grappling with financial and resource constraints.

SWAG SARCO 2021 guidelines differ from EWGSOP2 in the following aspects:

- Diagnosis involves the loss of any two muscle components (mass, function, or strength) without prioritizing any single component.
- Emphasizes the significance of secondary sarcopenia and sarcopenic obesity.
- Includes calf circumference in the SARC F

- The cut-offs for hand grip strength are Male < 27.5 kg and Female < 18kg
- Suggests using imaging primarily when clinical and biochemical evaluations are insufficient for making diagnostic or treatment decisions. Choice of imaging depends on availability, accessibility, affordability, and advocates skeletal muscle ultrasound (USGM)
- The algorithm used is 5S (Suspect, Screening, Secondary sarcopenia, Severity, and Shared decision-making)

OSTEOPOROSIS

The risk assessment is carried out by:

- A detailed history, identifying the risk factors and physical examination
- Clinical Risk Assessment Tools:

o The Osteoporosis Self Assessment Tool (OSTA) for Asians and Simple Calculated Risk Estimation Score (SCORE) are simple and cost-effective to screen women at risk for osteoporotic fracture.

o The WHO Fracture Risk Assessment Tool (FRAX) is a country-specific, online tool (www.shef.ac.uk/FRAX) designed to identify osteopenic patients who are most likely to benefit from treatment. It estimates an individual's 10-year absolute fracture risk, and a cost-effectiveness analysis helps establish the intervention threshold beyond which treatment becomes economically viable.

BMD (Bone mineral Density) testing via DXA for osteoporosis screening should be guided by the indications given by the Indian Menopause Society for our Indian population. Those found to have sarcopenia and with high risk on clinical assessment tools too should be advised BMD.

Total hip, femoral neck, and/or lumbar spine (L1 to L4) are the preferred measurement sites.

INDICATIONS FOR BMD – IMS 2020¹⁰

- All postmenopausal women who are more than five years into menopause.
- Women less than five years into menopause but with high-risk factors.
- Women in menopause transition who have associated secondary causes of osteopenia/osteoporosis.
- In cases of radiological evidence of osteopenia along with vertebral compression fractures.
- In cases of fragility fractures are detected on radiology.
- Before starting pharmacological treatment for osteoporosis.
- New indications include assessing total body fat and lean tissue mass.

Osteopenia and osteoporosis are classified by the World Health Organization (WHO) according to bone mineral density (BMD) (Table 5).

Categories	T score value
Normal	-1.0 or greater
Osteopenia	-1.0 and 2.5
Osteoporosis	-2.5 and below
Severe osteoporosis	<-2.5 + fragility fracture

MANAGEMENT OF OSTEOSARCOPENIA

Aim of the treatment:

- To prevent a decline in muscle activity and function.
- Early intervention can potentially reduce or prevent falls and disability.
- Aims to decrease hospitalization rates and lower mortality in those affected.

NONPHARMACOLOGICAL (INCLUDING DIETARY SUPPLEMENTS)

- 1) Lifestyle modification the therapeutic benefits of smoking and alcohol cessation have been observed. They should avoid or limit their intake of caffeine, tobacco, and salt.
- 2) Nutritional strategies:
- a) The role of dietary calcium and calcium supplements produce marginal increases in bone mineral density and intake of (1000–1300 mg/day) calcium is recommended, especially in the postmenopausal age group.
- b) Role of dietary protein and protein supplements -Proteins also have been observed to be important for muscle health. Expert consensus groups recommend at least 1.2–1.5 g/kg/day with 2.5–3 g of leucine per meal and 25-30 gm of protein in each meal. Low dietary protein (≤0.45 g/kg/day) in elderly persons (aged ≥65 years) was associated with muscle atrophy¹².
- Exercise: Resistance exercises or high-impact activities like running positively impact bone by improving BMD. Similarly, resistance exercises positively affect sarcopenia by directly benefiting muscles¹³.
- Patients should be encouraged to perform the recommended exercises regularly, at least three times a week, according to their capacity.
- Ensure proper warm-up before starting resistance and aerobic exercises, and adequate cool-down afterward.
- Balance, flexibility, and strength training should ideally be done before aerobic exercises to promote stability and reduce the risk of falls.
 - 4) Vitamin D: It plays a crucial role in bone and muscle physiology by facilitating calcium and phosphate

absorption, contributing to calcium-dependent muscle functions. Many scientific organizations recommend the intake of at least 1,000 IU of vitamin D per day for adults aged 50 years and older (Fig 2).

Figure 2: Nonpharmacological and dietary supplements for the osteosarcopenia



PHARMACOLOGICAL

Pharmacological treatments specifically designed for osteosarcopenia are yet to be developed. However, denosumab, a RANK ligand inhibitor, has shown positive effects on both muscle and bone health.

Table 6: Pharmacotherapy for the osteosarcopenia

Pharmacological agent	Osteoporosis	Sarcopenia
Denosumab	It has a significant increase in BMD at sites such as the lumbar spine, hip, and radius. ¹⁴	No significant effect on muscle function was observed. ¹⁵
		It increases muscle strength and insulin sensitivity in osteoporotic humans. ¹⁶
Testosterone	Intramuscular injections of testosterone increased lumbar Spine bone density, especially in men. ¹⁷	In those with decreased serum testosterone levels injections of testosterone can improve muscle mass, strength, and physical performance. ¹⁸
Growth hormone	Growth hormone may not cause bone density increase but it reduces fracture risk in women with age- related bone loss ¹⁹ .	Low growth hormone levels with age contribute to a decrease in lean body mass and an increase in adipose tissue ²⁰ .
Antimyostatin antibodies	Antimyostatin antibody along with resistance exercise has been shown to improve bone health in rats. ²¹	 (1) Antimyostatin antibodies increased muscle mass and strength in a few studies.²² (2) Antimyostatin antibodies increase lean
		mass and may improve functional measures of muscle power.

CONCLUSION

Osteosarcopenia is a disease of the elderly. Individuals with osteosarcopenia have a poorer outcome than individuals with either osteopenia or sarcopenia alone. Therapeutic strategies that simultaneously target both bone and muscle are essential for managing osteosarcopenia.

KEY POINTS

- Individually, osteoporosis and sarcopenia remain under-detected and undertreated and diagnosis is made only when a fragility fracture develops.
- The detection of either condition should trigger an evaluation for osteosarcopenia, considering the high prevalence of co-occurrence between osteoporosis/ osteopenia and sarcopenia in older adults.
- Assessing for osteosarcopenia includes a comprehensive history review (covering medical, social, falls, fractures, and medication histories), risk factor identification, physical evaluations, and targeted investigations.
- An effective strategy to address osteosarcopenia involves combining resistance and balance exercises with nutritional supplementation (such as whey protein, vitamin D, calcium, and creatine) for individuals with deficiencies.
- All medical, metabolic, endocrine, and psychological conditions contributing to secondary sarcopenia should be managed using both pharmacological and non-pharmacological approaches, such as medical nutrition therapy (MNT), psychotherapy, exercise, and more.
- In terms of pharmacotherapies, denosumab may provide dual benefits for both muscle and bone. Further research for new pharmacological modalities is urgently needed
- Gospel for prevention is to Maximize muscle and peak bone mass in youth and young adulthood, Maintain in middle age, and Minimize loss in older age

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Menopause Hormone Therapy

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INTRODUCTION

Natural menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity or follicle depletion. Natural menopause is recognized to have occurred after 12 consecutive months of amenorrhea for which there is no other pathologic or physiologic cause. (WHO) The mean age of menopause in India is 46 years which is earlier than in the western women which is around 52 years.

Menopause is associated with decreasing estrogen levels. This causes vasomotor flushes, bone loss, increased glucose intolerance, hypertension, mood changes, vaginal atrophy leading to vaginal itching, sexual dysfunction, etc.

Menopausal hormone therapy describes the use of hormones like Estrogen and Progestins for the treatment of menopausal symptoms. It has replaced the previously used term Hormone replacement therapy. One can use estrogen alone (ET) in women who have had a hysterectomy or both Estrogens and Progestins (EPT) in women with a uterus. Systemic hormones are needed for indications like Vasomotor flushes and Premature ovarian failure. Local low-dose estrogens are indicated for vaginal atrophy which is now termed as Genitourinary syndrome of menopause (GSM).

MHT can be prescribed for women within 10 years of menopause or less than 60 years of age.¹ This window of opportunity should be used to provide hormone replacement when indicated. This improves bone health, vasomotor flushes, and vaginal atrophy.

In this article, we will review the indications of Menopause hormone therapy (MHT), therapies available, their side effects, contraindications, and prescription guidelines.

ESTROGENS

The commonly used estrogen preparations include conjugated equine estrogens, conjugated estrogens, Micronized 17 β Estradiol, Ethinyl Estradiol, Estradiol valerate, etc. Estrogens are mostly derived from plant sources. Only conjugated equine estrogen is derived from pregnant mare's urine. Those derived from plants undergo procedures to get the needed composition. They may be called synthetic but are originally obtained from plants.² Bioidentical hormones:

A bioidentical hormone is one whose molecular structure resembles the hormones produced endogenously in the body. $^{17}\beta$ Estradiol is a preferred prescription hormone over other estrogen preparations because it resembles naturally produced estradiol from the premenopausal ovary. It is available in micronized form because it can be absorbed from the gut only in this form.

Ethinyl estradiol is a potent synthetic estrogen. It is an esterified form of estrogen and it is used in smaller doses for MHT.

Conjugated equine estrogen(CEE) is prepared from pregnant mare's urine and is made of estrone sulfate and other estrogens. Estrone sulfate is present in postmenopausal women. It is converted to estrone which is weak and estradiol which is more potent.

Estradiol Valerate is available which after absorption is converted to 17 beta-estradiol and valeric acid. It has fewer adverse effects as compared to ethinyl estradiol.

Estriol (E3): It is one of the metabolites of estradiol and estrone. Commercially it is available for local use in GSM. Due to its weaker potency, systemic absorption is minimal or negligible.

Estrogens are available in many forms: oral tablets, local gels, transdermal patches, vaginal creams and tablets, injectables, etc. They are available alone and also in combination with progesterones. A particular usage will depend on indication, availability, and affordability.

