



FOGSI FOCUS

THE MENOPAUSE

JANUARY - 2010



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The Menopause **FOGSI** Focus

President's Message



Dr. C. N. Purandare

“It does not matter how slowly you go so long as you do not stop”

- Confucius, Chinese philosopher & reformer (551 BC - 479 BC)

Menopausal years are increasingly important as one third of women's life is spent in menopause. Menopause is growing to become a significant public health issue in India. This FOGSI FOCUS is designed to give you a glimpse into the scope of clinical practice in this exciting & rewarding area of women's health. The aim of this FOCUS is to increase knowledge of every gynecologist to the constant change and evolution that is occurring in managing menopause and to suit the fast changing needs of our female patients.

There are a lot of modifications and newer molecules for managing menopause and choices now available to us as practitioners for our patients. The aim is to approach Menopause in a holistic manner and ensure that a healthy lifestyle and mindset is the way to positive health for our patients. The purpose is to be able to deal with the subject with much depth and details, and hence all details of symptomatology along with life style changes, nutrition and exercise and all the different types of hormone therapy are highlighted in this FOGSI FOCUS.

I would like to thank all of you for your support during this year, Emcure Pharmaceuticals for agreeing to print this important FOCUS and Dr. Mandakini Parihar for doing an excellent job in editing this FOGSI FOCUS on Menopausal Health.

I wish you all a very happy 2010.

With regards,

Dr. C. N. Purandare





Messages from Vice President of FOGSI

Dr. Shirish Patwardhan,



Dear Friends,

Namskar and Greetings and Best Wishes for the New Year from FOGSI, AMOGS and POGS! It is my proud privilege to extend Best Wishes for FOGSI Focus on Menopause which is edited by Dr. Mandakini Parihar. I am sure that with all the hard work put in by you and your team, it would be a great help to fellow FOGSIANS.

While caring for the clients, many of us neglect our own health. This is indeed a serious issue. Let us ensure that all our constituent Society's are Anemia Free to begin with. Let us not forget our staff and see to it that our Hospital / Clinic too are Anemia Free. Do join in for Earning – Energy – Enthusiasm (E Cube) or Sexcellence Workshop held in Leh every May and in Society's which request for it.

Wishing all the members Srimanti and Anand in years to come.

Professor Alka Kriplani



It is a pleasure to know that FOGSI Focus on Menopause is being released. FOGSI Focus is a very good endeavour for the practicing Gynaecologists as they provide ready clinical material for the FOGSI Members. Its scientific contents are comprehensive and useful in day-to-day practice.

Menopause is a pertinent subject. With so many women entering menopause, dealing with the problems associated with it, is relevant in today's practice. This issue of FOGSI Focus addresses all the problems related to menopause for which Dr. Mandakini Parihar is praiseworthy. I am quite sure that this issue will be of immense benefit for all the FOGSI members who will find it useful for day-to-day patient care.

I wish all the best.

Dr. H. P. Pattanaik



I am happy to know that, the new FOGSI FOCUS is going to be released at AICOG 2010, Guwahati. This FOCUS is devoted to Menopausal Health. Menopause as you know today is of great importance so far as health of the mature women is concerned. With added years to life, women today in post menopausal years want a much better quality of life, free from hot flushes, neurological, cardiological and above all osteoporotic problems. We gynaecologists have a great role in serving and treating these ailments of these elderly women to make them more useful to the society.

With emergence of new drug, modalities particularly low dose HRT and alternative therapies like phytoestrogens and nutraceuticals we have lot many things in our hand to treat menopausal problems. This issue of the FOGSI FOCUS is dedicated to all these menopausal problems and the treatment modalities offered. Dr. Mandakini Parihar has done an excellent job as editor.

I hope the FOGSIans will be immensely benefited from this issue.

Happy new year.

The Menopause **FOGSI** Focus

Editorial



Dr. Mandakini Parihar

Knowledge rests not upon truth alone, but upon error also.

-Carl G. Jung

Menopause is the permanent cessation of reproductive fertility. The term was originally coined to describe this reproductive change in human females, where the end of fertility is traditionally indicated by the permanent stopping of monthly menstruation or "menses". While menopause used to mean withdrawal from active life for many women, this is not true today. Women may experience a wide range of feelings, from anxiety and discomfort, to release and relief. Most adapt to the changes and continue to live well and remain healthy through these transitions.

Most of today's women will live 25 to 30 years-one third of their lives-after menopause. An understanding of the body's changes during this phase of life can ease the transition, and equally important, better prepare us to safeguard our patients health during the later years. In this FOGSI FOCUS-ON MENOPAUSE, we are discussing all that is relevant to manage menopausal women effectively and improve the quality of their life by addressing their health needs and preventing diseases. The focus is divided into different sections to cover all the relevant topics. In Basic Understanding of Menopause, covers the reproductive endocrinology of hormones, the details of the New staging systems, along with the Symptoms and System Manifestations. There is detailed discussion on the silent killer Osteoporosis and all forms of effective therapies are discussed. The science of hormone therapy discusses all options for effective menopause management with the latest evidence regarding HT and dispelling all the myths and facts associated with all the different studies on menopausal health and finally a holistic approach to these important years with tips on diet and exercise during menopause. Many mistakes were made by us in managing menopausal women and we have now corrected those mistakes today. Setting up of a menopausal clinic and preventing cancer should form an integral part of our management protocols which are discussed in the FOCUS.

There are risks and costs to a program of action, but they are far less than the long-range risks and costs of comfortable inaction. So let us use this knowledge to empower ourselves for better understanding of the menopausal years and work towards a better quality of life in these autumn years for our patients.

I would like to thank our President, Dr. C. N. Purandare for giving me the opportunity to be the editor of this important FOGSI FOCUS and to all the contributors for their well researched and timely chapters. A special thanks to my family for their never-ending support and Emcure Pharmaceuticals for burning the midnight oil to get this focus released on time.

With warm regards

A handwritten signature in black ink, appearing to read 'Mandakini Parihar'. The signature is fluid and cursive, with a horizontal line underneath.

Dr. Mandakini Parihar



Thoroughly Modern Granny

I have a little granny,
She's really very old,
but also unconventional
in the most unusual mould

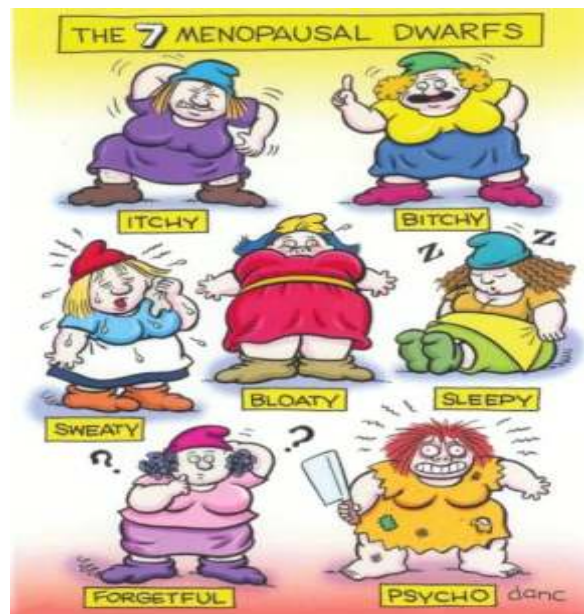
She doesn't wear her spectacles
perched upon her nose,
she's into contact lenses
and varnishes her toes

How I sometimes wish,
she'd stay and tuck me into bed,
she's off to study yoga
and standing on her head

Unlike all other grannies
who are home before it is dark,
she is dressed up in her track suit,
jig-jogging in the park

She goes for day trips with her Gang,
the over-sixties club,
they racket down the country side
and end up in the pub

I really love my granny
and I think she's really great.
And if, this is what growing old is like,
I simply cannot WAIT



The Menopause **FOGSI** Focus

Index

Section 1 - Understanding Menopause

1. Basics of Reproductive Hormones - **Dr. Hemaleka Kumarasamy** 6
2. Physiological changes in Menopause and the quality of life - **Dr. Sucheta Kinjawdeker, Dr. Anu Vij** 10
3. Staging of Menopause - **Dr. Behram Anklesaria** 15

Section 2 - Symptoms and System Manifestations in Menopause

4. Psychological & Cognitive Functions - **Dr. P. K. Shah, Dr. Sonal Yadav** 18
5. Vasomotor Problems - **Dr. Sujata Misra, Dr. Ritu Joshi** 21
6. Uro-Genital Complaints - **Dr. Nirmala Vaze, Dr. Pravin Mundada** 25
7. Bone Health in Menopause - **Dr. H. P. Pattnaik** 29
8. Cardiovascular Dysfunction - **Dr. Urvashi Jha, Dr. Indranil Ganguli** 31

Section 3 - The Silent Killer Osteoporosis

9. Osteoporosis - the extent of the problem - **Dr. Jaishree Gajraj** 37
10. Measurement of Bone Quantity & Quality - **Dr. Anand Parihar, Dr. Deepti Mhatre, Dr. Ketki Kulkarni** 39
11. Role of Calcium Vitamin D and Micronutrients in bone health - **Dr. Smita Kokare** 44
12. Role of Estrogen in Prevention & Treatment of Osteoporosis - **Dr. C. N. Purandare, Dr. Madhuri Patel, Dr. Nikhil Purandare** 47
13. Anti-resorptive agents for prevention & Treatment of Osteoporosis - **Dr. Mohini Prasad** 51
14. Anabolic drugs and newer therapies in treatment of Osteoporosis - **Dr. Ranu Patni** 59

Section 4 - The science of hormone Therapy in Menopause

15. Risk assessment and Investigations - **Dr. Atul Munshi** 62
16. Hormone Therapy Preparation, Routes of Administration, Indication & Contraindications - **Dr. Mandakini Parihar, Dr. Manisha Damani, Dr. Hemaleka Kumarasamy** 68
17. Current Recommendations for Replacement
 - (a) ERT - **Dr. Meeta Singh** 74
 - (b) Tibolone - **Dr. Jaideep Malhotra, Dr. Ruchika Garg** 78
 - (c) Androgen Replacement - **Dr. Sunila Khandelwal** 82
18. Role of Phytoestrogens - when and for how long? - **Dr. Madhuri Patel, Dr. Nikhil Purandare, Dr. Khyati Patel** 85

Section 5 - Facts & Myths of Different Studies on Menopause

19. WHI Study - **Dr. Jyoti Unni** 90
20. HERS Study - **Dr. Survarna Khadilkar** 92
21. PAM - newer insights in therapy - **Dr. Suchitra Pandit, Dr. Rana Khan, Dr. Priti Vyas** 99
22. THEBES Study - **Dr. Rashmi Shah** 106

Section 6 - Holistic Approach to Menopause

23. Diet & Nutrition - **Dr. S. S. Mehendale, Dr. Shirish Patwardhan** 109
24. Exercise - how soon - how far? - **Dr. Manindra Ahuja** 112
25. Setting up of an One step Menopause Clinic - **Dr. Sonia Malik** 118
26. Prevention of cancer - **Dr. Alka Kriplani, Dr. Beenu Kushwah** 121



1 Basics of Reproductive Hormones



Dr. Hemaleka Kumarasamy

DNB., DGO

Clinical Associate, Mandakini fertility center and IVF clinic, Mumbai

Introduction:

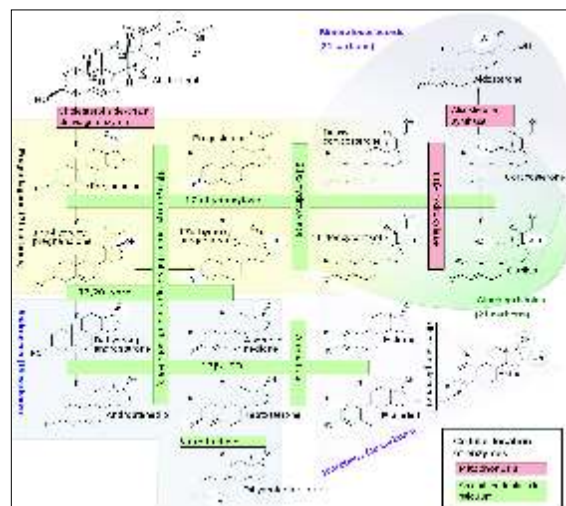
Diagnosis and appropriate management of reproductive dysfunction is facilitated by a comprehensive knowledge of the physiological origin and the mechanism of action of the various hormones. Hormones are generally recognized to be chemical signals in a complex system of internal biologic communication, and the reproductive hormones are rather specifically involved in virtually every facet of reproductive function in both males and females. A substantial fraction of reproductive dysfunction is caused by the inappropriate release of a hormone or hormones by the source endocrine gland or by aberrant reception of the hormone by its target tissue. Menopause is end stage of cessation of ovarian hormone production.

Steroidogenesis:

An understanding of the steroidogenic pathway is a necessary prerequisite for physicians interested in reproductive endocrinology.

Cholesterol or other substrates as acetate form the basis for steroidogenesis in the gonadal and adrenal tissues. Cholesterol is transported into mitochondria where the side chain cleavage enzymes at the inner mitochondrial membrane can cleave the cholesterol side chain to form pregnenolone. The pregnenolone is further metabolized into **progesterone**. By side chain cleavage progesterone and pregnenolone are further metabolized to **androgens** by enzymes present in the smooth endoplasmic reticulum. In the 5 α pathway pregnenolone is converted to DHEA, in the 4 pathway progesterone is converted to androstenedione and ultimately further metabolized to testosterone and from testosterone to **estrogens**. All this happens under the influence of gonadotropins from the pituitary, which is further under hypothalamic control.