FIRST, PASS HEPATIC METABOLISM

Oral estrogens when absorbed pass through the liver and undergo first-pass hepatic metabolism. This causes increased production of proteins by the liver like Sex hormone binding globulin, Thyroxine binding globulin, corticosteroid-binding globulin, Triglycerides, Highdensity lipoprotein, etc. Cholesterol secretion in bile also increases. Systemic estrogens are available as Tablets and Transdermal patches. Estrogens when absorbed through transdermal patches do not undergo this first-pass hepatic metabolism and these concentrations of proteins are minimally increased.³

Transdermal patches containing 17-beta estradiol are available in different strengths. The dose may vary from 0.014 to 0.1 mg/day (i.e., 14 to 100 mcg/day). If the uterus is present then micronized progesterone or dydrogesterone may be used along with it.

TOPICAL ESTROGENS

They are available as emulsions like lotions to be applied on thighs or legs available in individual foil packets for each leg. Gels are available as metered-dose pumps and also as individual doses in separate foil packets. Also, sprays are available for spraying on the inner surface of the medial side of the forearm. They deliver different doses of estrogens.

DOSE EQUIVALENTS

For a long time, conjugated estrogen 0.625 mg has been used for therapy and in studies. This is considered to be a standard dose of estrogen. The doses of other estrogens that have equal effect for the treatment of hot flashes as 0.625 mg of CEE include:

- 1 mg micronized 17-beta estradiol
- 0.05 mg/day transdermal 17-beta estradiol
- 1.25 mg piperazine estrone sulfate

VAGINAL ESTROGENS

Vaginal rings are available which release 0.05mg or 1mg of estradiol per day for 3 months.

For Genitourinary syndrome of menopause or vaginal atrophy, much lower doses are needed. Vaginal ointments, gels, and tablets are available for GSM. These low doses used locally are not absorbed and do not cause cardiovascular complications.

Depot estrogens: These may be available in some countries as estradiol cypionate or estradiol valerate injections to be given three to four weekly. These are not recommended routinely.

PROGESTIN PREPARATION

Menopause hormone therapy if given as only estrogens unopposed by progesterone may cause endometrial hyperplasia or malignancy in a woman with a uterus. So progestins should be added to estrogens which may be given by any route. In a hysterectomised woman, progestins are not needed. Adequate doses and duration of progesterones are important to counter the effect of endometrial hyperplasia and cancer produced by unopposed estrogens. Commonly used preparations are medroxyprogesterone acetate, 19 nor derivative norethindrone acetate, and levonorgestrel all of which are synthetic progestins.

Micronized progesterone (MP) is a naturally occurring bioidentical hormone and is preferred over medroxyprogesterone acetate used in the past. MP does not negate the advantageous effect of estrogens on the lipid profile. It does not increase the cardiovascular risks and breast cancer risks. The dose of 100 mg/day is given orally for the continuous regimen and 200 mg/day for the sequential regimen.⁴ Micronized progesterone is also available vaginally which may have similar protection but presently is not recommended for the above purpose.

Dydrogesterone is also a bioidentical progesterone. The dose recommended is 10-20 mg / day for a cyclical regimen and 5-10 mg / day for a continuous regimen.

Medroxyprogesterone acetate (MPA): This has been the most commonly used synthetic progestin. It is used in a cyclic method (5 to 10 mg/day) or continuous (1.25 to 2.5 mg/day) regimen. MPA can prevent endometrial hyperplasia caused by estrogens but is associated with an increased risk of breast cancer and possibly coronary heart disease (CHD) with unfavorable effects on lipids.

Levonorgestrel intrauterine system (LNG IUS): This is an intrauterine system releasing levonorgestrel. In women who cannot tolerate oral progestins, this may be used for the prevention of endometrial hyperplasia in women on MHT.

TISSUE SELECTIVE ESTROGEN COMPLEXES (TSECS)

It is a combination of a selective estrogen receptor modulator (SERM) and an estrogen. The combination of bazedoxifene and conjugated estrogen is available though not in India for the treatment of menopausal vasomotor symptoms and osteoporosis prevention. Bazedoxifene prevents estrogen-induced endometrial hyperplasia so progestin is not needed. It may be useful where standard estrogen-progestin therapy is contraindicated or for women who cannot tolerate any type of progestin therapy because of side effects. Bazedoxifene is associated with an increased risk of venous thromboembolic events.⁵

COMBINATION OF ESTROGENS AND PROGESTERONES

Estradiol and MPA combinations are available also with norethindrone and drospirenone. With estradiol and drospirenone combination, endometrial hyperplasia is not seen and favorable changes in lipids were observed.⁶ An oral capsule containing 1 mg 17-beta-estradiol (E2) combined with 100 mg MP (both bioidentical) is effective and approved for the treatment of hot flashes; it is also endometrial protective.⁷

TRANSDERMAL

Combination patches are also available. 17-beta estradiol (0.05 mg/day) with norethindrone acetate (0.14 or 0.25 mg/day) to be applied twice weekly patch is available. This preparation is effective for the relief of vasomotor flushes and the prevention of endometrial hyperplasia.⁸

Also, 17-beta estradiol (0.045 mg/day) with levonorgestrel (0.15 mg/day) to be applied once a week is there.

TIBOLONE

Tibolone, is a synthetic steroid having estrogenic, androgenic, and progestogenic properties. Tibolone reduces vasomotor symptoms. It has a beneficial effect on bone mineral density (BMD) and improves symptoms of sexual dysfunction. It increases the risk of recurrence of breast cancer and may increase the risk of stroke in women over age 60.⁹

CONTRAINDICATIONS TO MHT

Contraindications to MHT use are unexplained vaginal bleeding, Active liver disease, Active gallbladder disease, Hypertriglyceridaemia, or known thrombophilias such as factor V Leiden (with or without a personal history of venous thromboembolism [VTE]), Coronary heart disease, Stroke or transient ischemic attack, history of breast cancer or other estrogen-dependent cancer, endometrial cancer.¹⁰

Side effects: Frequent side effects are: nausea, bloating, weight gain, fluid retention, mood swings(progestogenrelated), breakthrough bleeding, and headaches. Estrogens may cause breast tenderness or soreness. Risks of hormone therapy for women aged younger than 60 years: There is an increased risk of breast cancer with EPT and stroke. An increased risk of endometrial hyperplasia and cancer when unopposed estrogens are used. There is a risk of venous thromboembolism and gallbladder disease.¹¹

INDICATIONS FOR MHT

Menopause hormone therapy is indicated in women with symptoms of menopause. It is approved for four indications: moderate to severe VMS; prevention of osteoporosis in postmenopausal women; treatment of hypoestrogenism, bilateral oophorectomy, Premature ovarian insufficiency, and treatment of moderate to severe vulvovaginal symptoms.

For treatment of genitourinary symptoms due to menopause low-dose topical vaginal ET should be used in the absence of indications for systemic. (Level I).

VASOMOTOR SYMPTOMS

The majority of women with moderate to severe vasomotor symptoms are associated with poor sleep, quality of life, and

difficulty functioning at home and work. MHT is indicated for these women. (Level I) In mild symptoms, MHT is not indicated and lifestyle management, diet, exercise, and add-ons like soybean may help.

HYPOESTROGENISM

MHT is indicated in hypoestrogenism due to premature ovarian insufficiency, bilateral oophorectomy, and hypogonadism. Hormone therapy is given in higher doses to these younger women as compared to MHT and should be continued until the average age of menopause (age 50 to 51 years) to prevent premature bone loss, coronary heart disease (CHD), stroke, and an increased risk of dementia.

GENITOURINARY SYMPTOMS

The genitourinary syndrome of menopause (GSM) includes symptoms of genital dryness, burning, and irritation; dyspareunia; and urinary symptoms of urgency, dysuria, and recurrent urinary tract infections (UTI).

Local Estrogen therapy is an effective treatment for GSM for moderate to severe symptoms of vulvovaginal atrophy and dyspareunia because of menopause but with a preference for low-dose vaginal therapy. Non-estrogen alternatives FDA-approved for dyspareunia include ospemifene and intravaginal DHEA. (Level I)

OSTEOPOROSIS

Hormone therapy is not recommended for the treatment of osteoporosis.¹²

Various oral and transdermal estrogen preparations, alone or in combination with progestogens or BZA, are beneficial for the prevention of osteoporosis. (Level I).MHT prevents bone loss in healthy menopausal women.

The Indian Menopause Society Guidelines recommend HT as a preventive measure against all categories of fractures.¹³

PRESCRIPTION

The lowest, effective dose of systemic ET which relieves symptoms with minimal risks should be given. (Level III). The treatment should be individualized. Bioidentical hormones should be preferred.

Initiation of MHT to be a safe option for healthy, symptomatic women who are within 10 years of menopause or younger than age 60 years and who do not have contraindications to MHT.

A detailed history of complaints, and medical disorders should be taken:

• The patient's age, and severity of menopausal symptoms should be noted. A menopause rating scale may be used.

- The Stage and duration of Menopause should be defined.
- Detailed examination should be done.
- Patient's risks should be calculated for cardiovascular disease and breast cancer before initiating MHT.

RISK ASSESSMENT

Breast

A woman may be categorized in her risk for developing invasive breast cancer by the Gail Model, the limitation being that it has not been validated in India. (Available at https://www.cancer.gov/bcrisktool)

CVD

10 Yr probability risk of myocardial infarction/stroke -Based on WHO SEAR: WHO/ISH Risk prediction charts for India, use the SEAR D. They are simple to use by the paramedics and the clinician.(https://www.who.int > ncds > management > WHO_ISH_Risk_Prediction_.)

Skeletal health

Risk Assessment for Osteoporosis may be done by OSTA/ SCORE / FRAX (http://www.shelf.ac.uk/FRAX).

Muscle health

Assessed by the SARC-F, a 5-item questionnaire.

For women at moderate risk of cardiovascular disease (CVD; 5 to 10 percent 10-year risk), transdermal rather than oral estrogen should be used. Micronized progesterone should be used.

Nonhormonal therapies for symptomatic women who are at high risk (>10 percent 10-year risk) for CVD or moderate (1.67 to 5 percent five-year risk) to high risk (>5 percent) for breast cancer.

RECOMMENDED LABORATORY TESTS

Complete blood examination, Urine test routine, Fasting glucose level/Hb1Ac Lipid profile, Serum TSH, Stool for occult blood, PAP smear, vaginal pH, Transvaginal US, Mammogram or USG.¹³

In postmenopausal women with irregular bleeding endometrial sampling should be done to rule out hyperplasia or cancer before starting therapy. Perimenopausal women have irregular cycles so a biopsy is needed only if heavy bleeding is there.

ROUTE AND DOSAGE

Dose: 1mg of 17-beta estradiol (oral 1 mg/day or transdermal 0.05 mg/day) is adequate for symptom relief.¹⁴ In younger women with oophorectomy or with POI, the dose is 2 mg oral estradiol or 0.1 mg transdermal estradiol or their equivalent), after a few years, the dose can be tapered down.

Lower doses, such as transdermal estradiol (0.025 mg) or oral estradiol (0.5 mg/day) may be started and increased to relieve symptoms. Lower doses are associated with less vaginal bleeding, breast tenderness.¹⁵ Progestin should be given to women with intact uterus.

Oral natural micronized progesterone (200 mg/day for 12 days/month [i.e, a cyclic regimen that is designed to mimic the normal luteal phase of premenopausal women] or 100 mg daily [continuous regimen]) is safe for beast and lipid profile.¹⁶

REGIMES OF MHT

Late menopause transition or early menopause: cyclical regimen:

17 beta-estradiol for moderate symptoms: 0.025 mg patch twice weekly /oral estradiol 0.5 mg per day. For severe symptoms .05 mg patch twice weekly /oral estradiol 1mg per day. With oral micronized progesterone 200mg/day for 12 days first 12 days of the month.

WOMEN >2 TO 3 YEARS POST MENOPAUSE

Continuous estrogen is used (oral 17-beta estradiol 1 mg, transdermal estradiol 0.05 mg) with MPA 2.5 mg/day or natural progesterone 100 mg/day in women with uterus.

Continuous EPT causes amenorrhoea in most women. Irregular bleeding lasting for months is a side effect when clinically amenorrhoea is expected. Eventually, amenorrhoea develops.

GENITOURINARY SYNDROME OF MENOPAUSE

For mild symptoms lubricants and moisturizers can be used. If not relieved Low-dose vaginal estrogen is considered the gold standard for postmenopausal women experiencing only vulvovaginal symptoms

It is preferred to insert vaginal products (except for the vaginal ring) in the proximal, lower third of the vagina rather than in the upper third. This improves efficacy for genitourinary symptoms and decreases estradiol absorption.¹⁷

AVAILABLE PREPARATIONS

Vaginal route:

- 1. Conjugated estrogen vaginal cream Each gram contains 0.625 mg of conjugated estrogens.
- 2. Estriol vaginal cream- Each gram contains: Estriol 1 mg of, and one application (applicator filled to the ring mark) contains 0.5 g.

Regime For Local Therapy In GSM For correction of deficiency-Estriol cream - 0.5mg / day of vaginal application OR Conjugated equine estrogen- 0.3 m g - 1. 25 m g / day of vaginal application for 15 days.

For Maintenance Therapy -Tab estriol 1mg/daily or Estriol Cream 0.5mg or Conjugated equine estrogen- 0.3 mg- twice weekly for two months to one year.¹³

FOLLOW-UP AND MONITORING

Start with lower estrogen doses.(eg, oral estradiol 0.5 mg/ day or 0.025 mg transdermal estradiol) And titrate up to relieve symptoms. Vasomotor flashes improve after three to four weeks. If symptoms are not relieved, increase the dose. If initially severe symptoms are present, start with the higher dose. (1 to 2 mg oral estradiol or 0.05 to 0.1 mg transdermal estradiol)

If hot flashes are relieved and the patient is comfortable, continue the regimen. Taper after two to three years.

Review after one month of starting MHT for efficacy and side effects, after three months, and yearly to assess effects and compliance. At each visit, assess the degree of symptoms, check weight and blood pressure, conduct a physical examination, revise the medical and family history, and perform relevant investigations. Reinforce a discussion on lifestyle and strategies to prevent or reduce chronic diseases.

If on therapy there is persistent bleeding beyond 6 months endometrial biopsy should be done to rule out malignancy. Treatment should be stopped if a contraindication develops like jaundice or deterioration in liver functions. An increase in blood pressure or migraine or blurring of vision.

The standard recommendation for the duration of menopausal hormone therapy (MHT) use has been five years (and not beyond age 60 years).¹⁸

PREPARATIONS AVAILABLE IN INDIA

Estrogen: Oral-CEE 0.3 mg / 0.625 mg (Premarin),

17 beta- estradiol 1 mg/2 mg (Estrabet),

Estradiol valerate 1 mg/2 mg

Transdermal estrogen gel - 0.75mg per 1.25gm of gel and 1.5mg per 2.5 gm of gel (Estrabet gel ,Oestrogel gel)

Dydrogesterone 10mg,

Micronized Progesterone -100,200,300,400 mg,

Levonorgestrel Intrauterine Device -52mg-release 20 mcg/ day Combination of Estrogen and Progesterone:

Continuous sequential-17-beta estradiol 1 mg and 5 mg dydrogesterone (Femoston 1/5)

Continuous sequential-17-beta estradiol 2 mg and 10 mg of dydrogesterone (Femoston 2/10)

Continuous combined-17 beta-estradiol and dydrogesterone 5 mg daily (Femoston 1/5)

Tibolone -2.5mg/day

Estrogen Therapy For Genitourinary Syndrome; Estriol cream -0.5mg/ 0.5gm (Evalon cream); Conjugated equine estrogen 0.625 mg/1 gm of cream(Premarin cream)

KEY POINTS

- 1) Treatment of moderate to severe vasomotor flushes relieves women of a problem that affects their quality of life. It improves bone density in these women.
- 2) At present MHT is not indicated for primary prevention of cardiovascular disease.
- 3) Genitourinary syndrome is aptly treated with lowrisk local estrogens. Bioidentical hormones in the lowest doses should be used.
- 4) Individualized treatment and appropriately selected women are key to the successful outcome of menopause hormone therapy.

CONCLUSION

Menopausal hormone therapy in women less than 60 years and within ten years of menopause is relatively safe in those without risk of breast cancer or moderate to severe cardiovascular risks.

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Non-Hormonal Management of Menopausal Symptoms

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INTRODUCTION

The transition from menstruation to menopause is referred to as menopausal transition or climacteric and lasts from the onset of menstrual cycle irregularities till one year after the last menstrual period. Symptoms are more pronounced during this phase and include alterations in vaginal bleeding patterns, mood disturbances, vasomotor symptoms (hot flushes) and genital problems (dyspareunia and vaginal dryness). This transition is physiological but may prove to be troublesome with 25% of women experiencing problematic vasomotor symptoms & seek treatment.¹

COMMON SYMPTOMS OF MENOPAUSE

- 1. Vasomotor symptoms: Its incidence peaks in late transition with 87% of women experiencing them on a daily basis and 33% report having more than 3 episodes per day.² Hot flashes are seen in upto 80% of women nearing menopause. The sensation of extreme heat in the upper body lasting for 1-5 minutes followed by perspiration, flushing, chills, anxiety and even palpitations in some, is characteristic.³
- 2. Genitourinary symptoms: Vaginal atrophy is a direct consequence of estrogen withdrawal resulting in vaginal dryness, itching, dyspareunia and discharge. There is also loss of vaginal elasticity and epithelial thinning leading to increased fragility predisposing to fissures and tears. More severe symptoms may present as narrowing of introitus, fusion of the labia minora and shrinking of the clitoris and prepuce. These symptoms altogether affect a woman's quality of life and self-esteem.^{2,4}
- 3. Sleep disturbances: With increasing age, sleep disturbances are quite common and these are exacerbated by the onset of menopause, with 50-60% women reporting sleep difficulties like nighttime awakenings. Fluctuations in FSH and estrogen levels also lead to difficulties in falling and then staying asleep. Insomnia also leads to increased predisposition for other conditions like obesity, coronary artery disease, stroke and diabetes.⁵

4. Bone health: Osteoporosis is a well-known consequence of menopause and is characterized by low bone mineral density and deterioration of bone micro-architecture.⁶ This is further compounded by weak muscles and frail joints predisposing to falls and fractures.7 It has been recommended for women above 65 years of age to know their bone mineral density by undergoing a DEXA scan (Dual Energy Xray Absorptiometry), considered to be the gold standard for diagnosis of osteoporosis. This can also be used to calculate the 10-year risk of fractures by using the patient's country of origin, age, bone mineral density, gender and various other clinical risk factors. A score of $\geq 3\%$ for hip fractures on or ≥20% for osteoporotic fractures FRAX (Fracture Risk Assessment Tool) requires medical intervention.⁷

Women's Health Initiative study results highlighted the risks of hormonal therapy on cardiovascular health, stroke and breast cancer. There emerged a need among patients and medical personnel for non-estrogen treatments to manage menopausal symptoms.

Non hormonal options for the management of common menopausal symptoms are addressed below.

Symptom-wise management of menopausal symptoms (Non-Hormonal)

1	Table 1: Medical management of vasomotor symptoms ⁸⁻¹⁰
(a) Pharmacological

Type of drug and dose	Efficacy	Side effects
Selective serce	otonin reuptake inhib	oitors (SSRIs)*
1. Paroxetine 10-25 mg/ day	upto 64% hot flash reduction, also helps improve sleep quality	 Nausea (dose related) Potent inhibitor of CYP2D6 (cannot be given in patients on tamoxifen therapy)

2. Fluoxetine 10-30mg/day	24% reduction in hot flashes	 Nausea (dose related) 18% withdrawal rate 10% dropout rate Nausea Decreased sexual function 	
3. Sertraline 25-100 mg/ day	Modest effect on hot flashes		
4. Citalopram 10-20 mg/ day	 - 49-55% hot flush reduction (can be a first line alternative to paroxetine) - Mild inhibitory effect on CYP2D6 - Can be used in tamoxifen users 	- 20% withdrawal rate	
5. Escitalopram 10-20 mg/ day	 - 24% reduction in hot flashes - Best tolerability profile 	- Nausea - Weakness and drowsiness	
Selective norepi	nephrine reuptake in	hibitors (SNRIs)*	
1. Duloxetine 30-120 mg/ day	- 62% hot flashes reduction	- Nausea - Weakness and drowsiness - Insomnia - Dry mouth	
2. Venlafaxine [#] 37.5-150 mg/ day	- Immediate effect 30-58% hot flash reduction - Improved sleep	 - Nausea - Headache - Dry mouth - Insomnia - Decreased appetite 	
3. Desvenlafaxine [#] 100-150mg/day	 - 24-29% reduction in severity of hot flash - Safest choice in tamoxifen users 	Only in the first week of treatment - nausea, dizziness and headache	
Gabapentin and Pregat		alin	
Gabapentin 300-900 mg/ day given for 8-12 weeks	Almost 45% reduction in severity and incidence of hot flashes	 Somnolence Dizziness 13% withdrawal rate Suicidal thoughts and behaviours 	
75-150 mg/day	flash frequency	- Drowsiness - Unsteadiness - Dizziness - 12-17% withdrawal rate - Suicidal thoughts	

Clonidine				
0.1 mg/ day for 12 weeks	26% relief in hot flashes	 Dry mouth Constipation Hypotension Potential hypertension (if suddenly interrupted) 		
	Oxybutynin			
2.5-5 mg twice a day	- Improved weekly hot flash frequency	- Dry mouth - Dry eyes - Urinary retention - Abdominal pain		
	Fezolinetant*			
Neurokinin receptor 3 antagonist 3 mg/ kg/ day	- Improved hot flash severity and frequency	- Trials are still underway for long term safety and efficacy		

[#]Not available in India

These drugs should be started at the lowest dose for at least two weeks and then titrated up to the standard dose. At weaning off, the lowest dose is to be given for two weeks and then the drug stopped.