Fig 1: The pathways for steroid biosynthesis



The Menopause **FOGSI** Focus

Role of Estrogens:

1. Vaginal cornification
2. Enlargement of uterus
3. Breast-Enlargement, increased vascularity, pigmentation of areola, epithelial growth
4. Modulates pituitary hypothalamic axis
5. Negative feedback of FSH
6. Ovarian follicular growth
7. Myometrial hypertrophy and development of gap junctions in pregnancy
8. Endometrial proliferation, increased vascularity, and fluid retention
9. Fallopian tubes-hypertrophy, increased vascularity, enhanced ciliary activity.
10. Reduces bone resorption, increase bone formation
11. Alteration in lipid balance or bile salt production
12. Reduces urinary calcium secretion, inhibit bone reabsorption
13. Stimulation of hepatic protein synthesis-globulin, fibrinogen, TBG, TeBG
14. Increase in factors 2,7,10, fibrinogen, decrease in Antithrombin 3 activity.
15. Increase HDL, triglyceride, decrease in LDL
16. Salt and water retention



Role of Progesterones:

1. Converts endometrium into secretory phase
2. Makes cervical mucus thick and impermeable to sperm
3. Maintenance of pregnancy
4. Decreases contractility of uterine smooth muscle
5. Fetus metabolises placental progesterone in the production of adrenal steroids
6. Raises Epidermal growth factor 1
7. Thermogenic function during ovulation
8. Relaxes smooth muscles
9. Regulates immune response
10. Reduces gall bladder activity
11. Acts in conjunction with estrogen for breast development



Role of Androgens

1. Regulation of the differentiation of male phenotype during embryonic development
2. Development and maintenance of male secondary sexual characteristics beginning at the time of puberty
3. Support of spermatogenesis
4. General anabolic and growth promoting effects
5. Behavioural effects
6. Regulation of gonadotrophin secretion
7. Females-axillary and pubic hair, axillary sweating, apocrine glands

Fig 2: Reference ranges for Estradiol and progesterone in menstrual cycle expressed in mass and molar concentration

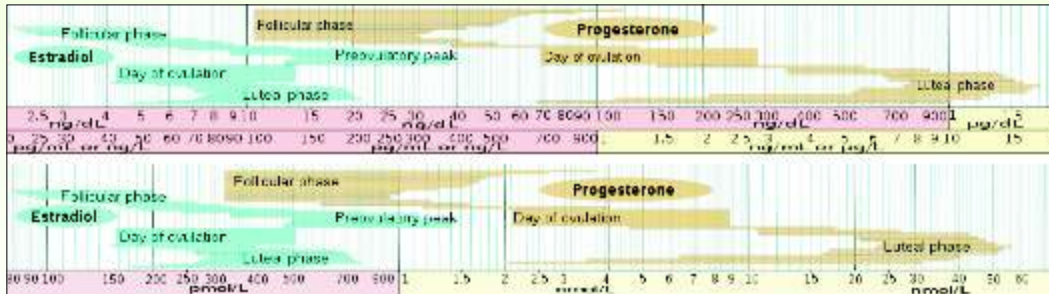
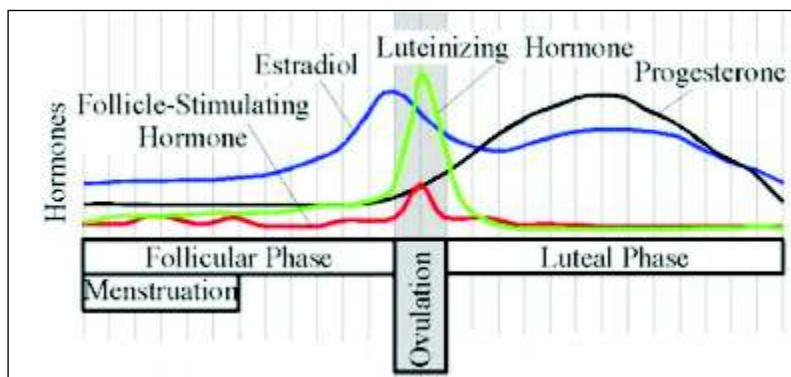


Fig 3: Progesterone levels (black line) during menstrual cycle



Endocrinology of perimenopausal women:

During the perimenopause, midcycle estrogen concentrations have been observed to be normal or increased, and levels of progesterone and androgens have been observed to be normal or decreased, independent of major changes in sex hormone-binding globulin

Sherman and associates^{1,2} followed six women for several years, including the time of their last menstrual period, and noted:

- (1) A monotropic rise in follicle-stimulating hormone (FSH) occurred even with normal menstrual cycles
- (2) Occasional anovulatory cycles occurred
- (3) The last menstrual period occurred immediately after an ovulatory cycle.

The increase in FSH that occurs during the menopause transition has been attributed to a loss of ovarian Inhibin B along with aging.^{3,4}

Age at which the FSH rise first appears may not necessarily correlate with menopause. Longitudinal studies have shown that an increase in FSH occurs as early as the early 40s in normal women. Along with the elevation in FSH, there is a lesser, but still significant, rise in perimenstrual levels of luteinizing hormone (LH). In comparison to midreproductive age women, women in the menopausal transition have higher levels of FSH and LH but not lower estrogen levels. Therefore, elevated FSH concentrations are not due to low estrogen but are likely to be caused by other factors, such as inhibin B.

The Menopause **FOGSI** Focus

Changes in estrogenic environment

An important but often clinically frustrating aspect of peri-menopause is that estradiol levels do not gradually decrease; instead, they fluctuate greatly around the normal range until menopause, when no more responsive follicles are available. The anovulatory cycles often seen may be associated with elevated levels of estradiol. Thus, as a woman ages, there is not a downward spiral in the estrogenic milieu, but instead a roller coaster in estrogen production. The perimenopausal fluctuations in estradiol may result from the aging ovary's being less responsive to FSH

Changes in the progesterone milieu

Both normal^{5,6} and decreased⁷ levels of progesterone secreted by the corpus luteum have been observed in the perimenopause. Further clarification regarding perimenopausal progesterone levels would be clinically very useful, because if decreased levels of progesterone are associated with increased levels of estradiol, this may also predispose women to dysfunctional uterine bleeding and endometrial hyperplasia.

Changes in the growth hormone and insulin like growth factors

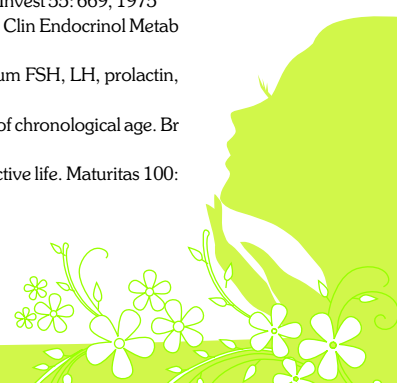
Age itself may be a more important factor affecting GH concentration than estrogen alone. Recent studies have shown that a decrease in somatotrophic axis activity is detectable before any changes occur in menstrual cyclicity or decreased production of estradiol. Older, regularly cycling women (age 42–46) have lower daytime GH concentrations than younger, regularly cycling controls (age 19–34). This occurred in the older women despite higher estradiol levels on the day of sampling (compared with their younger controls) and overall normal parameters of gonadal hormones. It remains to be shown whether the changes in function of the somatotrophic axis and hormonal environment affect sensitivity to insulin. This is an important association to be determined, because during the perimenopause, insulin sensitivity decreases, especially when there is weight gain. Wing and colleagues noted a direct correlation with perimenopausal weight gain and insulin resistance. Thus, aging is associated with decreased GH and IGF-1 levels, decreased insulin sensitivity, increased insulin resistance and weight gain.

Menopausal changes- summary

The climacteric or perimenopausal period normally begins as early as 40 years of age with commencement of the regression of ovarian function. Depletion of primordial ovarian follicles results in diminution of estradiol levels leading to intermittent menstrual irregularities, vasomotor symptoms, and genital atrophy. As a result of the decrease in estradiol negative feedback and diminished levels of inhibin, there is increased secretion of FSH. The postmenopausal ovary secretes androgens but virtually no estrogen and that is what causes all the symptomatology in menopausal years.

Suggested Reading

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6. Lenton EA, Landgren B, Sexton L et al: Normal variation in the length of the follicular phase of the menstrual cycle: Effect of chronological age. *Br J Obstet Gynecol* 91: 681, 1984
7. Lenton EA, Sexton L, Lee S et al: Progressive changes in LH and FSH and LH:FSH ratios in women throughout reproductive life. *Maturitas* 100: 35, 1988



2**MENOPAUSE: Understanding the Change****Dr. Sucheta Kinjawadekar**Consultant Obstetrician & Gynecologist,
Navi Mumbai**Dr. Anu Vij**Secretary NMOGS
Consultant Obstetrician and gynecologist,
Navi Mumbai

Menopause, also known as “the change” or “change of life,” is a normal part of a woman's life. The years leading up to that last period, when women might be experiencing menopausal symptoms like changes in their monthly cycles or hot flashes, are called the menopausal transition.

Changes at Midlife

The medical definition of menopause is the end of menstruation, so menopause can only be diagnosed after the fact. But the bodily changes leading up to menopause may take place over a decade. Most women reach menopause between the ages of 45 and 55.

Changes to Expect

Some women continue to menstruate normally until the onset of menopause and then simply cease to have periods. But for most women, the transition is not so orderly.

1) Changing Hormonal Patterns

Menopause results from loss of ovarian sensitivity to gonadotropin stimulation, which is directly related to follicular decline and dysfunction. Thus, the variable cycle length during perimenopause can be due to anovulation or to irregular maturation of follicles.

Despite having no pelvic pathology and continue to be ovulatory, a shorter menstrual cycle is the most common change⁴. Because follicles, which are stimulated by FSH during the first part of the menstrual cycle, have declined in number, less recruitment of oocytes occurs and the follicular phase shortens accordingly. However, once ovulation occurs, the luteal phase remains fairly constant, at 14 days.

As aging progresses follicles become more resistant to gonadotropin stimulation, circulating FSH and LH levels increase. Elevated FSH and LH lead to ovarian stromal stimulation, resulting increase in estrone levels and a decrease in estradiol levels.

Inhibin levels also drop during this time because of the negative feedback of elevated FSH levels.⁵

With the commencement of menopause and a loss of functioning follicles, the most significant change

The Menopause **FOGSI** Focus

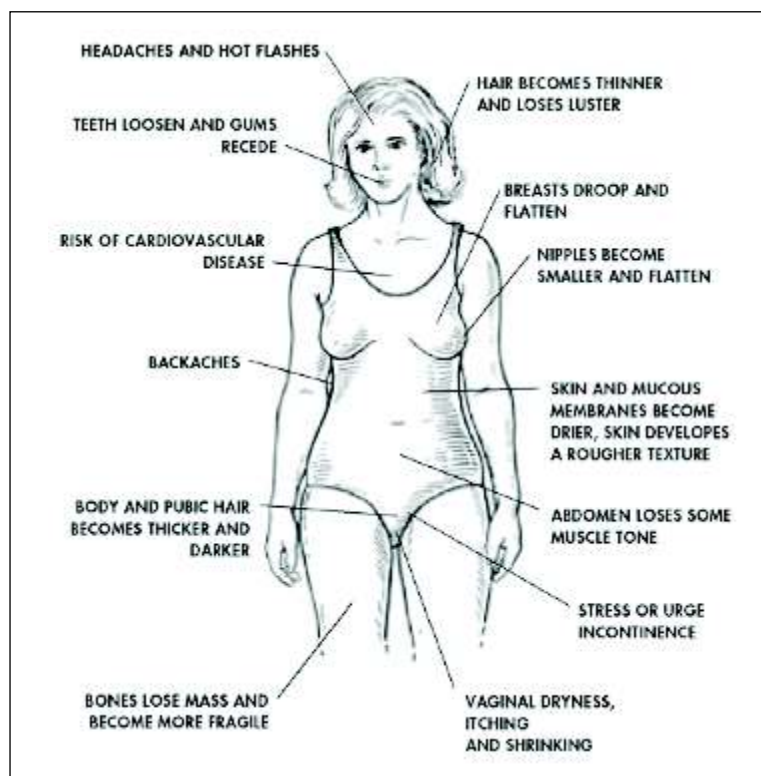
in the hormonal profile is the dramatic decrease in circulating estrogen levels. Without a follicular source, the larger proportion of postmenopausal estrogen is derived from ovarian stromal and adrenal secretion of androstenedione, which is aromatized to estrone in the peripheral circulation. Testosterone levels also decrease with menopause,⁶ but this decrease is not as marked as the decline in 17-estradiol.⁷

With cessation of ovulation, estrogen production (by stromal and extragonadal sites) continue, unopposed by progesterone production by a corpus luteum. Perimenopausal and menopausal women are thus often exposed to unopposed estrogen for long periods, which can lead to endometrial hyperplasia.

The laboratory indication that menopause has occurred is the measure of an elevated FSH level. A slightly elevated FSH level in a perimenopausal women may not be a reliable indicator of menopause because of the wide variation of FSH and LH levels in response to increased release of gonadotropin-releasing hormone (GnRH) by the hypothalamus and increased pituitary sensitivity to GnRH. Measuring FSH and LH levels again in the perimenopausal patient after 2-3 months is helpful in establishing whether the woman is progressing through menopause. Women with elevated, but not postmenopausal, FSH levels are still at risk for pregnancy and contraception should still be used until FSH levels remain in the postmenopausal range

Because estrogen plays many roles in the female body -- including maintenance of bone density, stimulation of breast tissue, and nurture of the vaginal membranes -- its loss has numerous ramifications, collectively known as the "Change."

Menopause at a glance





Changes in the Menstrual Cycle

The perimenopausal years may be marked by skipped menstrual periods, heavier or lighter than usual bleeding, and changes in the frequency of cycles. During some menstrual cycles are anovulatory cycles.

Muscle Tone and Elasticity

Skin and mucous membranes in various parts of the body become drier. As the body ages and the estrogen level declines, the fatty layer beneath the skin surface that makes the skin appear supple and youthful begins to shrink from a loss of elasticity and moisture. The outer skin layer is now looser than the deeper layers, and begins to fold and wrinkle. The skin may also develop a rougher texture.

Vaginal Changes are the first sign of approaching menopause for some while many do not notice changes until five to ten years after menopause. As estrogen levels drop, the vulva and vagina lose elasticity, resulting in vaginal dryness, itching and a shrinking process known as vaginal atrophy. Vaginal membranes also become thinner, hold less moisture, and lubricate more slowly. The thinner vaginal lining becomes more susceptible to tears, vaginal infections, and painful intercourse.

Breast Changes - Glandular tissue shrinks and loss of elasticity causes the breasts to droop and flatten. Nipples become smaller and flatter and may lose their erectile properties.

Women who have been bothered by breast tenderness and cysts related to the menstrual cycle are often relieved to find that these symptoms disappear after menopause.

Abdominal wall tone may lessen gradually, resulting in a protruding stomach.

Hair, Bones, and Teeth

Hair all over the body can change in texture and quantity. The increased effects of the body's androgens can result in darker, thicker and wiry body hair on the pubis, underarms, face, chest, lower abdomen, and back.

A loss of luster occurs because individual hair shafts begin to thin and dry as a result of hormonal changes. The replacement process for normal daily hair loss becomes slower.

Bone strength- As estrogen and progesterone levels fall drastically, the bones begin to lose mass. Osteoporosis strikes at least half of all women age 50 and older, leaving a woman vulnerable to bone fractures, especially in the hip, spine, and wrist. In fact, by the time a woman is 80, she may have lost 40 percent of her bone mass.

Teeth and the mouth are similarly affected. Dental problems that can occur around midlife, such as receding gums or loose teeth.

"Classic" Menopausal Changes

Hot flashes, flushes, or night sweats are the most common. Some experience a simple warming sensation throughout the body, others feel acute flushes that begin with a sensation of pressure in the head similar to a headache, which then leads to a feeling of heat or burning in the face, neck, and chest, followed immediately by an outbreak of sweating. In most cases, hot flashes are mild and disappear after a year or two.

The Menopause **FOGSI** Focus

The exact physiological cause of this upset is not yet known. The feeling may be precipitated by a hormonally induced imbalance in the body's temperature- control center.

Short term memory loss has been cited as a problem. Forgetfulness may be related to stress or lack of sleep.

Emotional issues - Though there is no increase in serious psychiatric disorders minor emotional distress, however, may be a natural response to the changes a woman faces during this period.

Hot flashes may keep one up at night, leading to chronic sleep deprivation which can reduce one's mental and coping abilities. Vaginal changes that result in painful intercourse may interfere with one's sexual pleasure and psychological health.