(b) Cognitive behavioural therapy (CBT) : CBT has been studied extensively with promis-ing results.¹¹ CBT, both group (group sessions weekly over 4-6 weeks totalling 8 hours) and self-help (booklets with same content as group therapy and 1.5 hour of au-dio guidance over 4 weeks), have shown to improve both the frequency and severity of vasomotor symptoms by up to 50% with the effects maintained at 6 months.¹

Group CBT had the additional benefit of improving quality of life as compared to the self-help group. CBT has also been shown to reduce the frequency of night sweats by almost 39%.¹

- (c) Hypnosis: Randomized controlled trials have shown significant outcomes in cases after hourly sessions spanning over five weeks plus at-home practices. The reduction in night sweats was nearly 74% in the clinical hypnosis group vs controls.¹
- (d) Weight reduction: Increased weight has been found to increase the severity of these symptoms. Even a 10% reduction in weight has been found to improve the frequency of hot flushes.^{12,13}
- (e) Lifestyle modifications: Various techniques like environmental control and cooling op-tions, clothing changes, and identifying triggers have been tried but evidence as to their efficacy is still lacking.
- i. Environmental control and cooling: these aim to lower the core body tem-perature as fluctuations of the same can trigger a hot flash. Wearing loosefitting clothes, dressing in layers, and wearing sleeveless blouses and cotton material can help. Other interventions include using hand fans or electric fans, coolers, and air conditioners, turning the pillow to the

cool side when feeling warm, and drinking plenty of cold liquids.¹²

- ii. Avoiding triggers: Various reported triggers include spicy foods, smoking, and alcohol intake, avoidance of these triggers might help.
- iii. Regular exercise: Even though exercise has no proven benefits in vasomo-tor symptoms, it may improve other aspects like quality of life, sleep patterns, cognitive functions, fatigue, bone density, cardiovascular disease, and weight reduction.
- (f) Yoga: There is limited evidence on the effectiveness of yoga on vasomotor symptoms. Various randomized controlled trials have observed that yoga may alleviate conditions such as anxiety, mood disorders and sleep disturbances.¹⁴
- (g) Paced breathing: This has been shown to help alleviate anxiety that can be associated with hot flashes.¹²
- (h) Acupuncture: Though its mechanism is still unclear, some studies suggest that the en-dorphins released on acupuncture can help modulate the thermoregulation in the hypo-thalamus, thus relieving the vasomotor symptoms. It has also been said to up-regulate the parasympathetic system thereby counteracting the sympathetic overactivity associat-ed with a hot flush.¹⁵
- (i) Stellate ganglion block: Neural temperature regulation can be disrupted by injecting a local anesthetic agent into the neck (stellate ganglion). Disadvantages include its inva-sive nature and cost.
- (j) Phytoestrogens and herbal remedies: Plant-derived sources like soybeans, soy products are rich in isoflavones like genisten and daidzen and have biological activity similar to estrogens. Other herbal treatments include ginseng, ginkgo biloba, and St John's wort.⁹ The data concerning their safety and efficacy are limited.²

INSOMNIA

 Cognitive behavioral therapy for insomnia (CBT-I): CBT is an evidence-based and well-established alternative to pharmacological methods. This is advocated as first-line therapy for insomnia by the American Academy of Sleep Medicine and the European Sleep Research Society, especially in chronic insomnia patients.¹⁶ Studies have shown better outcomes with CBT as compared to pharmacological methods alone.17 CBT-I has been studied in groups of perimenopausal and postmenopausal women and results show significant improvement in sleep patterns after 8 weeks of CBT-I, with lasting ef-fects even 6 months post-treatment.¹⁸ The limiting factors for its widespread use include time-consuming inperson therapies, cost, transportation difficulties, and scheduling sessions. This can be overcome by telephone-based menopause education control.¹⁸

CBT-I includes therapy that aims to change the beliefs and attitude of the patient about sleep and also teaches them techniques like sleep hygiene (better sleeping conditions) to improve sleep efficiency, sleep restriction, stimulus control therapy, and relaxation train-ing to improve sleep quality. It also focuses on cognitive therapy that corrects dysfunctional thoughts about sleep.¹⁶

- 2. Benzodiazepines and Z-class drugs: Used for treating insomnia by acting on the GABAA receptor complex. These drugs help reduce sleep latency, decrease night time awakenings, increase total sleep time, and improve sleep quality. Z- class drugs (Zolpidem, Zopiclone, and Zaleplon) are more selective in binding to the type 1 GABAA receptor and thus have fewer side effects.16 Their usage must be restricted to ≤4 weeks at the lowest possible dose due to uncertainties about their long-term effects, the potential for dependence, intolerance, and abuse. Side effects include headache, dizziness, daytime drowsiness, delirium, falls, and fractures because of muscle relaxa-tion effects.
- 3. Antidepressants (SSRIs and SNRIs): Since depression is associated with insomnia, menopausal women with co-existing depression may be offered SSRIs and SNRIs as treatment. Mirtazapine has been shown to have a sleep-inducing effect with a side ef-fect profile of weight gain and dry mouth. The US FDA has approved Doxepin (3-6mg/day) for treating insomnia. Off-label use of Trazodone (25-50mg) can be used in sleep maintenance. It has the added benefit of not being prone to abuse or depend-ence.¹⁶
- 4. Melatonin: Ramelteon is a melatonin receptor agonist and has been proven to improve sleep quality and is US-FDA approved for treating insomnia. A prolonged release mela-tonin supplement (2mg) was introduced in some European countries with inconsistent results.¹⁶
- 5. Orexin antagonist and Gabapentin: Orexin is a neuropeptide that promotes wakefulness and its levels are found to be increased in menopause. Suvorexant, an orexin receptor antagonist is approved for the treatment of insomnia and is well tolerated and efficacious.¹⁶ gabapentin in a dose of 300mg helped with nighttime awakenings and enhanced sleep.

GENITOURINARY SYMPTOMS

- 1. **Lubricants:** They help alleviate the symptoms of vaginal dryness and consequent dyspareunia. Lubricants may be oil, water, or silicone-based and can be used alone or in conjunction with estrogens. Some oil-based lubricants may cause latex condom breakdown and patients must be counseled regarding sexually transmitted infections.¹⁹
- 2. Moisturisers: They are hydrophobic and have bio-

adhesiveness. They get absorbed into the skin and retain moisture after adhering to the superficial cells of the vagina. This moisture is then released, thus providing lubrication akin to physiological vaginal secretions.¹⁹

- 3. **Hyaluronic acid:** It is a natural polysaccharide and has moisture-retaining properties. It can help retain water and provide relief in atrophic vaginal tissues. Studies have shown good tolerability and minimal to no side effects.
- 4. Laser: There has been growing popularity of vaginal lasers for genitourinary symptoms. Most commonly employed are non-ablative lasers like Erbium: YAG and CO2 lasers. The temperature rises as a result of these causes of neovascularisation, elastin formation, vasodilation, and collagen remodeling and synthesis.19 However, the US FDA has cautioned against the routine use of energy-based devices to relieve these symptoms as it needs fur-ther research. The potential side effects include burning, numbness, bladder disturbances, scarring, and dyspareunia.
- 5. Ospemifene: It is a synthetic, non-steroidal agent approved for the treatment of genitouri-nary syndrome of menopause (GSM). It improves the superficial cell count of the vaginal epithelium and lowers the pH to a premenopausal state. The effects can be seen after 4 weeks upto 1 year of use. Additionally, it also helps in other symptoms such as alleviating bladder incontinence and sexual dysfunction. Ospemifene in a dose of 60mg once a day was found to be well tolerated and even more effective than locally applied estrogens.¹⁹ Side effect profiles ranged from muscle spasms, vaginal discharge, and vulvovaginal can-didiasis to vaginal bleeding and hot flushes. It is contraindicated in women with undiagnosed post-menopausal bleeding and suspected estrogen-dependent neoplasia under treatment.

BONE HEALTH¹⁹

- 1. Exercise: Improved muscle tone contributes to less risk of falls and thus prevention of frac-tures. Popular exercises include yoga, tai-chi, and high-load and low-load resistance train-ing.
- 2. Calcium and vitamin D supplementation: A daily calcium intake of 1000-1500mg/day and vitamin D 600-800IU/day is necessary for optimal bone health.
- 3. Selective Estrogen Receptor Modulators (SERM): Include Raloxifene and bazedoxifene. They inhibit bone resorption, increase bone mineral density, and reduce vertebral fracture risk by up to 40%.
- 4. Bisphosphonates: They should be considered especially in women over 60 years of age. Their effect on bone remodeling reduces the risk of fractures and they are generally well tolerated. Side effects include gastric irritation which can be overcome by adhering

to dos-ing instructions and using effervescent forms or using Risedronate. Adequate renal function and normal serum vitamin D levels are prerequisites for prescription.

- 5. Denosumab: It is a monoclonal antibody that has been approved for osteoporosis treatment. By binding to the receptor activator of the nuclear factor-kb ligand, it reduces osteoclast ac-tivation and bone resorption. It can be used in women with compromised renal function. Serious side effects include atypical femur fractures and osteonecrosis of the jaw, similar to bisphosphonates.
- 6. Teriparatide: It has been shown to reduce vertebral fractures by up to 65% and non-vertebral fractures by 35%. Routine use is limited by the need for daily injections and the high cost. Long-term use has been associated with the development of osteosarcomas and thus, dosage is limited to a maximum of two years.

LIBIDO AND SEXUAL FUNCTION²⁰

- 1. Education and correcting modifiable factors: Counselling women on normal sexual func-tioning, sexual stimulation, involving partners to address issues like demanding behavior for sex, partner's pressure, and partner's sexual dysfunction. Pelvic floor physiotherapy and the use of dilators and vibrators may also help.
- 2. Cognitive behavioral therapy and mindfulness: Can treat hypoactive sexual disorder, or-gasmic dysfunction, and arousal problems.
- 3. Ospemifene: At a dose of 60mg/day, it has been shown to be effective in treating moderate to severe dyspareunia. It is endometrial neutral, safe for bone health, and has no stimulation on the breast tissue.
- 4. Vaginal moisturizers and lubricants: These can help in easing dyspareunia as outlined above.
- 5. Lasers therapies: CO2 and Erbium: YAG laser can be used to improve vaginal elasticity and epithelization.
- 6. Platelet-rich plasma and hyaluronic acid: This combination was studied in postmenopausal women in a phase 2 pilot study and results showed an improvement in vaginal dryness and dyspareunia after 6 months of treatment.19 Further research is necessary for clinical imple-mentation.

CONCLUSION

Non hormonal therapies open up a vast avenue of options for managing menopausal symptoms. They include solutions that go beyond estrogen deficiency. Education of both, the patients and healthcare professionals, is crucial and necessary for individualizing treatment. However, the lack of robust data on the harms of non-hormonal interventions needs to be kept in mind.

KEY POINTS

- Menopausal Transition: Begins with menstrual irregularities and lasts until one year after the last period, featuring symptoms like hot flashes, vaginal dryness, and sleep disturbances.
- With the recent concerns on the use of hormone replacement therapy for perimenopausal symptoms, the focus has shifted to alternative strategies including non-hormonal medications. The available non-hormonal treatment options for the symptoms are elucidated below.
- Hot Flashes Management
 - Medications: SSRIs (e.g., Paroxetine) and SNRIs (e.g., Duloxetine) can reduce hot flashes, though they may cause side effects.
 - Non-pharmacological options: Cognitive Behavioral Therapy (CBT) and hypnosis have been effective in reducing hot flashes and improving quality of life.
 - Lifestyle Changes: Weight reduction and cooling techniques can help manage symptoms.
 - Sleep Disturbances
 - CBT for Insomnia: Recommended as a first-line treatment, showing lasting improve-ments in sleep patterns.
 - Pharmacological Options Benzodiazepines and Z-class drugs can be effective short-term but carry risks of dependence and side effects.

1. Genitourinary Symptoms

- Lubricants and Moisturisers Help alleviate vaginal dryness and discomfort.
- Laser Therapy Non-ablative lasers may improve vaginal health but require more re-search.

2. Bone Health

- Exercise and Supplements Regular exercise and calcium/vitamin D supplementation are crucial for maintaining bone density.
- Medication options like bisphosphonates and denosumab can help manage osteoporo-sis.

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1. Postmenopausal Dysgerminoma: Unveiling a Rare Ovarian Tumour

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ABSTRACT

Ovarian germ cell tumours (OGCTs) account for 2-5% of ovarian malignancies with an annual incidence of 1:100000 and typically occur in young women and adolescents. A pure ovarian dysgerminoma in a postmenopausal female is a rare phenomenon. We report a case of a 48-year-old female who has been postmenopausal for 3 years and presented to gynae opd with pain in the lower abdomen. On clinical examination an abdominopelvic mass enlarged to 18-20week gravid uterus size. All tumour markers were normal except lactate dehydrogenase raised to 1375. On imaging, a well-defined large solid cystic heterogeneous mass arising from the left adnexa suggests neoplastic etiology. Staging laparotomy done. A final diagnosis of ovarian dysgerminoma was made on histopathological examination.

KEYWORDS

Ovarian germ cell tumours, Yolk sac tumour, Cluster of differentiation, Placental alkaline phosphatase, Spalt-like transcription factor, Cell lineage abnormal, Epithelial membrane antigen, Octamer-binding transcription factor

INTRODUCTION

Ovarian germ cell tumours comprise approximately 15% to 20% of all ovarian masses and 2% to 5% of all ovarian malignancies¹. The most common forms of malignant OGCTs are dysgerminoma, yolk sac tumor(YST), and immature teratoma. Dysgerminoma is a rare malignant tumour of the ovary prominent in patients diagnosed with gonadal dysgenesis. The majority of patients reported with dysgerminoma are under 30 years of age. Dysgerminoma occurrence in postmenopausal is extremely rare and atypical. Its rarity poses a challenge to its diagnosis and accurate management. We report a case of dysgerminoma in a postmenopausal who presented with pain lower abdomen.

CASE REPORT

A 48-year-old female, postmenopausal for 3 years, presented to gynae OPD with complaints of pain lower abdomen since 1 year and there was no complaint of postmenopausal bleeding. On clinical examination, the patient was stable with normal vitals. On per abdomen examination an abdominopelvic mass enlarged to 18-20 weeks gravid uterus size, irregular margin, mobile nontender was felt. On per speculum examination cervix midposition, multiparous and vagina seems normal. On per vaginal examination, the uterus seems pushed posteriorly, with a solid firm mass 18 to 20 weeks size with irregular margins, mobile, non-tender felt anterior to uterus. All tumour markers were normal except lactate dehydrogenase which was raised to 1375 U/L. On the CEMRI pelvis, a well-defined large solid cystic heterogenously enhancing soft tissue signal intensity lesion, arising from left adnexa extending up to supraumbilical line. No significant lymphadenopathy was seen, suggestive of neoplastic etiology of the left ovary. She underwent staging laparotomy. Intraoperatively 20-25 cm solid mass was seen arising from the left ovary and fallopian tube with increased vascularity (Fig 1 & 2). The final histopathological diagnosis was ovarian dysgerminoma FIGO Stage 1A was confirmed. Peritoneal fluid cytology and omental histopath were negative for malignancy, hence did not receive any adjuvant chemotherapy and kept on routine follow-up.

Figure 1: Left ovarian solid mass seen intraoperatively







DISCUSSION

Ovarian germ cell tumors (OGCTs) comprise approximately 15% to 20% of all ovarian masses and 2% to 5% of all ovarian malignancies¹. The most common forms of malignant OGCTs are dysgerminoma, yolk sac tumor (YST), and immature teratoma². Dysgerminoma is a rare malignant tumor of the ovary prominent in patients diagnosed with gonadal dysgenesis (46, XY pure gonadal dysgenesis patient). The majority of patients reported with dysgerminoma are under 30 years of age³. As germ cells are not histologically identified in the ovaries of postmenopausal patients, the origin of dysgerminoma from germ cells is most unlikely in this age group. In the largest case series (37 patients) of ovarian germ cell tumors in postmenopausal women, only one patient had a pure dysgerminoma⁴. The incidence of Dysgerminomas in postmenopausal women is unknown. Only a few cases of pure dysgerminoma in postmenopausal women have been reported. Our patient was a 48-yearold lady in a post-menopausal state for 3 years. Clinical signs of dysgerminoma can range from asymptomatic, abdominal pain, abdominal distension, urinary symptoms, abdominopelvic mass, ovarian torsion (adnexal torsion), menstrual irregularities, vaginal bleeding, decreased appetite, nausea, vomiting or fever⁵. The tumoral mass often grows quickly and is usually quite large when it is diagnosed⁶. Similarly, in our case, the patient presented with lower abdominal pain, frequent micturition, lethargy weight loss, and a palpable large abdominopelvic mass.

Serum tumor marker testing in postmenopausal women usually includes serum CA-125 and CEA.

Dysgerminoma is commonly associated with elevated levels of lactate dehydrogenase (LDH) and occasionally with elevated beta human chorionic gonadotrophin (beta-HCG). Elevations in alpha-fetoprotein (AFP) and Cancer Antigen 125(CA-125) are less common⁷. In our patient, all above mentioned markers were within normal limits except LDH which was raised significantly. Ultrasound imaging of a dysgerminoma may demonstrate a septate ovarian mass with varying echotexture, and a CT scan may illustrate a multilobulated solid mass with prominent fibrovascular septa⁸. Despite CT is widely used in detecting female pelvic masses, MRI has proven to be superior in its characterization. On MRI, Dysgerminoma manifests as a large, multilobulated, predominantly solid tumor with heterogeneous signal intensity (SI) and prominent fibrovascular septa^{9,10}. Similarly our patient demonstrated heterogeneous mass on USG and a well defined large solid cystic heterogeneously enhancing soft tissue signal intensity mass lesion from Left adnexa. Although the physical appearance of dysgerminomas varies, in general, they are solid, pink to tan to cream-colored lobulated masses, very similar to appearance in this case.

The pathological features of dysgerminomas on H&E staining can show a variety of architectural patterns. Most notably, as in our case, the neoplastic cells can express significant mitotic activity in the background of fibrous septa with an abundance of lymphocytes¹¹. Microscopically, there is a monotonous proliferation of large, rounded, polyhedral clear cells that are rich in cytoplasmic glycogen and contain uniform central nuclei with one or a few prominent nucleoli.

IMMUNOHISTOCHEMISTRY

As these tumors originate from undifferentiated pluripotent germ cells, they are positive for pluripotency markers eg. nuclear staining for OCT-3/4, SALL-4, NANOG, and cytoplasmic staining for LIN28. The more commonly used markers include PLAP, CD-117, and D2-40.

Focal cytokeratin expression may be seen but EMA is negative. It is negative for glypican-3, CD30, and AFP.

MOLECULAR GENETICS

c-kit mutation is present in a third to half of dysgerminomas and chromosome 12 abnormalities may be seen in up to 80%. The tumour cells are histologically identical to the seminoma of the testis and closely resemble primordial germ cells of the embryo¹².