Weight gain, is not directly related to menopause. There is a natural redistribution of fat over the abdomen and hips. Weight gain most likely results from reduced muscle tone, reduced physical activity, increased appetite .

Cardiovascular Health

A women's risk of cardiovascular disease rises dramatically after menopause .The younger a woman is when her ovaries stop functioning, the greater her risk for MI.

Thus menopause itself is a risk factor for cardiovascular disease, along with high blood pressure, smoking, family history, poor diet, high blood cholesterol, diabetes, and obesity.

Bladder Control

Women in peri - and postmenopause may experience mild stress incontinence, urge incontinence. These problems occur when declining estrogen levels cause cell deterioration and diminished muscle control in the urethra, bladder, and vagina.

Repeated UTIs, are also common. The deterioration of cells in the urinary tract produces an easily torn and bruised surface, creating an hospitable environment for the bacteria.

Effect of Menopausal Symptoms on Overall Quality of Life

Women feel their quality of life is severely compromised by menopausal symptoms but further studies concluded that menopause brings about a significant decrease in quality of life that is independent of other factors, such as age, marital status and other socio demographic variables. Many scales are now developed to quantify quality of life (QOL). These are questionnaire based on physical, psychological /emotional, changes/ symptoms Perceived by affected population. Total score is calculated to evaluate pre and post HRT status and evaluate benefit of HRT.



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The Menopause **FOGSI** Focus

3

Staging of Menopause



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Menopause is an important part in a woman's life, a time of transition from reproductive years to non-reproductive years. It is defined as a period when menstrual function stops completely. However, patient may present with symptoms for many years before the actual stopping of the monthly periods. For a few preceding years there are a lot changes occurring and patient would present with symptoms many years before menopause will set in. it is important for us to realize the different stages of menopause.

In 1997, when this staging system was first published, long term HRT was popular in the West. Subsequently this staging has been widely published, in India and abroad. (See references.) In 2008, it was adopted by the Indian Menopause Society and presented at the World conference of the International Menopause Society at Madrid. Meanwhile, WHI and other studies, considerably reduced the popularity of long term HRT. However our staging system has become even more relevant, because HRT and other interventions are now critically 'time bound'. For example, the "window of opportunity" period for initiation of long term HRT, happens to correspond exactly with "Stage II" of this system!

Individualized management of 40+ women with their diverse cultural and regional needs is not possible without Clinical Categorisation. Individualisation of treatment involves another more important aspect. The same 'patient' develops different needs at various 'stages' of menopause. A good physician will encourage the 'patient' to report regularly and will alter the management to suit her ever changing needs. This simple scientific 'staging system', widely disseminated, has helped us to do just that.

Table1: Stages of Menopause, Dr. Behram. S. Anklesaria, 1997

STAGES	Stage I		Stage IIA	Stage II B	Stage III
YEARS	Roughly 3-5 years before the menopause		ONE YEAR	Up to five years after the menopause	From five years after menopause up to her life time.
EVENTS	* Menstrual irregularity * Vasomotor instability * Early psychosomatic symptoms	M E N O P A U S E	C O N F I R M A T I O N	* Local atrophic changes * Late psychosomatic symptoms (see detailed staging)	III A: Late atrophic changes III B: Ischemic heart disease III C: Osteoporosis III D: Very late complications: e.g., Cerebro-Vascular accidents, Alzheimer's disease, etc.
ACTION	ESTABLISH COMMUNICATION !			TREAT !	PREVENT !





Stages of Menopause in Detail

Stage 1:

From the Earliest Perimenopausal Symptom
(Usually Vasomotor Instability or Menstrual Irregularity)
To Menstrual Cessation (Menopause)

Stage 2:

“FIVE YEARS AFTER MENOPAUSE”

Stage 2: A

“From the cessation of menstruation Up to one Year,”
(That is up to confirmation of Menopause by WHO definition.)
The main symptoms of menopause during this stage are URETHRAL Syndrome and Vasomotor Instability.

Stage 2: B

From end of 2: A, up to Four Years, the usual Symptoms are:

- (a) Atrophic Symptoms, Vaginitis, Dyspareunia
- (b) Urinary Symptoms, e.g. Urgency, SUI
- (c) Weight gain , Abnormal Weight Distribution
- (d) Skin and Hair changes
- (e) Genital Prolapse
- (f) Late Psychological Symptoms
- (g) Sexual Disorders.

Stage 3:

From five years after menopause up to her life time.
III A: Late atrophic changes III B: Ischemic heart disease
III C: Osteoporosis III D: Very late complications:
e.g. Cerebro –Vascular accidents, Alzheimer's disease, etc.

Practical Usage:

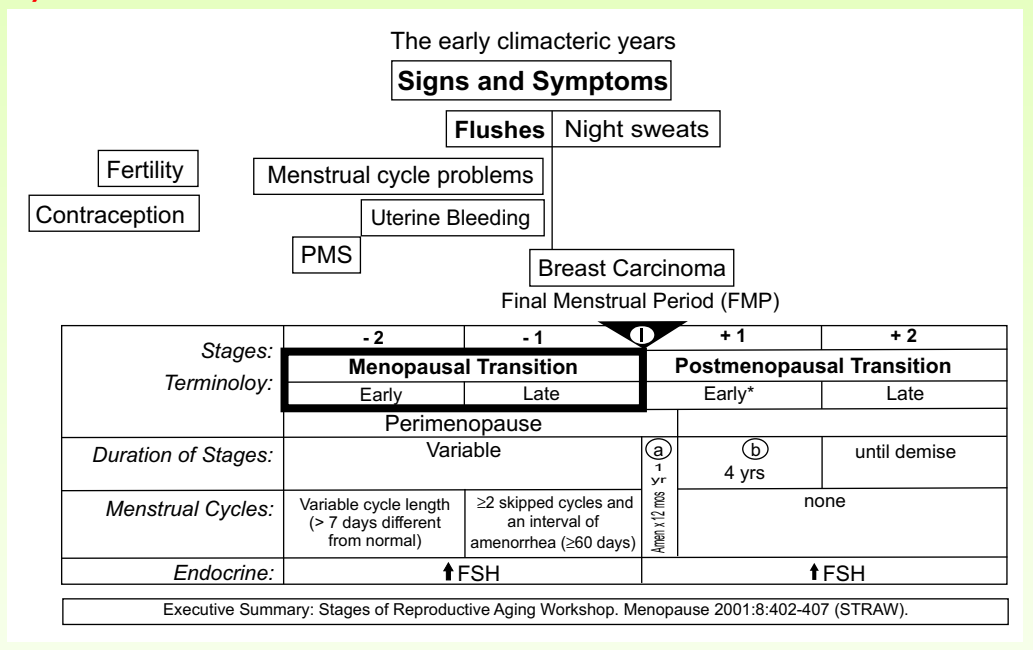
The Five Year Rule of the Thumb

- Each stage duration is highly variable, but a rough five years per stage calculation is clinically useful
- Consider the case of lady 'A' who reaches her menopause at say age 50
- From 45 – 50 she is in stage I when she needs initial counseling
- From 50-55 she will be in stage II : The window of opportunity
- From 55 to 70 she will go through the earlier stage III complications which could have been prevented!
- At 70+ she enters stage III D and beyond. She now needs very different management than the earlier stages

The author has presented here, his staging system, first published in India in 1997. Four years later in 2001, the `Stages of Reproductive Ageing Workshop (STRAW) and the American Society for Reproductive Medicine published another staging system. This is an excellent system for Reproductive Ageing, useful for managing infertility problems of older women. However, in dealing with symptomatic and preventive aspects of menopause, we feel that our older staging system is superior.

The Menopause **FOGSI** Focus

2) STRAW SYSTEM (Stages of Reproductive Aging Workshop)



Summary:

The most important sociomedical change of the present era has been the dramatic increase in life expectancy and the subsequent rise of “older” populations. Woman's liberalization, emancipation and professionalism have led to spreading concepts of Menopause as a 'Positive' change. Greatly encouraging is the rising awareness of the benefits of life style changes. Estrogen therapy for treatment and prevention has become complicated. However the most important development has been the crucial importance of the TIMING of various interventions in Menopause Management. That is why our 'Staging of Menopause' has now become the best method to understand the symptomology, the complications and the management of a woman's best years – the Menopause!

Questions for the Reader:

- Why is Stage I known as the Stage of Communication?
- Why is Stage II Extremely Important for the Initiation of Modern HT?
- Which of the complications of Stage III can be or cannot be prevented by HT?

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4 Psychological and Cognitive Functions in Menopause



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Menopausal health is gaining importance as longevity in women has increased, while the age of menopause has remained the same. We are experiencing a relatively new phenomenon: we can expect to become old. We are on the verge of becoming a rectangular society. This is a society in which nearly all individuals survive to advanced age.

The Menopause is that point in time when permanent cessation of menstruation occurs following the loss of ovarian activity.

Climacteric, an older, more general and less precise term indicates the period of time when a woman passes from the reproductive stage of life through the perimenopausal transition and the menopause to the postmenopausal years.

Symptomatology: Most Indian studies locate the median age at 48 years, while those from the west reveal the same to be about 51.

(WHO Scientific Group 1981)^{1,2}. Vasomotor instability symptoms like hot flush are the most common symptoms in menopausal patients. Other symptoms include urogenital problems, Psychological symptoms and other major systemic features due to estrogen deficiency.

Psychological symptoms such as anxiety, irritability, depression and insomnia are most common just before the onset of menopause.

Mechanism of psychological symptoms in menopausal women:

Sex steroids have been shown to have a modulatory role on brain monoamine receptors. Falling estrogen level may contribute directly to mood changes and psychosomatic symptoms.

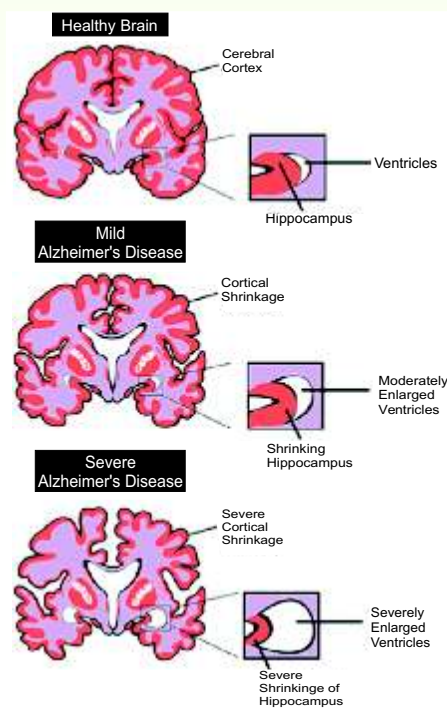
But the view that menopause has a deleterious effect on mental health is not supported in the psychiatric literature, or in surveys of the general population^{3,4}. A negative view of mental health at the time of the menopause is not justified; many of the problems reported at the menopause are due to life events^{5,6}. Thus, there are problems encountered in the early post menopause that are seen frequently, but their causal relation with estrogen is unlikely. These problems include fatigue, nervousness, insomnia, depression, irritability, joint and muscle pain, dizziness and palpitations.

The Menopause **FOGSI** Focus

In the American SWAN study, the prevalence of mood changes increased from the premenopause to the early perimenopausal, from about 10% to 16%⁷. There are three possible explanations: 1. The decline in estrogen at menopause affects neurotransmitters that regulate mood. 2. Mood is adversely affected by vasomotor symptoms (domino theory). 3. Mood is affected by the vicissitudes of life that are commonly prevalent around menopause.

Cognition and Alzheimer's Disease:

Up to 3 times as many women as men develop Alzheimer's disease. Estrogen is capable of protecting central nervous system functions by means of multiple mechanisms. For example estrogen protects against neuronal cytotoxicity induced by oxidation; estrogen reduces the serum concentration of amyloid P component (the glycoprotein found in Alzheimer's neurofibrillary tangles); and estrogen increases synapses and neuronal growth, especially dendritic spine density^{8,9}. Case control and cohort findings have indicated that Alzheimer's disease and related dementia occurred less frequently perhaps as much as 60% less in estrogen users and the effect was greater with increasing dose and duration of use¹⁰. WHI concluded that Estrogen Progestin therapy increase risk for probable dementia in women 65 years and older and didn't prevent mild cognitive impairment. But this hypothesis was derecognized by WHI itself in view of older age, preexisting cardiovascular disease and established atherosclerosis which itself increase the risk of vascular dementia¹¹. Zandi et al concluded that a reduction in the risk of Alzheimer's requires long term treatment initiated at least 10 years before symptoms of dementia appear. The favorable effect of hormone therapy on cognition and risk of Alzheimer's disease appear to be limited to women who initiate treatment close to their menopause.



Treatment:

A negative view of mental health at the time of the menopause is not justified; many of the problems reported at the menopause are due to life events. Thus, there are problems encountered in the early post menopause that are seen frequently, but their causal relation with estrogen is unlikely. Thus the overall quality of life reported by women can be improved by better sleep and alleviation of hot flushing. However it is still uncertain whether estrogen treatment has an additional direct pharmacologic antidepressant effect or whether the mood response is totally an indirect benefit of relief from physical symptoms and, consequently, improved sleep.

The short-term administration of unopposed estrogen to patients with Alzheimer's disease has been reported to improve cognitive performance. Most revealing is a prospective cohort study of the men and women living in Cache County, Utah. Hormone therapy provided about a 41% reduced risk of developing Alzheimer's with any use and an 83% reduction with 10 or more years of use. Most importantly, if women had initiated hormone therapy within a period of time that encompassed 10



years before the development of clinical symptoms, there was no effect. The Utah strongly suggests that hormone therapy must be used for a significant duration of time very early in the postmenopausal period in order to have an impact on the risk of Alzheimer's disease.

Conclusion:

So the most common cause of perimenopausal mood problems is already existing depression^{12,13}, but there does exist a small population of women whose moods are sensitive to hormonal changes.

The perimenopausal transition, therefore, is not a cause of clinical depression; however, labile emotions do seem to be improved in many women administered hormone therapy.

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The Menopause **FOGSI** Focus

5

Vasomotor Problems



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The vasomotor phenomenon is viewed as the hallmark of female climacteric experienced by most postmenopausal women. Hot flush and night sweats are the most disruptive symptom of estrogen decline in pre and post menopausal women and the classic symptom associated with estrogen deficiency is the hot flush.

Incidence

Hot flushes are experienced by at least one half of all women during natural menopause and by even more women after surgical menopause.¹ Exact estimates of the prevalence are hampered by inconsistencies and differences in methodologies, cultures and definitions.²

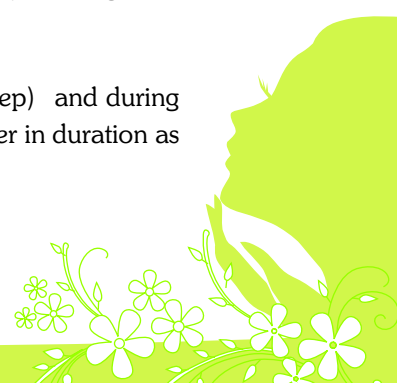
It shows a cultural variation with western countries reporting between 60-80% (USA 82%, Sweden 60%, Australia 62%)³⁻⁵ whereas the eastern countries report lower rates of 10-30 percent (Indonesia 10-20%, Chinese 10-25%, Indian 20-30%).

Hot Flush

This symptom is described as 'recurrent transient periods of flushing, sweating and a sensation of heat, often accompanied by palpitations, feelings of anxiety and sometimes followed by chills.'⁶

There is a sudden onset of reddening of the skin over the head, neck and chest accompanied by a feeling of intense body heat which, at times, is concluded by profuse perspiration. The duration varies from a few seconds to several minutes and, rarely for an hour. The frequency may be rare to recurrent. The entire episode usually lasts for 1 to 3 months and may recur as many as 30 times per day, although 5 to 10 times per day is probably more common.

They are more frequent and severe at night (after awakening the woman from sleep) and during times of stress. In a cool environment, hot flushes are fewer, less intense, and shorter in duration as compared to that in a warm environment.⁷





Although the flush can occur in the premenopausal phase, it is a major feature of postmenopausal period, lasting in most women for 1-2 years but in some (approximately 25%) for longer than 5 years. In cross sectional surveys, up to 40% of premenopausal women and 85% of menopausal women report some vasomotor complaints.⁸

Hot flushes may be accompanied by fatigue, nervousness, anxiety, irritability, depression and memory loss.⁹ Hot flushes that occur at night, referred to as night sweats are believed to interrupt sleep patterns. Early in the menopausal transition, vasomotor instability may manifest as an intermittent sleep disturbance in the absence of obvious hot flushes..

Overweight women report more hot flushing, perhaps reflecting the effect of body fat causing a higher core body temperature.¹⁰

Physiology

Hot flushes are implicated to originate in the hypothalamus and is brought about by a decline in estrogen. However, all hot flushes are not due to estrogen deficiency. They may be secondary to diseases, including pheochromocytoma, carcinoid, leukemias, pancreatic tumors and thyroid abnormalities.¹¹

When the clinical situation is not clear and obvious, estrogen deficiency as the cause of hot flushes should be documented by elevated levels of FSH. Prescribing estrogen inappropriately (in the presence of normal levels of gonadotropins) only temporarily postpones the symptoms due to a placebo effect.

The flush is accompanied by a discrete and reliable pattern of physiological changes.¹² It coincides with a surge of LH and is preceded by a subjective prodromal awareness that a flush is beginning. This aura is followed by measurable increased heat over the entire body surface. However, its relationship to LH surge and temperature changes within the brain is not clearly understood. The observation that hot flushes occur even after hypophysectomy indicates that it is not dependant on nor directly due to LH release. It is probably secondary to hypothalamic changes in the neurotransmitters that increase neuronal and autonomic activity.¹³

Physiologically, hot flushes correspond to marked, episodic increase in the frequency and intensity of gonadotropin-releasing hormone (GnRH) pulses from the hypothalamus. It is postulated that this increased pulsatile activity is a marker for some central disturbances of the body temperature regulating center that is responsible for the hot flushes.¹⁴ With the increase in body surface temperature, there are changes in skin conductance, followed by a fall in core temperature. It is basically a sudden inappropriate excitation of heat release mechanism.

Release of hypothalamic neuropeptides/neurotransmitters from tonic inhibitory influence of estrogens are currently implicated in the pathogenesis of vasomotor symptoms.¹⁵ Noradrenergic neurones have been shown to be present in the medial preoptic area of the hypothalamus,¹⁶ are known to modulate LHRH secretion¹⁷ and thermoregulation.¹⁸ There is considerable incidence for estrogen modulation of the central noradrenergic activity.¹⁹ Though plasma norepinephrine levels do not show any change during hot flushes,²⁰ Freedman RR showed increased plasma concentrations of 3-methoxy 4-hydroxy phenylglycol (MHPG- the main metabolite of brain norepinephrine) before hot flushes.²¹

The Menopause **FOGSI** Focus

Other neurotransmitters thought to be involved in the pathogenesis of vasomotor symptoms are the opioids and tachykinins. Like noradrenergic neurons, opioids containing neurons bind estrogen,²¹ and influences thermoregulation²². In post menopausal women proopiomelanocortin (POMC) mRNA levels decline

Management:

Counselling is of paramount importance. Many women have mild hot flushes that they do not feel require therapy. The patients can be advised that, without treatment, the symptoms usually subside slowly over a period of 3-5 years.²³ A striking and consistent finding in most studies dealing with menopause and hormonal therapy is a marked placebo response (at least 51% in the first weeks of treatment)²⁴ in a variety of symptoms, including flushing.

Treatment (Steroidal)

Estrogen replacement therapy results in the reduction of hot flushes in most women in a matter of days. After oophorectomy, a higher dose of estrogen is commonly needed. In women without risk factors for cardiovascular disease; low dose oral contraceptives can be used with excellent results. Alternatively, the daily estrogen dose can be increased stepwise to as high as the equivalent of 2.5mg of conjugated estrogens to resolve persistent hot flushes. The estrogen dose should be tapered slowly over a period of months to no more than 1.25mg of conjugated estrogen per day, because the risk of cardiovascular disease actually may be increased in women taking larger doses.²⁵

In women in whom hormone replacement is contraindicated effective alternatives are medroxyprogesterone (10-30mg daily orally)²⁶ or megestrol acetate (20-40mg daily orally)²⁷

If either of these progestins result in intolerable side effects, the use of alternative progestins may be considered, though very few data exist regarding their efficacy.

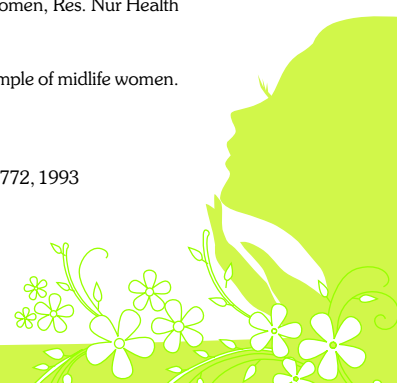
Treatment (Non Steroidal)

One of the best studied is the L₂-adrenergic agonist, Clonidine. This drug probably works through both central and peripheral mechanism and can be given either orally (0.05mg twice daily) or by a transdermal patch (0.1mg weekly)²⁸

Formulations containing a combination of phenobarbital, ergotamine and belladonna, used in the past, are currently not recommended. In addition to having a marked sedative effect and they can potentially be habit forming. Moreover, controlled studies show little long-term effectiveness of this treatment.

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The Menopause **FOGSI** Focus

6

Uro-Genital Complaints



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Dr. Pravin Mundada

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Signs of atrophic changes in the urinary and genital organs due to estrogen deficiency play a very important role and contribute significantly towards the loss of physical & psychological well being. The complaints in the lower urinary tract occur within first 5 to 10 years after menopause. Estimated 10 - 40% of post menopausal women suffer with these symptoms but only 20 - 25 % of them seek medical advise¹.

Female genital tract & lower urinary system both develop from primitive urogenital sinus during embryonic phase. Estrogen & progesterone receptors are present in urethra, bladder, pelvic musculature, vagina & urogenital ligaments². During menopause estrogen deficiency affects both systems. The changes are mild in early years of menopause and marked in later years of menopause. Response to HRT is limited when marked structural damage occurs.

Anatomical changes in the genital tract in menopause -

- Vulva - Atrophic vulval skin, gaping of introitus, shrinkage of labia, disappearance of hair follicles
- Vagina - Dryness, shortening, disappearance of rugae, pale vaginal lining, smaller caliber, loss of elasticity
- Cervix - Stenosis, atresia of cervical canal, reduced cervical secretion

Urogenital Complaints are divided into genital and urinary complaints.

Genital Complaints:

Post menopausal bleeding, vaginal dryness, vaginal discharge, vulvovaginal itching, vaginal infection, dyspareunia, prolapse, loss of libido, genital herpes, labial atrophy.

Management -

- Detailed history including duration of symptoms, severity & recurrence, relevant past medical history, drug intake should be taken.
- Examination of vulva, vagina, cervix for any apparent lesion, atrophic changes, labial fusion, adhesions, introital stenosis, pale vagina, urethral caruncle, genital prolapse.





Lab findings & investigations -

- pH of vagina > 5
- Cytology of upper vagina - abundant parabasal cells & reduced superficial cells
- Infective agents - candida, trichomonas & other bacteria
- TVS - thin endometrium
- Out patient endometrial sampling
- Hysteroscopy, D & C

Treatment - Local benign lesions should be treated according to the causes. Different operative procedures for prolapse & relevant management for any malignant cause of post menopausal bleeding should be followed. HRT can be prescribed in benign cases where it is indicated, provided there is no contra indication, in minimum effective doses, for a short duration with regular follow up & counseling of the patient. Topical estrogen preparations are preferred in patients with urogenital complaints because of greater absorption across thin and atrophic vaginal epithelium. Low dose oral estrogen (conjugated estrogen, estradiol, & estriol), local estrogen pessaries, cream, & tablets have been used with beneficial effects on vaginal symptoms³ & for senile vaginitis with little or no side effects. Estradiol vaginal ring has shown better compliance, less side effects, it is safe & well tolerated³.

Urinary Complaints:

- 1] Recurrent Urinary Tract Infection
- 2] Urinary Incontinence
- 3] Dysurea
- 4] Increased Urinary frequency

Incidence of urological complaints amongst Indian menopausal women is 35 %, 74%, & 60% respectively according to different authors^{4,5}.

1] Recurrent Urinary Tract Infection is the most common bacterial infection in elderly. Estrogen deficiency causes atrophy of epithelium of urethral opening, defective closure mechanism, resulting in ascending infection from periurethral bacterial flora. Although E. Coli is most common organism, other gram +ve organisms are also responsible. Polymicrobial infections are found in 10-20% of cases⁶. Predisposing factors are instrumentation, catheterization, other morbid conditions such as – diabetes, malignancy, chronic debility and use of steroids.

Most UTI in elderly are asymptomatic. However when symptoms do occur, the virulence of organism is often similar as found in younger population.

3] Dysurea & 4] Frequency comes under urethral syndrome

Treatment is aimed at treating infective elements with appropriate antibiotics . Supportive local estrogen therapy is the main stay.

2] Urinary Incontinence is mainly of two types – Stress and Urge Incontinence.

In 2005, Oskay UY et al in their study of 500 post menopausal women reported that 68.8% of women had urinary incontinence, amongst those 28.8% had severe urethral incontinence required to use

The Menopause **FOGSI** Focus

pad. They also reported that amongst these 37.2% of women had SUI, 32.3% had urgency incontinence & 30.5% had mixed incontinence⁷.

a) Stress Urinary Incontinence [SUI]

In SUI there is passage of few drops of urine during activities that increases abdominal pressures like coughing, sneezing, laughing, walking, lifting without any detrusor activity. Pressure in bladder exceeds pressure in urethra due to increase in intra abdominal pressure rather than detrusor contraction. Urethral incompetence is due to urethral hypermobility [80-90%], or intrinsic sphincter dysfunction [10-20%].

Management -

Proper pre operative evaluation is mandatory. Social stigma & embarrassment often prevents ladies from presenting their problems. Market & Opinion research International [MORI]⁸, estimated that there were 2.5 million female sufferers in UK alone in 1991. Detail history is very important as there is often discrepancy between symptoms & uro dynamic findings. Patient should be examined with full bladder. It is important to elicit leakage of urine & the degree with rise in intra abdominal pressure.

Investigations & Diagnosis -

- Urine- routine & culture
- Bonney's & Q- tip test to confirm urethral hypermobility.
- Bladder ultrasound - pre & post void volume
- Electromyography of pelvic floor
- Uro dynamic studies - not mandatory in all cases of SUI, no advantage in genuine SUI, indicated in mixed aetiology, helps in finding out actual site of defect, mode of treatment & prevention of unnecessary surgical intervention.

Treatment -

i) Conservative -

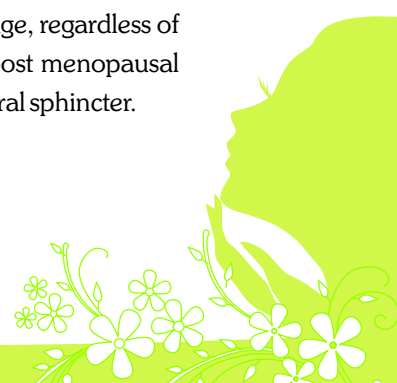
Pelvic floor exercises, physiotherapy, Kegel's exercise, vaginal cones, Bio feed back & external stimulation, mechanical devices [Contiform, Interol]

ii) Surgical -

- 1] Vaginal surgery - anterior colporrhaphy, Kelly's repair
- 2] Retropubic surgery - Colposuspension - open or laparoscopic, 5 yr. follow up success rate is 90% & 56.7% respectively
- 3] Paraurethral injection of collagen or other biodegradable materials
- 4] Sling operations - Mid urethral- TVT [Tension free Vaginal Tape] or TOT [Trans Obturator Vaginal tape], most popular, long term effects are awaiting

b) Urge Incontinence -

It is strong, sudden need to urinate followed by bladder contraction resulting in leakage, regardless of the amount of urine in the bladder. It is mostly because of detrusor instability. In post menopausal women it may get exaggerated because of recurrent UTI & weakness of internal urethral sphincter.





Management -

History in detail & examination to rule out any local causes is must.

Investigations -

- Urine - Routine & Culture
- Ultrasound
- Cystoscopy- to rule out stones & malignancy
- Uro Dynamic Studies in doubtful cases

Treatment -

- Diet
- Antibiotics
- Kegels Exercises
- Bladder Retraining
- Drugs -
 - Anticholinergics - Oxybutamine, Tolterodine, solifenacin, Darifenacin
 - Antispasmodics
 - Tricyclic Anti depressants
 - Chemodervation of Bladder by Submucosal injection of Botulinum Toxin
 - Surgery-as last resort, augmentation enteroplasty
 - Sacral nerve stimulation

Conclusion -

Urogenital problems in menopausal women needs more and more attention. Active diagnosis, timely intervention can prevent atrophic vaginitis, various routes of HRT may be used as appropriate to the individual. Alternative therapies, encouragement of continuation of sexual activity in preventing vaginal atrophy & shrinkage helps in physical & psychological well being. With good understanding and co operation between gynaecologist, surgeon & urologist, more & more defects will be corrected by latest technologies, which will help in alleviating the lives of distressed women.

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The Menopause **FOGSI** Focus

7

Bone Health in Menopause



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Bone health is a major concern for women particularly in the post menopausal period. Human bone is a dynamic tissue which undergoes continuous breakdown, repair and remodeling. Bone loss occurs when the rate of bone dissolution exceeds that of bone formation. Maximum bone density occurs in women in their mid-thirties & skeletal bone mass start decreasing after about age 40 i.e. in the perimenopausal period.

Human bone consists of 80% cortical bone and 20% trabecular bone. The cortical bone consists of the dense, compact outer layer and the trabecular bone forms the inner mesh work. Cortical bone seen mainly in the shaft of long bones and trabecular bone seen in vertebrae, epiphysis of long bones and iliac crests. Trabecular bone is metabolically more active and more affected by factors leading to bone loss.