In treating dysgerminoma, surgery is not only therapeutic but also required for diagnosis and staging and to guide the need for adjuvant therapy. Fertility-preserving surgery is reasonable in young women but is not recommended for patients who have completed child-bearing¹³. In young patients, the standard treatment for dysgerminoma is usually fertility-sparing surgery with unilateral salpingooophorectomy¹⁴. Preservation of the contralateral ovary leads to "recurrent" dysgerminoma in 5 to 10% of retained gonads during the next 2 years. Indeed, at least 75% of recurrences develop within the first year of diagnosis¹⁵. A midline incision with a thorough inspection of the peritoneal cavity followed by a total hysterectomy, bilateral salpingectomy-oophorectomy, paraaortic and bilateral pelvic lymph node dissection, and omentectomy is performed. In our patient, TAH+BSO with Pelvic Lymphadenectomy with Infracolic omentectomy was done. After surgical staging, all patients, except patients with stage IA Grade 1 and 2 pure dysgerminomas, should receive adjuvant chemotherapy. Adjuvant chemotherapy is recommended based on several small studies including results from treatment of testicular seminomas¹⁶. The

National Comprehensive Cancer Network (NCCN) guidelines endorse a multi-chemotherapy regimen of bleomycin, etoposide, and cisplatin (BEP) as the initial treatment for a FIGO Stage IB - IVB ovarian dysgerminoma (Network and Cancer, 2022). Our patient's final pathological stage was IA therefore did not receive any chemotherapy. Pure dysgerminoma has a very favourable prognosis with a 5-year survival of around 90%. The recurrence rate ranges from 18% to 52% with 80% of recurrences occurring in the first 2 years after diagnosis, and it has been reported that more than 75% occur in the first year¹⁷. Patients who develop recurrent disease after surgery and adjuvant chemotherapy have alternatives. One regimen is a combination of paclitaxel, ifosfamide, and cisplatin (TIP) (Network and Cancer, 2022). Immunotherapy may offer another treatment option for patients with recurrent OGCTs. A recent phase II clinical trial of Pembrolizumab in patients with advanced, heavily pretreated metastatic germ cell tumors, immunotherapy agent was well tolerated but robust antitumor activity was lacking¹⁸.

CONCLUSION

Dysgerminoma in postmenopausal age is a very rare condition. Imaging Tumour marker plays an important role in making preoperative diagnosis. In treating dysgeminoma surgery is not only therapeutic but also required for diagnosis and staging and to guide the need for adjuvant therapy. In young patients, the standard treatment for dysgerminoma is usually Fertility sparing surgery with unilateral salpingo-oopherectomy. After surgical staging, all patients except patients with stage 1A pure dysgerminoma should receive adjuvant chemotherapy.

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2. Krukenberg Tumor – A Rare Occurrence

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ABSTRACT

Krukenberg tumors typically present as bilateral ovarian involvement resulting from metastatic deposits of adenocarcinoma, most commonly originating from the stomach, though they can rarely arise from other gastrointestinal (GI) and non-GI organs. The exact route of metastasis remains unclear, and there is ongoing debate about whether surgical resection of ovarian metastases and/or the primary tumor significantly improves patient outcomes. Here, we present a case highlighting this uncommon disease entity and explore current insights into the disease's management, including chemotherapy and surgery.

KEYWORDS

Krukenberg tumor, metastatic mucinous adenocarcinoma, signet ring cell mucinous adenocarcinoma, palliative chemotherapy, surgery.

INTRODUCTION

In 1896, Friedrich Krukenberg described five cases of a peculiar ovarian tumor that he initially classified as a new type of primary ovarian sarcoma, which he named "fibrosarcoma ovarii mucocellulare (carcinomatodes)"^{1,2}. Although Krukenberg initially proposed that these tumors originated in the ovary, further research later confirmed that the majority of such tumors are almost exclusively secondary to gastrointestinal (GI) malignancies, particularly stomach cancer.³ The term "Krukenberg tumor" has since been used to describe metastatic tumors to the ovaries, most commonly from primary gastric adenocarcinoma.

Though gastric carcinoma remains the predominant source of Krukenberg tumors, other GI malignancies such as those arising from the colon, biliary system, jejunum, and pancreas have also been implicated. Non-GI malignancies, including breast cancer, uterine endometrial cancer, thyroid cancer, kidney cancer, and lung cancer, have been reported infrequently as primary sources of ovarian metastases.^{4,5}

Krukenberg tumors are known to affect predominantly pre-menopausal women, with the average age ranging from 55y to 60 years. Approximately 80% of cases involve bilateral ovaries. Here, we report a rare case of Krukenberg tumor with an unknown primary. Ovarian histopathology shows mucinous adenocarcinoma with signet ring cells. Emphasizing the critical role of diagnosing and management in the context of such an unusual presentation.

CASE REPORT

A 44-year-old P2L2 housewife, presented with a five-month history of lower abdominal pain, which was diffuse and affecting the lower abdomen mainly. Over a short period i.e. 2 months, she noticed a lump in the abdomen, which prompted medical consultation. There were no menstrual or bowel-bladder complaints. No significant history of weight loss and anorexia is appreciated as well.

An ultrasound of the lower abdomen revealed a 4x3 cm intramural fibroid, which initially seemed to explain her symptoms. However, further imaging with magnetic resonance imaging (MRI) revealed a solitary, relatively well-defined 61x138x139 mm solid-cystic lesion in the abdominopelvic region, with the variable enhancement of the solid component and uterus with sub-serosal fibroid. These findings raised concerns for a more complex pathology. All relevant tumor markers, including CA-125, CA 19-9, S.LDH, beta HCG, and carcinoembryonic antigen (CEA), were within normal limits, providing no clear direction for diagnosis at this point.

With the complex nature of the lesion, an exploratory laparotomy was performed. During surgery, a large twisted left ovarian solid mass approximately 20x18 cm in size with firm consistency and bosselated surfaces was identified in the abdomen whereas the right ovary was 5*3cm in size. Other abdominopelvic organs including the uterus were nonsignificant. Mild free fluid was present and sent for cytology. With the evidence not in favour of malignancy, total abdominal hysterectomy with Bilateral salpingo-oophorectomy was performed along with infrasonic omentectomy. The surgical specimen was sent for histopathological examination, which revealed metastatic mucinous adenocarcinoma with signet ring cells involving both ovaries and the omentum findings consistent with a diagnosis of Krukenberg tumor. (Figure 1)

Post-operative surgery and oncology opinions were taken to investigate for primary tumor and further management. The patient underwent an upper GI endoscopy showing normal findings. In a colonoscopy, the scope couldn't negotiate through the ascending colon. ? A carcinoma colon impression was made and a biopsy was taken which reported active colitis. PET CT showed FDG avid uptake at splenic flexure of the ascending colon and few mesenteric lymph nodes.

She received six cycles of chemotherapy with fluorouracil and oxaliplatin, the standard protocol for metastatic mucinous adenocarcinoma. Her 6th cycle of chemotherapy was completed on 4th September 2024. Figure 1: Histopathology showing signet ring cells



DISCUSSION

Krukenberg tumors represent a unique and challenging manifestation of metastatic disease, most commonly secondary to gastric adenocarcinoma. While gastric cancer remains the primary site in most cases, reports in the literature have documented metastasis from sites such as the small intestine, breast, pancreas, biliary tract, and gallbladder.⁶⁷ Here in our case the metastasis is probably from colonic malignancy.

The predilection of Krukenberg tumors is with average age of diagnosis being between 40 and 46 years. One explanation is the rich vascular supply of the ovaries, which may facilitate the hematogenous spread of tumor cells from a distant primary site. Additionally, it has been suggested that the rupture of the ovarian surface during ovulation may release growth factors as part of the wound-healing process, which promotes cell migration—a phenomenon known as chemotaxis. This process could theoretically attract metastatic tumor cells to the ovary, resulting in secondary ovarian malignancies.

Histologically, Krukenberg tumors are typically characterized by poorly differentiated intestinal-type adenocarcinoma cells, often with signet ring cell morphology. The presence of signet ring cells is a hallmark feature of gastric carcinoma, but here no gastric involvement is identified on imaging as well as in endoscopy. In our case, colonoscopic and imaging findings are consistent with cancer ascending colon with ovarian metastasis. Immunohistochemical markers like CK7, CK20, E-cathedral, ER, and PR may help in diagnosis.

The prognosis of Krukenberg tumors remains poor, as they are indicative of advanced metastatic disease. Despite this, the optimal treatment approach is still a matter of debate. Systemic chemotherapy, such as the fluorouracil and oxaliplatin regimen administered to our patient, is commonly employed to control tumor growth and alleviate symptoms. However, the benefit of surgical intervention remains uncertain. While some studies suggest that cytoreductive surgery, including resection of the ovarian metastases and primary tumor, may prolong survival in selected patients, others argue that the advanced stage of disease at the time of diagnosis renders surgical resection largely palliative.

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3. A Rare Case of Sertoli Leydig Cell Tumor of Ovary Masquerading as PCOS in a Patient of Infertility

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ABSTRACT

Ovarian Sertoli-Leydig cell tumors are rare mixed-sex cord-stromal tumors, accounting for <0.5 % of all ovarian malignancies. The tumor has variable clinical presentations thus complicating the diagnosis and making the treatment even more difficult in these patients.

Herein, we report a case of a 28-year-old, married, nulliparous female who presented with secondary amenorrhea, features of virilization, and infertility with a solid ovarian tumor on imaging.

Histopathological examination revealed well welldifferentiated Sertoli-Leydig cell tumor confined to the left ovary. Postoperatively, her menstrual cycle got regularized along with gradual relief in features of virilization.

KEYWORDS

Sex cord tumors, Leydig cell tumor of ovary, solid tumor, virilization.

INTRODUCTION

Sertoli Leydig cell tumors (SLCTs) of the ovary are extremely rare accounting for less than 0.5% of ovarian malignancies¹. Mostly unilateral, these tumors are also known as arrhenoblastoma and neuroblastoma. Though they may present in any age group, they are most commonly seen in the third and fourth decades of life². One-third of the cases of SLCTs present with symptoms of androgen excess with signs of virilization like hirsutism, and oligomenorrhoea followed by amenorrhea, deepening of voice, breast atrophy, and clitoromegaly being present invariably. Sometimes there might be a delay in diagnosis as patients usually present with few symptoms of virilization and are misdiagnosed as PCOS.