The important minerals in bone are calcium salt and phosphates. 90% of body calcium are in bone & mainly as crystalline hydroxyapatite. Bone remodeling takes place by osteoblasts - the bone forming cells & osteoclasts – the bone resorbing cells.

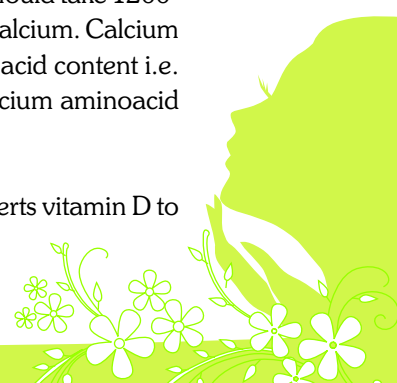
Osteoporosis is gradual microscopic reduction of bone tissue leading to fragility of bone finally to increased risk of fractures. This usually starts in forties in both sexes and there after in women with ovarian failure when there is accelerated bone loss due to oestrogen deficiency. It is estimated that in old women about two third of bone loss is due to menopause and one third to ageing. This is mainly due to osteoclastic activity. The trabecular bones breakdown and there is no bone structure on which new bone formation can occur. Osteoporosis commonly affects the callus bone than the cortical bone.

In the immediate postmenopausal age the bone loss is as high as 5% on the trabecular bone and 1.5% of cortical bone every year. The age related bone loss is 1% per year. The accelerated bone loss lasts about 2 to 4 years. It has been estimated that women loose 35% of the cortical bone and 50% of the trabecular bone in their lifetime.

Oestrogen inhibit osteoclastic activity and thus slows down bone loss but has no action on osteoblastic activities and so can't form new bone. Testosterone & progesterone appear to stimulate osteoblast and thereby possibly stimulate bone growth.

Calcium deficiency contributes to 25% of increased bone loss. So, menopausal women should take 1200-1500mg of calcium daily. Daily dietary intake of standard American diet gives 700mg of calcium. Calcium carbonate is the most widely prescribed salt. But its absorption is reduced in low gastric acid content i.e. hypochlorhydria which usually occurs in post menopause. The preferred calcium is calcium aminoacid chelate which does not require gastric acid for its absorption.

Magnesium is important for the formation of a functional bone matrix. Magnesium converts vitamin D to





its active form D3 which helps in absorption of calcium. Women with poor bone health may be deficient in D3. Menopausal women are deficient in magnesium. Folic Acid and Vitamin B6 (Pyridoxin) have a pivotal role in promoting bone health. They help in metabolism and excretion of homocystein. Hyperhomocysteinaemia is associated with defective bone formation and with cardiovascular disease. Menopausal women show impaired ability to metabolise and excrete homocysteine also they are low in folic acid and vitamin B6.

Manganese, silicon and vitamin K are necessary for construction of bone matrix around which bone mineralisation occurs. Vitamin K is found low in individuals with significant bone loss. Overdose of Vitamin K affects clotting mechanism so daily intake should be 200 μg approximately.

Zinc and copper are also important minerals for bone health that tend to be low in menopausal women. Both enhance the effectiveness of vitamin D which promotes calcium absorption. Zinc and copper must be supplemented in proper ratio or else it may affect proper bone formation.

Micronutrient Boron supplementation reduces calcium loss in post menopausal women. Vitamin C play vital role in immune support and also helps in building bone matrix and connective tissue.

Soy intake is linked with bone health. Dietary soy intake is associated with decrease rate of bone loss. Isoflavone, the active ingredient of soy, given in 55-90mg daily to postmenopausal women for 6 months slows down bone loss.

Oestrogen supplementation in form of hormone replacement therapy was advocated for prevention of osteoporosis and promotion of bone health in post menopausal women. HRT has fallen out of grace because of infamous(?) WHI trial and today low dose HRT are recommended.

Phytoestrogens or oestrogens derived from plants sources are promoted for bone health particularly in this post WHI era when postmenopausal women are apprehensive about HRT. Femarelle (DT 56a) is a promising molecule which is extensively tried in different countries and proves to be effective for prevention and treatment of osteoporosis.

Hormones play pivotal role in remodeling of bones alongwith several vitamins and minerals. Supplementing key nutrients along with balanced diet and exercise programme are integral part of bone health in menopause.

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The Menopause **FOGSI** Focus

8

Cardiovascular Dysfunction in Menopause



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The incidence of cardiovascular disease (CVD) increases with age in women as well as in men. In women there is an additional risk due to the menopause consequent to the loss of ovarian function¹

Globally, it is also the leading cause of morbidity and mortality in women (54% in women vs 43% in men) Although, the death rate has fallen in men, it has increased in women because of the rising prevalence of hypertension, diabetes mellitus, sedentary habits, obesity and less decline in smoking.

Cardiovascular disease (particularly coronary artery disease and stroke) is the most common cause of death amongst postmenopausal women.² Before menopause, the extent of atherosclerosis in a woman is equivalent to that of a man 10–15 years younger to her. However, after menopause the risk of a fatal myocardial infarction secondary to atherosclerosis of the coronary vessels doubles.^{3,4} Similarly, the risk of stroke resulting from atherosclerosis of the carotid artery triples in postmenopausal women.^{5,6} Epidemiologic studies have noted that 16 percent of women die of a stroke, whereas only 8% of men die of a stroke.⁷

These high rates of disease amongst women have been shown to result from a decrease in the estrogen level, with a consequent increase in atherogenic risk factors.⁸ Specifically, there is an increase in the total cholesterol level, low-density lipoprotein, (LDL cholesterol) level and lipoprotein(a); a decrease in the high-density lipoprotein, (HDL cholesterol) level; increased thrombotic tendency; and an occasional development of insulin resistance.⁹ This insulin resistance is extremely important given that diabetes mellitus is associated with a doubling of the risk of an ischemic stroke and an 8-fold higher risk of coronary artery disease.^{10,11}

A constellation of risk factors which include android adiposity with androgenic hormone profile, higher LDL:HDL ratio, increased insulin resistance and raised blood pressure is found commonly in the Asian community. This is probably genetic and helps to explain the increased prevalence of coronary disease in both sexes with the development of symptomatic coronary disease in Asians approximately 10 years earlier than in Europeans.¹²





Biological Effects

There are a number of mechanisms by which HT benefits the cardiovascular system.

1. HT affects lipids and lipoproteins, which are important for the development of atheromatous disease. These effects vary according to the type of estrogen or progesterone used and their route of administration.
2. Oral estrogens reduce LDL cholesterol and appear more effective than transdermal oestradiol.¹⁵ Oral estrogens are also more effective than transdermal estradiol in increasing HDL cholesterol. This increase in HDL may be negated by the addition of a progestogen with androgenic properties.¹⁶
3. Transdermal estradiols reduce triglycerides, whereas oral estrogens increase them.¹⁷ The addition of androgenic progesterone prevents any rise in triglycerides.¹⁷
There may also be reductions in lipoprotein(a); changes in LDL particle size and clearance and reductions in LDL oxidation. Overall the various changes in the lipids and lipoproteins seen with HT are probably beneficial.
4. Estrogens also affect glucose and insulin metabolism. Estrogens increase pancreatic insulin secretion, insulin sensitivity and insulin elimination.¹⁸
Androgenic progestogens may oppose these effects but non-androgenic progestogens do not.¹⁸
5. Estrogens affect body fat distribution by helping to prevent the postmenopausal increase in central (android) fat.¹⁹
6. Estrogen affects coagulation and fibrinolysis, increasing both pro-coagulant and fibrinolytic activity but at high doses may result in over all increase in thrombogenesis²⁰.
7. Estrogens have direct effects on arteries through various genomic and non-genomic mechanisms.²¹ These include effects on the vascular endothelium, on ion channels and on the renin angiotensin aldosterone system.

At appropriate physiological doses, estradiol probably improves vascular remodeling, but at inappropriately high doses it may have adverse effects and cause plaque progression or instability.²² Specific studies concerning premature cardiac events and death in younger premenopausal women in Indian context need to be highlighted or conducted.

Cardiovascular Risk and HT

The incidence of cardiovascular disease (CVD) increases with age in women as well as in men. In women there is an additional increase in risk due to the menopause. This is due to the loss of ovarian function.¹ Globally, it is also the leading cause of morbidity and mortality in women (54% in women vs 43% in men). Although, the death rate has fallen in men, it has increased in women because of the rising prevalence of hypertension, diabetes mellitus, sedentary habits, obesity and smoking.

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The Menopause **FOGSI** Focus

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Primary Prevention

Epidemiological data and observational studies have demonstrated a 35–50% reduction of cardiovascular events in postmenopausal women on traditional HT.

However the results of the Woman's Health Initiative (WHI) a large prospective randomized controlled double blind study has confirmed that there is no primary cardio-protection in healthy women who take continuous combined CEE 0.625 mg and 2.5 mg MPA. The increase in cardiac events in the first year in the WHI trial could well be because the trial was dealing with a mean age group of women who were 63.3 years of age and were really an at-risk population. This observation is similar to the HERS trial on women with documented preexisting CHD where the mean age was 67 years. Women should be informed during counseling that this data need not necessarily apply to women in their 50s.

In the meanwhile consideration should be given to switching to micronized progesterone, preferably by the vaginal or the rectal route if acceptable to the women, since these are known to be more lipid friendly and more physiological.

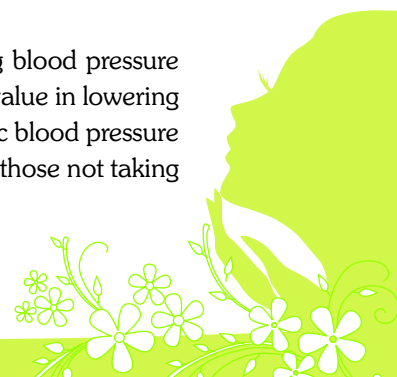
Coronary Artery Disease

The majority of observational and preclinical studies support the potential benefits of systemic ET/EPT in reducing coronary heart disease (CHD) risk. Most RCTs have not. Emerging data suggest that these disparities in findings may be related to the timing of initiation of ET/EPT in relation to the proximity of menopause. Neither ET nor EPT reduced overall CHD incidence in the WHI study. The role of ET/EPT in primary prevention of CHD remains unclear when considered for perimenopausal and early postmenopausal women if initiated early after reaching menopause and continued for a number of years thereafter. Thus, ET/EPT use for primary prevention needs further evaluation.

Data do not currently support recommendations for use of EPT regimens in secondary prevention of CHD. Pending additional data, the use of ET/EPT is not recommended as a single or primary indication for coronary protection in women of any age.

HT & Hypertension

ET plays a part in the synergic action with the antihypertensive drugs in reducing blood pressure values and ensures an improvement in the metabolic profile. This effect is of great value in lowering the cardiovascular risk in hypertensive postmenopausal patients. Increase in systolic blood pressure (SBP) over time is significantly lower in postmenopausal women taking ET than in those not taking ET. This difference is intensified at older ages.





HT does not pose a threat to postmenopausal women with underlying hypertension. The transdermal/non oral form of estrogen is recommended. Tibolone and raloxifene can be recommended without any adverse effect.

Venous Thromboembolism

Observational studies and RCTs have found a significant increase in the risk of venous thromboembolism (VTE) in postmenopausal women using systemic ET/EPT. The RCTs found an increased hazard ratio (HR) for VTE with both EPT and ET use. VTE risk appears during the first 1--2 years after initiation of therapy and decreases over time. In the WHI, excess VTE risk associated with EPT and ET use was low overall and even lower in women younger than 60 years when randomized to HT. Lower doses of oral estrogens may be safer than higher doses.

Stroke

Both ET and EPT appear to increase the risk of ischemic stroke in postmenopausal women, but RCT data have not been fully consistent in this regard. The WHI EPT and ET arms demonstrated an increased risk, whereas some other large trials have not. The absolute risk of stroke, however, is lower in women aged 50--59 years (one additional stroke per 10,000 women per year of ET) or within 5 years of menopause (three additional strokes per 10,000 women per year of EPT) than in older women more distant from menopause. HT should be particularly avoided for women who have an elevated baseline risk of stroke.

Are there Pharmacological Alternatives to Traditional HT for Cardioprotection?^{23,24}

The short answer to that is that no single agent has yet been demonstrated.

The relationship between estrogen and cardiovascular disease is far more complex than initially realized. Till more data is available, HT should be used for non coronary disease concerns. HT is approved and effective for the treatment of perimenopausal symptoms and osteoporosis.

With respect to cardiovascular disease, women and their physicians should follow AHA/ACC guidelines including lipid-lowering therapy in women with hyperlipidemia-an established intervention of CAD which is still underutilized. Statins have been found to be more effective in women than in men in major primary and secondary prevention trials of statins like 4S (Scandinavian Simvastatin Survival Study), CARE (Cholesterol and Recurrent Events), LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease), and WOSCOPS (West of Scotland Coronary Prevention Study).

Beneficial effects of tibolone on lipid profile and coagulation factors are well documented in human trials but the randomized control trials with tibolone on reduction of cardiovascular events are not yet available.

Antioxidants

Role of antioxidants is not established for prevention of CAD in women.

Summarized Recommendations for HT from American Heart Association AHA¹³

The Menopause **FOGSI** Focus

Primary Prevention

- EPT is not recommended for primary cardioprevention as demonstrated by the WHI trial randomized controlled clinical trial.
- There is insufficient data to suggest therefore that HT should be initiated for the sole purpose of primary prevention of CVD.
- Initiation and continuation of HT should be based on established non coronary benefits, risks and patient preference

Secondary Prevention

- HT should not be initiated for the purpose of primary or secondary prevention of CVD.
- The decision to continue or stop HT in women with CVD who have been undergoing long term HT should be based on established non coronary benefits and risks and patient preference.
- If a woman develops an acute CVD event or is immobilized whilst undergoing HT, it is prudent to consider discontinuance of the HT or to consider VTE (venous thromboembolism) prophylaxis while she is hospitalized to minimize risk of VTE associated with immobilization. Re-institution of HT should be based on established non coronary benefits and risks as well as patient preference.

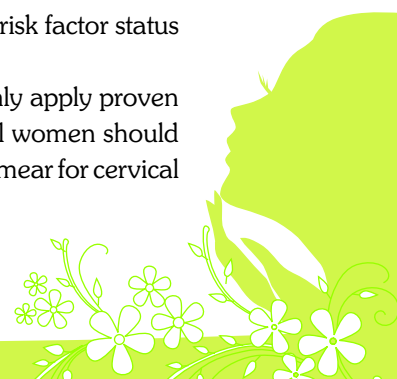
CVS Risk Factors and Role of HT in the Indian Context^{14,25,26}

Certain risk factors are more prevalent in Indian women that may alter the recommendations regarding HT use in Indian women. This would however further require validating these suggestions prior to changing clinical practice:

- a) Atherogenic dyslipidemia (increased triglycerides, low HDL, and increased small dense LDL-C).
- b) Insulin resistance syndrome (hypertension, diabetes mellitus, central obesity, Lp(a) and atherogenic dyslipidemia).
- c) Low level of HDL is a strong predictor of CAD in Indian women.
- d) Increased levels of Lp(a) and homocysteine are more prevalent in Indians, which predisposes them to premature CAD.
- e) In HERS I trial, women who were in the highest quartile of Lp(a) and received HT had impressive 54% decrease in the cardiovascular events. Although no Indian trials with the effect of HT on CHD are available, it may be possible to assume that benefits of HT may be greater in Indian women. However, this would require hard clinical evidence prior to making a recommendation.
- f) Indian women with a high risk factor (diabetes mellitus, family history of CAD, hypertension, and insulin resistance syndrome) should be subjected to special investigations such as Lp(a) and homocysteine assays along with lipid profile, PAI-I and C-reactive protein (CRP).
- g) We could consider adding HT to statins in certain subset of women like those with high Lp(a) after a fully informed counseling session which clarifies the lack of firm Indian evidence but is based on the subset beneficial effect seen in the HERS I trial.
- h) Syndrome X, where symptoms of angina with ECG changes and stress tests like stress thallium or stress echo show evidence of reversible ischemia with normal coronary angiogram, may be benefited with HT. Again this is an area for clinical research. AHA/ACC recommends lifestyle changes.