CASE REPORT

A 28-year-old nulligravida married for 7 years presented to the outpatient department with oligomenorrhoea for 6 years followed by secondary amenorrhea for 8 months associated with hoarseness of voice and excessive hair growth on face, chest, abdomen, thighs, and inability to conceive. She was previously diagnosed with PCOS by her treating physician and had been advised of combined oral contraceptive pills

to which she eventually stopped responding. She even received 4 cycles of ovulation induction for her infertility. On examination, she had a normal BMI with thick coarse hair on her face, chest, abdomen, thighs, and pubis with clitoromegaly and well-developed secondary sexual characteristics. All parameters during her infertility workup turned out to be normal. In her PCO profile laboratory values showed increased serum testosterone levels (11.8nmol/L) but normal DHEAS (1.1micromoles/L) with normal 17-OHP, cortisol, TSH, prolactin, LH, FSH, estradiol, progesterone. All other tumor markers were within normal range. Ultrasound pelvis revealed a 4.74 cm complex solid mass with increased vascularity in the left ovary. MRI pelvis corresponded to the findings of ultrasound showing a left ovarian 4.1x4.1 cm solid avid enhanced tumor, likely neoplastic. Laparoscopic left salpingo-oophorectomy with peritoneal washings was performed. Per-operatively a 5x5 cm left solid ovarian mass with smooth intact the capsule was found with grossly normal right ovary and uterus. Histopathological examination unveiled a well-differentiated Sertoli Leydig cell tumor of the left ovary with negative peritoneal fluid cytology (FIGO 1A). Immunohistochemistry showed positivity for WT1. After one month of surgery during her follow-up, the patient had resumed her periods with declining serum testosterone levels. She is being regularly followed up by both oncology and reproductive medicine teams.

Figure 1: CEMRI showing A round solid enhancing mass 41x41mm T1, T2/STIR mildly hyperintense signal intensity lesion in left adnexa



Figure 2: Intraoperative image showing smooth round solid ovarian mass with intact capsule

Figure 3: Cut section: Well-circumscribed homogenous area with lobulation with multiple tiny cysts



Figure 4: Histo-pathological examination showing Nest of Sertoli Cells with some Leydig cells



DISCUSSION

SLCTs being a rare sex cord tumor occur most commonly in 3rd to 4th decades of life but can be found in women of all age group2. Isolated case reports are available where SLCTs have been diagnosed in prepubertal as well as postmenopausal females. These tumors are mostly unilateral, confined to the ovary with highly variable sizes ranging from 3 to 35 cm with an average size of 12–14 cm³.

Though it has no pathognomonic symptom, it is the most common virilizing ovarian tumor with the usual and distinctive presenting complaints associated with increased androgen excess. Around 30-50% of these cases present with signs of virilization like hirsutism, hoarseness of voice, defeminization of physical characteristics, changes in psycho-sexual behavior, menstrual disorders such as oligomenorrhea or secondary amenorrhea, acne with hyper seborrhea, muscular, clitoris, and labia majora hypertrophy. Few patients may even present with a rare hyperestrogenic state with heavy menstrual bleeding or precocious puberty in prepubertal patients.

Overlapping symptoms with that of PCOS often leads to a delay or misdiagnosis in some of these patients. However, a divulging laboratory feature that differentiates these androgen-secreting tumors from PCOS includes virilization with many times elevated serum testosterone levels well above 7 nmol/L in contrast to only mild to moderate elevation and hirsutism in PCOS3⁴. These tumors are often embedded in the ovary with a polycystic appearance similar to PCOD. Though transvaginal sonography is the best imaging for initial assessment of the mass, they may be missed on grey scale ultrasound just as in the present case. Hence advanced imaging MRI or CT scan methods can be utilized⁵.

Ovarian SLCTs are usually firm, lobulated, wellencapsulated solid masses. Microscopically, they are made up of uncontrolled proliferation of varying degrees of tubular differentiation, lined by Sertoli cells and intervening nests of Leydig cells. Well-differentiated is the most common histological variant of these tumors, with poorly differentiated tumors offering a diagnostic challenge. IHC markers play an important role in the diagnosis of ovarian SLCTs to differentiate them from other tumours like granulosa cell tumors, endometroid carcinoma, serous carcinoma, hepatoid carcinoma of the ovary, and endodermal sinus tumor. Immunohistochemically (IHC), all SLCTs stain positive for Inhibin, Calretinin, and CD56, WT1, and negative for CK7⁶.

Management of these patients can be challenging due to the non-availability of a single standard protocol. As these tumors are found at an early stage and in young women, fertility-sparing surgery such as unilateral salpingooophorectomy via laparoscopy or laparotomy is usually recommended. As per the available literature, successful term pregnancies have been reported after fertility-sparing surgery⁷. A formal staging procedure + Total abdominal hysterectomy with bilateral salpingo-oopherectomy should be considered in patients with completed families and those with intermediate and high-grade tumors. Only 10 % of cases present with ovarian rupture and 2 % are metastatic at diagnosis, which mainly concerns intermediate to poorly differentiated tumors and also requires chemotherapy subsequently⁸. Bleomycin, etoposide, and cisplatin (BEP) appear to be an active combination regimen for first-line chemotherapy^{9,10}.

The majority of these tumors are diagnosed at stage I and have a good prognosis. The age of the woman and disease stage and grade are the most important factors in considering the patient's prognosis. For well-differentiated forms, the prognosis happens to be excellent with a five-year survival of 100 %; whereas in moderately to poorly differentiated forms, the five-year survival drops to 80 %. When the tumor remains localized to the ovary, the five-year survival is 95 %, conversely for metastatic forms it is close to 0 %^{11,12,13}. As per the available literature relapse rate of 95 % within 5 years occurs in the pelvis and abdomen and holds a very poor prognosis requiring multi multi-modal approach of surgery with chemotherapy.

CONCLUSION

With its rarity and no pathognomonic symptom, it can be easily misdiagnosed with PCOS especially in a young patient presenting with infertility. Fertility-sparing surgery forms the mainstay of treatment as most women are young with well-differentiated stage 1 disease at the time of diagnosis. Spontaneous successful pregnancies have been observed even in patients with poorly differentiated tumors following completed treatment. Features of virilization have been found to improve as soon as the tumor is removed. Although making a diagnosis of SLCTs is a challenging task, when it is diagnosed and treated early it can lead to an excellent outcome both in terms of future pregnancies and minimal recurrences.

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Journal Scan

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1. Factors underpinning an improved menopausal experience in the workplace for doctors: A UK-based qualitative study

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British Medical Journal

OBJECTIVES

A recent British Medical Association survey revealed that very few National Health Service (NHS) doctors felt comfortable discussing symptoms with their managers, and many feel unable to make changes to their working lives to accommodate their menopause. An improved menopausal experience (IME) in the workplace has been associated with increased job satisfaction, increased economic participation, and reduced absenteeism. Currently, existing literature fails to explore menopausal doctors' experiences and has no factors in non-menopausal colleagues' perspectives. This qualitative study aims to determine the factors underpinning an IME for UK doctors.

DESIGN

Qualitative study using semi-structured interviews and thematic analysis.

RESULTS

Four overarching themes underpinning an IME were identified: menopausal knowledge and awareness, openness to discussion, organizational culture, and supported personal autonomy. The levels of knowledge held by menopausal participants themselves, their colleagues, and their superiors were identified as crucial in determining menopausal experiences. Likewise, the ability to openly discuss menopause was also identified as an important factor. The NHS culture, gender dynamics, and an adopted superhero mentality – where doctors feel compelled to prioritize work over personal well-being – further impacted under the umbrella of Organisational culture. Personal autonomy at work was considered important in improving menopausal experiences at work for doctors. The superhero mentality, lack of organizational support, and lack of open discussion were identified as novel themes not found in current literature, particularly in the healthcare context.

CONCLUSIONS

This study highlights that doctors' factors underpinning an IME in the workplace are comparable to other sectors. The potential benefits of an IME for doctors in the NHS are considerable. NHS leaders can address these challenges by using pre-existing training materials and resources for their employees if menopausal doctors are to feel supported and retained.

EDITOR'S COMMENT

• This study reports the experiences of doctors undergoing menopause as well as the previously unreported experiences of doctors who have not undergone menopause, providing contrasting perspectives on the workplace menopausal experience in the National Health Service. Recommended targets for action include education, policy, formal and informal support structures, and strategies to enhance interpersonal and managerial support. In addition, workplaces may find Menopause Information Packs for Organisations a useful and potential source of research-based training.

2. Sleep disorders in menopausal women

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BACKGROUND

Sleep disturbance is one of the frequent signs and symptoms encountered in post-menopausal women. It affects the quality of life and may lead to depression in some women. The objective of the present study was to find out the prevalence of sleep disorders in post-menopausal women

METHODS

Prospective study done on the post-menopausal women coming to Gynaecology OPD of Dr Bheem Rao Ambedkar Hospital, Raipur. This study was a prospective crosssectional observational study, conducted in the outpatient department of Obstetrics and Gynecology from 1st August 2016 to 31st January 2017. It included 500 women of postmenopausal age. A detailed Performa was provided to assess sleep patterns and disorders associated with it. All the data was analyzed using the chi-square test

RESULTS

The prevalence of sleep disturbances was 29.58%. Homemakers were affected more in comparison to working women, 71,43% of women had problems in initiating sleep. About 2/3rd of women in the study group developed insomnia within 5 years of menopause, whereas 1/3rd took more than 7 years to develop insomnia. Co-morbidities were present in 48% of women. Our women have a mean age of menopause around 45 years.

CONCLUSIONS

Sleep disorders are common, with a prevalence of 29.5% in menopausal women in the present study. It significantly causes psychosocial problems in women. There is a need for it to be asked for and to be treated promptly.

EDITOR'S COMMENT

This study is done to highlight the sleep disorder faced by menopausal women. Sleep disturbances may lead to mood disorders and other psychosocial problems. The mainstay of diagnosis is based on the subjective complaints. It is important to address these problems in menopausal women and treat them promptly.