Key Points

- a) Pregnancy and preconception periods are optimal time to review common cardiac risk factor status and health behavior to reduce cardiovascular disease in future.
- b) A physician should focus on educating women about CVD risk and should uniformly apply proven CHD risk-reduction therapies with established benefits in women. Postmenopausal women should understand that the importance of a lipid profile for cardiac health is similar to a pap smear for cervical cancer prevention.





- c) Assessment of carotid atherosclerosis as a surrogate marker of general atherosclerosis by measurement of intimal medial thickness by B-mode carotid sonography may be utilized before giving a prescription of HT to diagnose subclinical atherosclerosis in certain subset of patients.
- d) The use of statins and aspirin should be recommended as first line measures.
- e) HT can have beneficial effects on CHD if started in younger women closer to menopause. Low dose HT may be initiated in older postmenopausal women if otherwise indicated for non-cardiac benefits.
- f) Benefits of HT in preventing atherosclerosis occur only when the therapy is started during the early postmenopausal years, known as the “window of opportunity” before advanced atherosclerosis develops.
- g) Initiation and continuation of HT should be based on established non-coronary benefits and risks and patient preference. AHA also recommends life style changes and healthy diet for preventing CHD.
- h) Mind modulation by Yoga and pranayama are good suggestions for prevention of CHD along with diet and exercise, avoidance of excessive alcohol, stress and smoking.

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The Menopause **FOGSI** Focus

9

Osteoporosis Extent of the Problem



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Bone loss with ageing is an universal phenomenon resulting in low skeletal mass. This along with microarchitectural deterioration of bone tissue leads to enhanced bone fragility and in turn to increased fracture risk. Strength of bone in the elderly woman is mainly determined by the quantity of bone mass. Bone mass itself is believed to be influenced by the genetic profile, calcium intake and physical activity.

Osteoporosis is a chronic disease that can affect people of any age but perhaps has major implications in the elderly. It is frequently referred to as a silent killer but the condition itself has to be recognized by clinicians as a silent epidemic.

Perimenopausal osteoporosis is caused by oestrogen deficiency which increases the rate of bone turnover along with an excessive resorption and inadequate formation at each remodeling site. The consequence of such an imbalance in remodeling is an acceleration in the loss of bone mass leading to progressive thinning and disruption of trabecular architecture. There is therefore a resultant disproportionate loss of bone strength.

Osteoporosis becomes clinically apparent very often only when an individual sustains a fragility fracture, by which time the disease is well established. No precise longitudinal data are known but a realistic estimate would be 1 in 3 women and 1 in 8 men over the age 50 would be affected by osteoporosis worldwide. Whilst breast cancer is diagnosed in every 8 th woman, every 3 rd woman is diagnosed to have some degree of osteoporosis.

Without doubt osteoporosis is a clinical and public health problem - but what is the extent of the problem

Life Expectancy

Globally life expectancy at birth has doubled in the last half century. Approximately 580 million men and women are over 60 years of age and by 2020 this figure is believed to touch 1 billion⁽¹⁾ of this 1 billion atleast 50% would be post menopausal women. In India the percentage increase in the elderly population by the year 2050 as compared to 1999 is expected to be 242%

From an average of 30 years in the late 1940s life expectancy has currently increased to well above 60. The number of women in the age group 50 - 59 years is projected to increase from 36 million in 2000 to 63 million in 2020.⁽²⁾

An inevitable fallout of this is the fact that women spend atleast one third of their life post menopause and are therefore more susceptible to Osteoporosis.





Osteoporosis

The actual risk of osteoporosis and osteoporosis related fractures varies from one country to another. In the United Kingdom there are over 200,000 osteoporotic fractures each year, a number which is expected to double over the next 50 years.⁽³⁾ In the USA the estimated lifetime risk of hip fracture to a white American woman is approximately 15% and 70% of postmenopausal women are osteoporotic by 80 yrs of age.

Seventy per cent of the 1.3 million fractures that occur annually in the USA in patients aged 45 years or older are attributable to osteoporosis. From the age of 50 years a woman has 32% risk of vertebral fracture, 16% risk of lower arm fracture and 15% risk of Hip fracture

In India, 30 million women suffer from osteoporosis of which 50% are postmenopausal. Indians have a lower peak bone mass than their North American or European counterparts. Osteoporotic fractures occur 10-20yrs earlier in Indians as compared to Caucasians.

The International Osteoporosis Foundation quotes that an approximate 36 million Indian women will be affected by this condition by the year 2013. Indian men and women are estimated to have a lower bone density as compared to Americans and Europeans.⁽⁴⁾ This high prevalence is probably related to nutritional Vitamin D and Calcium deficiency. In certain ethnic groups lack of exposure to sunlight can result in suboptimal levels of Vit D. Diabetes, Hypothyroidism, certain chronic infections, environmental and genetic factors can all influence the onset, progression and severity of Osteoporosis

80% of the urban Indian population has Vit D levels below 20 ng / ml as against the ideal 30 ng / ml. A region wise study also showed the Vit D levels amongst South Indians was 6 to 20 ng / ml compared to 2 to 12 ng / ml in North Indians. Vit D deficiency surprisingly is present in healthy children in the age group 10 to 18 years. 35% of these children had Vit D levels below 8 ng / ml.

Conclusion

Osteoporosis is now identified as one of the most important diseases affecting the human race, along with hypertension and diabetes mellitus. Advances in technology and communication have resulted in a downward trend in mortality in India. Analysis of the disease pattern shows an epidemiologic transition from communicable to non communicable diseases. Unfortunately preventable diseases form a major proportion of the mortality figures. Whilst at least 50% of Indian women above the age of 45 are believed to suffer from Osteoporosis at least 1 in 4 of those who sustain an osteoporotic fracture will die within a year !!

Facts and figures although difficult to digest help us to understand the extent of the problem and perhaps implement strategies to detect, prevent and treat osteoporosis.

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The Menopause **FOGSI** Focus

10

Measurement of Bone Quality And Quantity - Clinical Uses & Recent Advances



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“A stitch in time saves nine”

- Old English proverb

Introduction

Osteoporosis is called a silent killer, as it comes unannounced. The first time a person is diagnosed with osteoporosis is when they present with a fracture. Osteoporosis is an abnormal reduction in bone mass and bone deterioration leading to increased fracture risk. Bone is a living, growing tissue, and throughout our lifetime, new bone cells grow and old bone cells break down to make room for the new, stronger bone. It is postulated that 20% of the people who get a hip fracture will die within one year of the fracture. The relationship between low bone mineral density (BMD) and fracture risk is analogous to the relationship between high serum cholesterol and risk of myocardial infarction.

Osteoporosis develops as a result of mismatch between the osteoblastic and osteoclastic activity i.e. the old bone breaks down faster than the new bone can replace it. As this happens, the bone loses minerals. The measurement of bone mineral density is hence used as a marker for osteoporosis. Women who have gone through menopause are more likely to get osteoporosis than men or younger women. Methods that can give us an idea of the bone mineral density will be able to help us detect osteopenia and hence prevent osteoporosis in patients.

Definition of osteoporosis

WHO definition of osteoporosis is based on BMD levels

1. Normal-bone density within 1SD of young adult mean.
T score > -1 = BMD within normal range.
2. Low bone mass (osteopenia) bone density -1 to -2.5 SD below young adult mean.
T score -2.5 to -1 . Increased risk of fracture but not osteoporosis





3. Osteoporosis – 2.5 SD or more below young adult mean

T score more than -2.5 - Severe established osteoporosis - Bone density >2.5 SD below young adult mean and one or more broken bones

T-Score Means: Young Normal Reading

This is comparing the patients reading with that of a young healthy 30 year old adult of the same sex. This is a comparison between the solidness of the bones with average young healthy population and is measured in standard deviations (SD)

Z-Score means: Age matched reading

This measures the patient's own reading with what should be normal for his/her age, size and sex. Since the BMD is low in elderly, age matched reading are misleading.

Bone strength is the maximal load that can be applied before fracture occurs and is influenced by-

- 1) Mass
- 2) Geometry
- 3) Architecture
- 4) Bone tissue quality.

Bone tissue quality depends on degree of mineralization and matrix characteristics. The determinants of bone strength are as follows:

- 1) Bone mineral density. (BMD)
- 2) Bone dimensions - External diameters Predicts 55% of variance of bone strength
- 3) Cortical thickness
- 4) Bone micro-architecture

Bone Mineral Density

Serial BMD testing is an essential component of osteoporosis management and therefore high quality and cost-effective patient care requires that healthcare providers receive valid BMD reports from adequately trained interpreters. There are different methods of testing for bone quality using bone density measurements. BMD is most commonly used, non-invasive measure of early diagnosis of osteoporosis. The reports for BMD are mentioned as T-scores and Z-scores. Values obtained at proximal femur and lumbar spines are used to diagnose osteoporosis by applying criteria established by WHO. BMD predicts approximately 66-74% of variance of bone strength, and BMD corresponds to the ratio between bone mineral content (hydroxyapatite) and bone scanned area.

This is done by:

1. **Dual-energy X-ray absorptiometry (DEXA).** This is considered today as the gold standard in BMD measurements especially in case of suspected osteoporosis. The purpose of monitoring medical therapies is to ensure reduction of future fracture risk, stabilize or increase bone mass, and preserve or improve bone quality and strength. Central DEXA assessment of the hip or spine is currently the “gold standard” for serial assessment of BMD. However, biological changes in bone density are small compared to the inherent error in the test itself, and interpretation of serial bone density studies depends on appreciation of the smallest change in BMD that is beyond the range of error of the test. This least significant change (LSC) varies with the specific instrument used, patient population being

The Menopause **FOGSI** Focus

assessed, measurement site, technologist's skill with patient positioning and test analysis, and the confidence intervals used. Changes less than 3 to 6% at the hip and 2 to 4% at the spine from test to test may be due to the precision error of the testing itself.

2. **Quantitative Ultrasound** - using a peripheral bone like the calcaneum, tibia, patella or the phalynx for measuring the BMD. This is the most cost effective measures of doing **screening BMD** for the general population and detection of patients at risk. Peripheral skeletal sites do not respond in the same magnitude as the spine and hip to medications and thus are not appropriate for monitoring response to therapy at this time.
3. **Quantitative Computed Tomography** - is most commonly used for measuring the spine but can be used for other sites as well. Trabecular BMD of the lumbar spine can be used to monitor age-, disease-, and treatment- related BMD changes in men and women. Precision of acquisition should be established by phantom data and analysis precision by re-analysis of patient data.

Table: Comparison between the different methods of doing BMD

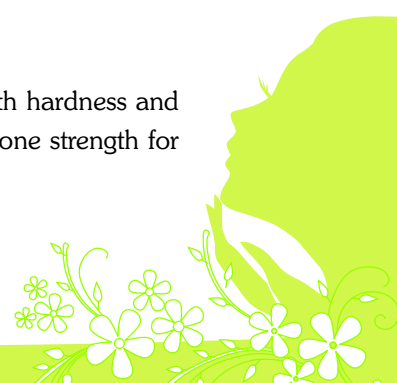
Technique	Site	unit of measurement	Uses	Advantages/disadvantages
DXA	Lumbar spine, proximal femur, transverse body, forearm, heel, phalanges.	area density g/cm ²	Diagnosis, monitoring	Very low radiation exposure, precise, quick. Disadvantage-APspine measurements influenced by degenerative changes and other artifacts. Two dimensional only.
QCT	lumbar spine, hip, forearm	Volumetric density(g/cm ³)	Diagnosis, monitoring	More sensitive than DEXA. Directly measures trabecular bone loss in central aspect of vertebral body. 3-dimensional. Disadvantages-high radiation exposure, less precise, more expensive.
Qualitative USG	Heel, patella, tibia.	Speed of sound, broad band, USG attenuation.	Risk assessment.	Inexpensive, easily transportable. No radiation.

Bone Micro-architecture is assessed by -

1. Histo-morphology - two dimensional evaluation of micro-architecture provides information of bone quality including structure and turnover.
2. Micro-computed tomography (micro CT) – shows the three dimensional micro architecture of bone as well as the relative bone volume and trabecular thickness.

Bone tissue quality showing the degree of mineralization

Nano-indentation technique applies to investigate tissue quality by measuring both hardness and elasticity of dry and wet bone tissue with a high spatial resolutionEvaluation of bone strength for different parts of skeleton





- Compression of vertebral body or proximal tibia
- 3-4 point bending test of long bones
- Shear test of femoral neck
- Load deflection curve

Clinical applications

Bone quality and strength is important for the diagnosis of certain conditions and also for evaluation of the treatment

- Post menopausal osteoporosis
- Family history of osteoporosis
- Surgical menopause
- Premature menopause
- Primary hypo or hyperthyroidism
- Hypogonadism
- Life style factors
 - low calorie intake
 - smoking
 - alcohol overuse
 - lack of exercise
 - chronic immobility
- Certain medications
 - long term >5 months steroid therapy
 - GnRH agonist therapy
- Osteopenia apparent on X-ray
- Medical conditions like Celiac disease, Crohn's disease

The Importance of screening for osteoporosis

Early detection of low bone mass is the most important step in prevention and treatment. If there is osteopenia or osteoporosis, a person can take action and remedial measures with life style modifications to stop the progression of bone loss. If acted upon early, prevention is possible. The best remedy for osteoporosis is regular exercise and proper nutrition.

Newer Applications and Advances

1. To determine the diagnostic accuracy of mandibular and maxillary bone density in detecting osteoporosis using receiver operating characteristic (ROC) analysis. Density of the premolar region reaches a fair diagnostic accuracy, which might improve when including additional factors in the analysis and refining the densitometric tool.⁵
2. The role of the dental surgeon in detecting osteoporosis: the OSTEODENT study.⁶ Those with osteoporosis tended to have a low OSIRIS score and a thinned cortical mandibular border. The area under the ROC curve for using both cortical width and OSIRIS to predict osteoporosis was 0.90 (95% CI = 0.87 to 0.92). Dentists have a role to play in the detection and referral of patients at high risk of osteoporosis.

The Menopause **FOGSI** Focus

3. Advanced imaging of bone macrostructure and microstructure in bone fragility and fracture repair.⁷ The methods available to quantitatively assess macrostructure include computed tomography and, particularly, volumetric quantitative computed tomography. Methods for assessing microstructure of trabecular bone include high-resolution computed tomography, microquantitative computed tomography, high-resolution magnetic resonance imaging, and micromagnetic resonance imaging. These new techniques help to illustrate the process of fracture-healing by defining the skeletal response to innovative therapies and assessing biomechanical relationships. Research into the molecular and cellular pathways focusing on bone fragility and fracture-healing has led to new potential treatments to aid in fracture-healing.
4. Investigating new BioMEMS techniques for early detection of osteoporosis.⁸ The biomarkers provide a promising challenge of clinical proteomics for early disease detection. Different techniques like optical and electrochemical testing are been studied comparatively. New peaks have been identified in UV-visible spectroscopy at 420nm and high sensitivity is achieved by electrochemical technique with ng/ml to pico/ml level detection of bonemarkers. An electrochemical technique is found to be the best suitable for developing a new bioMEMS chip.

Take home message: Osteoporosis - Facts

- 30 million women in India suffer from osteoporosis and expected to rise to 36 million by 2013.
- It is a silent killer
- 12-20% patients will die within one year of a hip fracture
- 30-50% of women and 15-30% of men will suffer from osteoporotic fracture in their lifetime
- In women over 45years, osteoporosis accounts for more days spent in hospital than any other disease.

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11

The Role of Calcium and Vitamin D and Micronutrients in Bone Health



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There is growing interest in the role of calcium supplied in different vehicles on indices of bone health in the population in general. Micronutrients encompass vitamins and minerals and a variety are implicated in the maintenance of bone health.

Ca and vitamin D

An adequate intake of calcium, lifelong, is necessary for the acquisition of peak bone mass and maintenance of bone health. The skeleton contains 99% of the body's Ca stores, when the exogenous supply is inadequate, bone tissue is reabsorbed from the skeleton to maintain serum ca at a constant level.

Type and timing of Ca supplements

Dairy products (e.g., milk, cheese, and yogurt) are the most common sources of dietary calcium. Calcium supplements may be used if patients are unable to consume adequate amounts of calcium through foods. The two most common calcium supplements are calcium carbonate and calcium citrate. Calcium phosphate and calcium gluconate are also available. Calcium carbonate contains 40% elemental calcium, the highest amount available among calcium formulations; it should be taken with food to maximize absorption capacity by providing an acidic environment. This option is cost-effective and may be preferred for most patients. Calcium citrate may be taken with or without food, but it is more expensive, contains less elemental calcium (21%), and is available in fewer formulations. Calcium citrate may be beneficial for patients with achlorhydria and those taking histamine H₂-receptor antagonists or proton-pump inhibitors.

There is growing support for the effect of Ca supplementation on the suppression of both PTH secretion and bone resorption, but controversy still remains as to the optimum timing of supplementation administration

Table 1: Dietary Reference Intakes For Calcium

Group	Calcium(mg/day)
0-6months	210
6m-1yr	270
1-3yrs	500
4-8yrs	800
9-18yrs	1,500
19-50yrs	1,200
>50yrs	1,500
Women, pregnant or lactating	1,500

The Menopause **FOGSI** Focus

In an interesting study presented by S Oetolani, Istituto Auxologico Italiano, Milan, Italy, and associates, a three way randomised study of 12 postmenopausal women was undertaken comparing no treatment with 2 different dosing schedules of Ca (1 dose of 1200mg at evening or 2 doses of 600mg at 12 hr interval). The aim of the study was to determine whether two separate doses of calcium lead to more steady suppression of bone resorption. Results indicated that serum Ca was increased and serum PTH reduced by Ca administration with either dosing schedule as compared with placebo and although overall suppression of PTH and bone resorption obtained with 2 daily doses of 600mg of calcium is similar to that of a single dose 1200mg, repeated doses provides a more steady suppression of bone resorption .

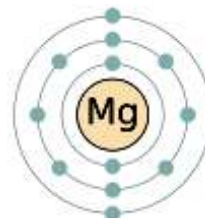
Another important paper is one presented by Palbertazzi and co-workers, University of Hull UK comparing two types of Ca preparations (ossein hydroxyapatite [OHC]v/s tri-Ca phosphate). Both preparations derived from porcine bone powder, but the second supplement type had the organic matrix destroyed by ashing. The study involved 153 postmenopausal osteopenic women who were randomised into 1 of 3 treatment groups. Measurements of bone resorption performed at baseline 3 months and 6 months and bone density at baseline and 6 months. Results indicated that both the OHC and TCP supplements significantly reduced marker of bone resorption compared with placebo group, but the effect was not as marked in the TCP group. Spine BMD was found to be increased by 0.5%with OHC and decreased with both placebo (0.8%) and TCP (0.7%).

Vitamin D promotes bone formation by improving intestinal absorption of Ca and phosphate and by stimulating maturation and mineralisation of the osseous ground substance - the osteoid. A daily allowance of 400-800 IU is required for healthy bone.

High dietary levels of phosphates (found for example in many carbonated drinks) are associated with a negative calcium balance.

Magnesium

Hypomagnesemia is one of the possible factors in osteoporosis. Food sources rich in magnesium are green leafy vegetables, unpolished grains, nuts, milk and meat.



Vitamin A

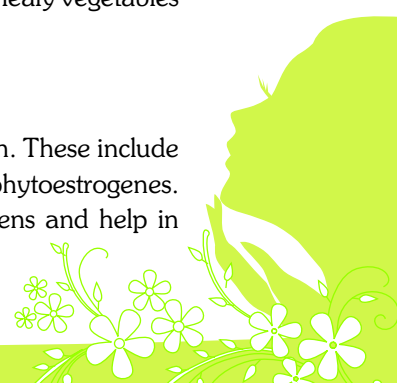
Vitamin A has many roles in maintenance of health. While it is important for normal vision, high vitamin A intake is associated with a higher risk for fractures as it is a vitamin D and Ca antagonist. Consuming a diet rich in fruit and vegetables is a reasonable way to meet vitamin A needs rather than taking supplements.

Vitamin K

It is now apparent that Vit K not only affects blood clotting but also plays a role in bone metabolism and potential protection against osteoporosis. Vitamin K is required for the gamma-carboxylation of osteocalcin. Studies suggest that long term use of coumarin based anticoagulants such as warfarin adversely affects vertebral BMD and fracture risk. Vegetables particularly dark green leafy vegetables are rich source of vitamin K.

Other micronutrients and dietary components

So many other nutrients and dietary factors are important for long term bone health. These include zinc, copper, manganese, boron, vitamin C, The B vitamins, potassium sodium and phytoestrogens. Phytoestrogens are plant substances that have similar effects like those of estrogens and help in



preventions of osteoporosis.

Other important groups are isoflavones and lignans. Isoflavones are found in soybeans, other legumes (beans and peas). The major isoflavones are genistein and daidzein. The major ligans are entrolactone and entrodinol found cereals, vegetables and fruit.

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The Menopause **FOGSI** Focus

12

Role of Estrogen in Prevention and Treatment of osteoporosis



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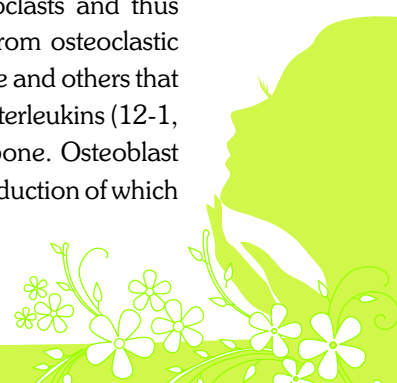
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Introduction

Osteoporosis is a systemic skeletal disease characterized by low bone mass and a deterioration of micro-architecture of bone tissue, leading to enhanced bone fragility which results into increase in the fracture rate even with little or no trauma. It is the most prevalent bone problem in the elderly and has become a major global public health problem due to tremendous increase in the elderly population throughout the world. Because of this demographic change, the number of hip fractures occurring in the world each year will increase approximately 6 fold from 1990 to 2050 and the proportion occurring in Europe and North America will fall from 50% to 25% as the number of old people in developing countries increase¹. It has a lot of impact on national economy. Twenty five million people suffer from osteoporotic fractures in U.S.A. and more than 1.3 million fractures occur per year in U.S.A. It is estimated that annual health costs due to fractures in U.S.A. amount to 10 billions U.S. dollars, DM 1 billion in Germany and 500 million £ in U.K.²

Effects of Estrogen on bone

Estrogens in women are essential for the formation and maintenance of sufficient bone mass. Osteoclasts and osteoblasts have estrogen receptors. Estrogen act both directly and indirectly on osteoblasts. Estrogen directly inhibits lysosomal enzyme production in the osteoclasts and thus decreases bone resorption. Indirectly estrogen inhibits maturation of osteoclasts from osteoclastic precursor cells. Osteoblasts precursors produce several cytokines, some that stimulate and others that inhibit osteoclast activity. The osteoblast derived osteoclast Stimulatory factors are interleukins (12-1, 12-2, 12-6, 12-11) where production of interleukins are inhibited by estrogen in bone. Osteoblast derived osteoclast-inhibiting factor i.e. transforming growth factor β (TGF- β), the production of which





is stimulated by estrogens. After menopause due to estrogen deficiency the above process is reversed hence there is increased in the bone resorption.

Prevention and treatment of Osteoporosis

1. Primary prevention: To ensure that each woman achieve peak bone mass, provided prevention should start at menarche and adolescent years. A combination of adequate and appropriate nutrition, physical exercise and healthy life style will help to achieve optimal peak bone mass.
2. Secondary prevention is to diagnose osteoporosis and preventive measure to be taken for prevention of osteoporotic fracture and further deterioration of the disease.
3. Tertiary prevention is by preventing further osteoporotic fracture where osteoporotic fracture has already occurred in the past.

Estrogen Replacement Therapy (ERT) in The Prevention and Treatment of Osteoporosis

Estrogen therapy is one of the most commonly prescribed treatment for the prevention of postmenopausal osteoporosis and for a treatment of established bone loss. Multiple trials have demonstrated the positive effect of estrogen in the improvement of the bone mineral density and lower doses have also proven efficacious with fewer side effect. Hence, many experts recommend that all women should use ERT after the menopause. But general treatment is obviously unrealistic hence, all experts agree that ERT is necessary when osteoporosis or risk factors for the disease already exists.

The prevention of Osteoporosis is very important because once osteoporosis sets in bones can never be completely restored and ERT after osteoporosis can prevent only further bone loss.

Mechanism of Action

The main action of estrogen is at the cellular levels where it inhibits the osteoclasts and thus decreases bone resorption. Estrogen has also been shown to antagonize PTH stimulation of bone resorption, increases calcium absorption from gastrointestinal tract and renal calcium conservation.

Numerous studies have shown that all estrogens, irrespective of the mode of administration are effective in maintaining BMD.^{3,4}

Table 1 : Shows commonly used estrogens recommended with doses which preserves bone density

Oral	Conjugated Equin Estrogen (Premarin)	0.625 mg
	Estradiol Valerate	2 mg
	Estropipate	0.625 mg
	Popemize Estrogen Sulphate (Harmogen)	1.5 mg
Transdermal	Estradiol	50µg twice weekly
Percutaneous	Estradiol Gel	1.5 mg daily
Subcutaneous	Estradiol	50 mg, 6 monthly

Despite the multitude of published studies on ERT / HRT in postmenopausal women, only 15 observational studies included fracture as a study endpoint. These trials reported that there was reduction in fracture risk in postmenopausal women who used ERT / HRT compared to case controls⁴. Epidemiological studies of ERT indicates that when ERT was taken for more than 5 years there was 50 to 60 percent decrease in fractures of arm and hip⁵ and when estrogen was

The Menopause **FOGSI** Focus

supplemented with calcium, an eighty percent reduction in vertebral compression fracture was observed.⁶ It has been observed that the more potent estrogen and its esters and CEE have a protective effect on bone turnover, but not estradiol.

In the postmenopausal women estradiol levels vary greatly from undetectable upto 25 pg/ml. The skeleton effects of endogenous serum estradiol were assessed in 274 women 65 years and older who participated in the study of osteoporotic fractures. Women who had estradiol levels from 10 to 25 pg/ml had 4.9%, 9.6%, 7.3% and 6.8% greater BMD at the total hip, calcaneous, proximal radius and spine, respectively compared to women whose estradiol levels were less than 5 pg/ml⁷. It has been observed that estradiol blood level of 40 to 60 pg/ml is required to protect against bone loss³. Women with premature menopause (less than 40 years), alcohol consumption and cigarette smoking will require higher doses of ERT.

Commencement of ERT

Since the greatest damage of bone mass occurs in the first few years after menopause, ERT is most beneficial when instituted as early as possible. However, even at later age when significant amount of bone mineral mass already have been lost, ERT can prevent further bone loss. When ERT was given in women over the age of 65 years, it has been documented to protect against fractures⁸. Optimum treatment should start as soon as possible after the last menstrual period and should continue at least for 8 to 10 years. Some experts even suggest that ERT should be used until the end of life which can provide maximum protection.

There is a risk of endometrial hyperplasia and carcinoma when estrogen alone is taken for a long time in an intact uterus. Hence, progesterone supplementation for ten or more days in each month is given to reduce endometrial proliferation. Smith and Studd reported endometrial hyperplasia in 5 – 6 percent cases of endometrial biopsy carried out in women with long term unopposed estrogen therapy⁹. Progestogens that have been clinically assessed for such protection are norethisterone (5 mg), medroxy progesterone acetate (5 mg) dydrogesterone (10mg) and Levonorgestrel (75 mcg). Some studies have reported that when progesterone is added to oestrogen, progesterone can lead to an apparent synergistic increase in bone formation associated with a positive balance of calcium^{10,11}. While other studies have failed to find a greater impact on bone, comparatively estrogen alone to estrogen plus progesterone.¹²

Some studies have reported that addition of testosterone to an estrogen therapy has additional beneficial effect on bone.^{13,14} Others have reported a greater increase in bone density with an estrogen – androgen combination compared with estrogen alone, but blood estrogen levels were higher than those associated with standard postmenopausal hormonal therapy.¹⁵

In the Women's Health Initiative (WHI) studies, the risk of breast cancer associated with estrogen with or without progesterone was evaluated. The risk of breast cancer was slightly increased with combined estrogen and progestin after 3 years of use. When estrogen alone was given in women with hysterectomies did not increase the risk of breast cancer compared to placebo in other portion of the hormonal replacement trial of WHI study. Other several studies also found a link between duration of estrogen and progesterone use and breast cancer risk.^{16, 17} Addition of progestin increases the risk of breast cancer compared to estrogen alone, because it has been observed that mitotic activity in the breast during normal menstrual cycle is greatest when progesterone levels are highest.





Effects of Stopping ERT

The protective effect of estrogen rapidly dissipates after treatment is stopped because estrogen withdrawal is followed by rapid bone loss, similar to that after menopause.¹⁸ In a Swedish case-control study, most of the beneficial effects of ERT was lost five years after discontinuing the treatment.¹⁹ Hence, maximum protection against osteoporotic fractures requires life long therapy.