3. Acute estradiol treatment reduces skeletal muscle protein breakdown markers in earlybut not late-postmenopausal women

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Steroids. 2019 Jun:146:43-49

OBJECTIVES

Menopause and decline in estradiol (E2) may contribute to sarcopenia (i.e., age-related decline in muscle mass and strength) in women. E2 may directly impact skeletal muscle protein breakdown via estrogen receptor (ER) signaling, primarily ERa. It is not yet known whether: 1) E2 regulates pathways of skeletal muscle protein breakdown; 2) E2-mediated changes in protein breakdown markers are associated with ERa activation and insulin sensitivity; and 3) the effects of E2 on protein breakdown markers differ by increasing time since menopause.

STUDY DESIGN

We studied 27 women who were ≤ 6 years past menopause (early postmenopausal, EPM; n = 13) or ≥ 10 years past menopause (late postmenopausal, LPM; n = 14). Fasted skeletal muscle samples were collected following 1 week of transdermal E2 or placebo treatment in a randomized cross-over design.

MAIN OUTCOME MEASURES

We analyzed for cytosolic protein content of the: 1) structural proteins myosin heavy chain (MHC) and tropomyosin;

and 2) protein regulatory markers: protein kinase B (Akt), muscle-specific ring finger protein1 (MuRF1), atrogin1, and forkhead box O3 (FOXO3) using Western blot.

RESULTS

In response to acute E2, FOXO3 activation (dephosphorylation) and MuRF1 protein expression decreased in EPM but increased in LPM women (p < 0.05). ERa activation was not associated with these protein breakdown markers, but FOXO3 activation tended to be inversely correlated (r = -0.318, p = 0.065) to insulin sensitivity.

CONCLUSIONS

These preliminary studies suggest the effects of E2 on skeletal muscle protein breakdown markers were dependent on time since menopause, which is consistent with our previous study on insulin sensitivity. Editor's comment Falls hip fractures, and the ensuing loss of independent living are significant health issues in aging women. Older women experience greater rates of morbidity and physical disability than older men [1]. The age-related decline in muscle mass and strength (i.e., sarcopenia) contributes to this physical disability and increases health costs in this population. This study emphasizes that estradiol (E2) is an important factor in the menopause-related reduction in muscle mass. E2-based hormone therapy (HT) has been shown to preserve muscle mass and function in postmenopausal women. The present study demonstrates that the effects of E2 on markers of skeletal muscle protein breakdown were dependent on time since menopause.

Obituary Dr Geeta Kinra (1949 - 2024)Dr Geeta Kinra was a reputed gynaecologist both nationally and in international circles. She was born in 1949 and did her graduation in 1971 from Government Medical College, Amritsar. She completed her MD from the prestigious AIIMS, New Delhi where she worked subsequently as a faculty for decades. She trained and shaped many doctor's lives and careers, many of who has her fond memories. After serving a long period in AIIMS, she was later associated with multiple private hospitals in south Delhi including Rejoice Hospital, and Rainbow Hospital. She was a published author with more than 100 articles and book chapters in many national and international journals and textbooks. She was a humble, pleasant, and honest person. It is sad and unfortunate to lose a great professional and pleasant human being. On behalf of all AOGD members, may our prayers lead her soul to our divine deity. Our condolences to the family. AOGD FAMILY



Jaya Chawla Professor Department of Obstetrics and Gynaecology, ABVIMS & Dr RMLH

Over 50 people hospitalised, 9 dead in Listeria outbreak: All you need to know about bacterial infection

TOI World Desk / TIMESOFINDIA.COM / Aug 29, 2024, 14:36 IST





The news of 12 states in the US and Canada being struck by Listeria is something everyone is now aware of (TOI Aug 29, 2024). It is a natural instinct for Obstetricians to want to know the implications for pregnant women and their offsprings. So here is a quick update on the salient features. (Jeffrey Man Hay Wong et al. CMAJ Aug 2024, 196 (28) E978;

The causative organism Listeria Monocytogenes spreads by ingestion of contaminated food namely unpasteurized dairy products and undercooked meat. The bacterium is resistant to refrigeration and hence is likely to survive in ready-to-eat meals.

The symptoms of Listeriosis are frequently mild ranging from fever with chills to myalgia, and gastrointestinal symptoms. More severe cases can present with neurological symptoms such as headache, imbalance, and neck stiffness. Since there is a long incubation period of about 70 days more than 2 months would have elapsed by the time the patient presents to seek medical help. What is more important is that pregnancy lends itself to heightened susceptibility owing to the element of lower immunity. While most pregnant women would be asymptomatic vertical transmission is a genuine concern.

Nearly 29% of women with invasive listeriosis, suggested by bacteremia or meningitis experience perinatal loss. Therefore, in afebrile patients presenting with flu-like symptoms and possible exposure to Listeriosis, a 14-day' course of Amoxycillin 500 mg eight hourly should be considered pending blood culture.

In case the patient presents with febrile illness and likely exposure to Listeria, blood cultures should be drawn immediately and intravenous Ampicillin in 1-2 g a day in divided doses should be initiated and continued for 14 days. Electronic fetal heart rate monitoring should be instituted. The newborn should be offered lab investigations, imaging, and CSF studies to rule out neonatal affliction.



FEZOLINETANT: WATCH OUT FOR SERIOUS HEPATIC INJURY!

The US FDA September 9, 2024, issued a warning regarding the potential of severe hepatic injury with the use of Fezolinetant, a Neurokinin (NK3) receptor blocker. It may be recalled that last year, on May 12, 2023, the U.S. Food and Drug Administration had approved a drug that was going to cause long-term ripples in the way vasomotor symptoms, (read hot flushes) were going to be dealt with by us Medics! The drug, Fezolinetant, also known by its trade name of Veozah works by blocking the neurokinin 3 (NK3) receptors that are known to be responsible for thermoregulation. The pill was to be taken daily at the same time at a dose of 45 milligrams a day. In the event of a dose getting missed the pill had to be taken as soon as recalled and the rest of the schedule continued as usual.

The efficacy and safety of the drug had been verified in two phase 3, double-blind placebo-controlled randomized trials each of which entailed administering the drug for 12 weeks. After the efficacy was clearly demonstrated the women randomized to the placebo arm were re-randomized to the drug for a period of 40 weeks thereby generating safety data for nearly 52 weeks of exposure to the drug. (Lederman, Samuel et al. The Lancet, 2023)

The package insert of the drug did instruct users to undergo liver function tests every three months until 9 months of use and stop if LFTs worsen. Presently, the adverse effect database of the drug received a case where a woman developed serious hepatic adverse effects within 40 days of using the drug. The symptoms reverted to baseline gradually after the drug was discontinued. After this, the FDA now recommends that a baseline LFT is offered before initiating therapy. If the levels of total bilirubin or transaminases exceed twice the upper limit of normal, therapy should not be initiated. If on follow-up the transaminases are found to increase by five times the baseline or more then the therapy should be discontinued. In addition, discontinuation of therapy is also warranted if the levels of transaminases have exceeded three times the baseline, in the presence of serum bilirubin levels that are more than double the baseline. In case the transaminases are elevated in isolation without the increase in bilirubin to twice normal, other causes of deranged liver function must be excluded and the patient kept under serial monitoring of LFTs.

In medicine, the clinical must always remain cardinal to the management of the patient. Going by the same dictum, a patient presenting with abdominal pain, gastrointestinal disturbances, or back pain must be evaluated further even if outside the standard follow-up 3-month plan.

Snitch Snatchers

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- 1. How much bone loss does a person have in the first 5 years of menopause?
 - A. 10% over the 5-year period
 - B. 5% over the 5-year period
 - C. Up to 20% over 5 to 7 years
 - D. 1% to 2% a year
- 2. Hot flashes are symptoms of the perimenopausal stage. How many perimenopausal people have them?
 - A. 100%
 - B. 75%
 - C. 50%
 - D. 30%
- 3. The following drugs are useful for prevention and management of post-menopausal osteoporosis except
 - A. Alendronate
 - B. Raloxifene
 - C. Teriparatide (Parathyroid hormone)
 - D. Gabapentin
- 4. The following are bone turnover markers (BTM) except
 - A. Serum C-terminal telopeptide (CTX)
 - B. Serum procollagen type 1 N-terminal propeptide (PINP),
 - C. alkaline phosphatase.
 - D. Serum calcium
- 5. Following is true about Denosumab except
 - A. It is a monoclonal antibody approved recently in India, specifically targets RANKL, and is approved for postmenopausal women with osteoporosis at high risk of fracture
 - B. It increases both trabecular and cortical bone strength; reduces vertebral, nonvertebral, and hip fracture risk;
 - C. The dose is 60 mg is given SC once in 3 months
 - D. It is well tolerated even in patients with creatinine clearance <30 ml/min where bisphosphonates and teriparatide are contraindicated

- 6. Post Menopausal bleeding is also associated with other non endometrial Cancers. The most common of these is
 - A. Fallopian tube Cancer
 - B. Breast Cancer
 - C. Cancer of the cervix
 - D. Colorectal Cancer
- 7. Post-menopausal complaints of dysuria, urgency and frequency are commonly termed as
 - A. Irritable bladder syndrome
 - B. Vaginal syndrome
 - C. Urethral syndrome
 - D. Ureteral syndrome
- 8. Atrophic changes due to oestrogen deficiency are the result of a rapid loss of
 - A. Fats
 - b. Collagen
 - c. Minerals
 - d. Vitamins

9. The false statement about the drug ELINZANETANT is

- A. Significantly reduces frequency and severity of moderate to severe hot flashes associated with menopause
- B. Elinzanetant is a neurokinin-1 and 3 receptor antagonist
- C. Elinzanetant's reported peak drug concentrations are reached within one hour and the terminal elimination half-life is approximately 15 hours.
- D. None

10. The gold standard for measurement of osteoporosis risk is

- A. Ultrasound screening
- B. Peripheral X-ray screening of proximal phalanx, calcaneum
- C. DEXA (Dual X-Ray Absorptiometry) measurement of lumbar spine and hip
- D. None
- Answer key to September quiz on Urogynaecology
- Q1 Ans: Inguinal Ligament of Cooper
- Q2 Ans: Midurethral Sling
- Q3 Ans: Sympathetic System
- Q4 Ans: Acetylcholine
- Q5 Ans: >15 ml/sec

- Q6 Ans: 102 Q7 Ans: Urinary Incontainance Q8 Ans: Perineal Membrane Q9 Ans: Llissosphincter
- Q10 Ans: 3 months

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