It is recommended to measure the bone density in treated women when they are in their late 60s as some of these women may have failed to respond to ERT. Hence, treatment in such cases can be modified. Along with ERT sufficient amount of calcium, vitamin D and physical activity are also necessary.

Largest trials by Women's Health Institute (WHI) reported adverse effects of estrogen and progestogen therapy. These include an increase incidence of thromboembolic phenomenon, cardiovascular disease and strokes. Hence, the trial's using continuous combine HRT in WHI have been stopped after 5 years. Therefore, today we recommend use of alternatives like Tibolone and SERMS, which have been successfully used for the prevention of postmenopausal osteoporosis.

Conclusion

Estrogen therapy had proven to increase bone mineral density at all skeleton sites. Prevention and treatment of osteoporosis and estrogen therapy has been supported by a wealth of data which includes a meta-analysis of 22 estrogen trials, Cohort studies, results of the WHI and Million Women study and trials with bone mineral density outcome. However, use of estrogen therapy has its attendant risks and therefore the risk to benefit ratio should be carefully weighed for each individual woman.

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The Menopause **FOGSI** Focus

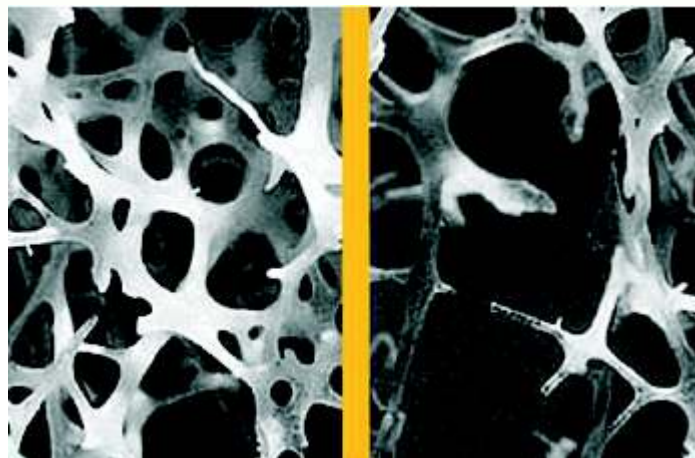
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Anti Resorptive Agents for Prevention and Treatment of Post Menopausal Osteoporosis



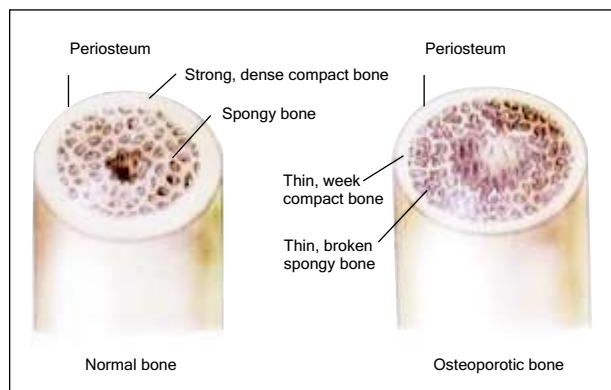
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Osteoporosis has been defined as a systemic, skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue with a consequent increase in bone fragility.

Osteoporosis is a silent disease until it is complicated by fractures - fractures that can occur following minimal trauma. These fractures are common and place an enormous medical and personal burden on aging individuals and a major economic toll on the nation. Osteoporosis can be prevented and can be diagnosed and treated before any fracture occurs. Importantly, even after the first fracture has occurred, there are effective treatments to decrease the risk of further fractures. Hence, prevention, detection, and treatment of osteoporosis should be a mandate of primary care providers.



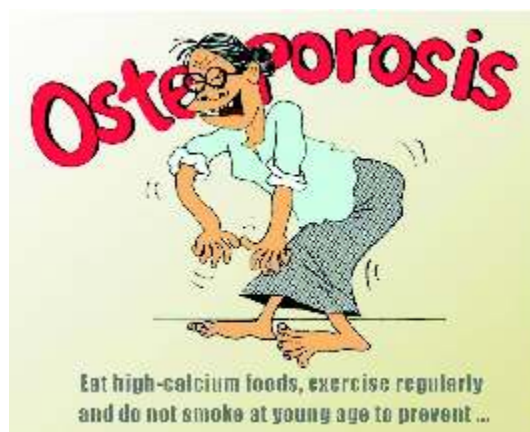
Synopsis of Major Recommendations to the Clinician

For postmenopausal women and men age 50 and older:

- Counsel on the risk of osteoporosis and related fractures.
- Check for secondary causes.
- Advise on adequate amounts of calcium (at least 1200 mg/d, including supplements if necessary) and vitamin D (800 to 1000 IU per day of vitamin D3 for individuals at risk of insufficiency).
- Recommend regular weight-bearing and muscle-strengthening exercise to reduce the risk of falls and fractures.
- Advise avoidance of tobacco smoking and excessive alcohol intake.
- In women age 65 and older and men age 70 and older, recommend BMD testing.
- In postmenopausal women and men age 50-70, recommend BMD testing when you have concern based on their risk factor profile.
- Recommend BMD testing to those who have suffered a fracture, to determine degree of disease severity.
- Initiate treatment in those with hip or vertebral (clinical or morphometric) fractures.
- Initiate therapy in those with BMD T-scores < -2.5 at the femoral neck, total hip, or spine by DXA, after appropriate evaluation.
- Initiate treatment in postmenopausal women and in men age 50 and older with low bone mass (T-score -1 to -2.5 , osteopenia) at the femoral neck, total hip, or spine and 10-year hip fracture probability 3% or a 10-yr all major osteoporosis-related fracture probability of 20% based on the US-adapted WHO absolute fracture risk model.
- Current FDA-approved pharmacologic options for osteoporosis prevention and/or treatment are bisphosphonates (alendronate, ibandronate, risedronate, and zoledronate), calcitonin, estrogens and/or hormone therapy, raloxifene and parathyroid hormone (PTH 1-34).
- BMD testing performed in DXA centers using accepted quality assurance measures is appropriate for monitoring bone loss (recommendation every 2 years). For patients on pharmacotherapy, it is typically performed two years after initiating therapy and at 2-year intervals thereafter.

Universal Recommendations for All Patients

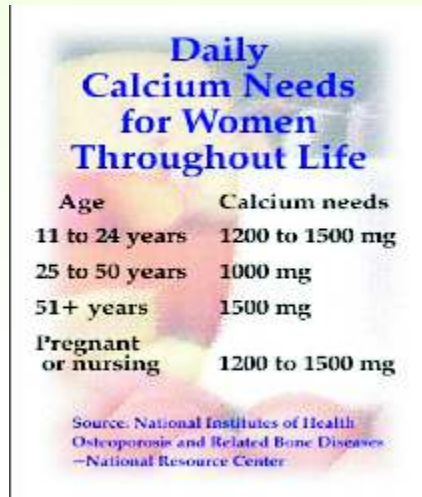
Several interventions to reduce fracture risk can be recommended to the general population. These include an adequate intake of calcium and vitamin D, lifelong participation in regular weight-bearing and muscle-strengthening exercise, avoidance of tobacco use, identification and treatment of alcoholism, and treatment of other risk factors for fracture such as impaired vision.



The Menopause **FOGSI** Focus

- **Adequate Intake of Calcium and Vitamin D**

1. **Calcium** - Lifelong adequate calcium intake is necessary for the acquisition of peak bone mass and subsequent maintenance of bone health.



Age	Calcium needs
11 to 24 years	1200 to 1500 mg
25 to 50 years	1000 mg
51+ years	1500 mg
Pregnant or nursing	1200 to 1500 mg

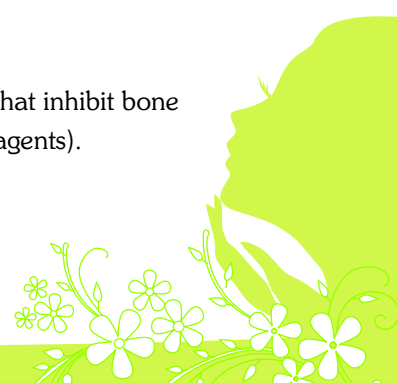
Source: National Institutes of Health
Osteoporosis and Related Bone Diseases
—National Resource Center

2. **Vitamin D** - Vitamin D plays a major role in calcium absorption, bone health, muscle performance, balance, and risk of falling.
3. **Regular Weight – Bearing Exercise** - Among its many health benefits, weight-bearing and muscle-strengthening exercise can improve agility, strength, posture, and balance, which may reduce the risk of falls. In addition, exercise may modestly increase bone density.
4. **Fall Prevention** - In addition to maintaining adequate vitamin D levels and physical activity, as described above, strategies to reduce falls include, but are not limited to, checking and correcting vision and hearing, evaluating any neurological problems, reviewing prescription medications for side effects that may affect balance and providing a check list for improving safety at home. Wearing undergarments with hip pad protectors may protect an individual from injuring the hip in the event of a fall. Hip protectors may be considered for patients who have significant risk factors for falling or for patients who have previously fractured a hip.
5. **Avoidance of Tobacco Use and Excessive Alcohol Intake** - Advise patients to avoid tobacco smoking. The use of tobacco products is detrimental to the skeleton as well as to overall health. The NOF strongly encourages a smoking cessation program as an osteoporosis intervention.

Recognize and treat patients with excessive alcohol intake. Moderate alcohol intake has no known negative effect on bone and may even be associated with slightly higher bone density and lower risk of fracture in postmenopausal women. However, alcohol intake of 3 or more drinks per day is detrimental to bone health, increases the risk of falling, and requires treatment when identified.

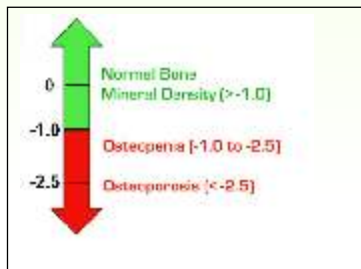
Pharmacologic Therapy

Medications used to prevent and treat osteoporosis fall into two categories: drugs that inhibit bone resorption (antiresorptive agents) and drugs that stimulate bone formation (anabolic agents).



Current FDA-approved pharmacologic options for the prevention and/or treatment of postmenopausal osteoporosis include, in alphabetical order: bisphosphonates (alendronate, alendronate plus D, ibandronate, risedronate, and risedronate with 500 mg of calcium carbonate, zoledronate), calcitonin, estrogens (estrogen and/or hormone therapy), estrogen agonist/antagonist (raloxifene), and parathyroid hormone [PTH (1-34), teriparatide].

Who Should Be Treated?



Postmenopausal women and men age 50 and older presenting with the following should be treated:

- A hip or vertebral (clinical or morphometric) fracture
- Other prior fractures and low bone mass (T -score between -1.0 and -2.5 at the femoral neck, total hip, or spine)
- T -score < -2.5 at the femoral neck, total hip or spine after appropriate evaluation to exclude secondary causes
- Low bone mass (T -score between -1.0 and -2.5 at the femoral neck, total hip, or spine) and secondary causes associated with high risk of fracture (such as glucocorticoid use or total immobilization)
- Low bone mass (T -score between -1.0 and -2.5 at the femoral neck, total hip, or spine) and 10-yr probability of hip fracture $\geq 3\%$ or a 10-yr probability of any major osteoporosis related fracture $\geq 20\%$ based on the U.S.-adapted WHO algorithm.

Anti Resorptive Agents

Antiresorptive agents reduce bone loss by decreasing osteoclastic boneresorption. While these therapies have no direct effect on osteoblast function and do not stimulate new bone formation, increases in BMD are observed. Antiresorptive agents slow remodeling and reduce the number and depth of resorption sites. Bone formation exceeds bone resorption at these sites, leading to a refilling of the remodeling space, more complete bone mineralization, and overall increases in BMD.

Before choosing the most appropriate antiresorptive therapy for a given patient, it is important to understand the benefits of these agents with respect to BMD and fracture risk and any nonbone benefits and risks.

- **Bisphosphonates**

Bisphosphonates are structural analogues of pyrophosphate, a naturally occurring bone resorption inhibitor. Bisphosphonates have a strong affinity for the hydroxyapatite crystals in bone, where they act as potent inhibitors of bone resorption by decreasing osteoclast recruitment, activity, and life span.

- Alendronate - Alendronate sodium is approved by the FDA for the prevention (5 mg daily and 35 mg weekly) and treatment (10 mg daily and 70 mg weekly [Tablet or liquid formulation] or 70 mg weekly

The Menopause **FOGSI** Focus

with 2,800 IU and 5600 IU of vitamin D3) of osteoporosis in postmenopausal women. Alendronate reduces the incidence of spine, hip and wrist fractures by about 50% over 3 years in patients with a prior spine fracture. It reduces the incidence of spine fractures by 48% over 3 years in patients without a prior spine fracture. Alendronate is also approved to increase bone mass in men with osteoporosis and for the treatment of men and women receiving glucocorticoids in a daily dose of 5 mg or greater of prednisone and who have low bone mass. In addition to tablet formulation, alendronate is available as a liquid with 70 mg in 75ml, to be followed by at least 2 oz of plain water.

- **Ibandronate -**

Ibandronate sodium as 2.5 mg per day orally, 150 mg per month orally, and 3 mg every 3 months by intravenous injection are approved by the FDA for the treatment of postmenopausal osteoporosis. The oral preparations are also approved for the prevention of postmenopausal osteoporosis. Ibandronate reduces the incidence of spine fractures by about 50% over 3 years.

- **Risedronate -**

Risedronate sodium (5 mg daily dose; 35 mg weekly dose; 35 mg weekly dose packaged with 6 tablets of 500 mg calcium carbonate, or 75 mg on two consecutive days every month) is approved by the FDA for the prevention and treatment of postmenopausal osteoporosis. Risedronate reduces the incidence of spine fractures by 41-49% and non-spine fractures by 36% over 3 years in patients with a prior spine fracture. Risedronate is approved for treatment to increase bone mass in men with osteoporosis and for the prevention and treatment of osteoporosis in men and women who are either initiating or continuing systemic glucocorticoid treatment (daily dose equivalent to 5 mg prednisone or greater) for chronic disease.

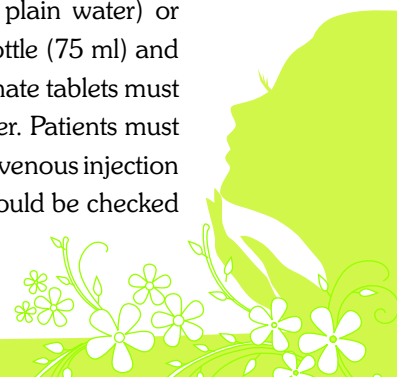
- **Zoledronate -**

Zoledronate (5 mg by intravenous infusion over at least 15 minutes once yearly) is approved by the FDA for the treatment of osteoporosis in postmenopausal women. Zoledronate reduces the incidence of spine fractures by 70%, hip fractures by 41%, and non-vertebral fractures by 25% over 3 years.

- **Side Effects and Administration of Bisphosphonates**

Side effects are similar for all oral bisphosphonate medications and include gastrointestinal problems such as difficulty swallowing, inflammation of the esophagus and gastric ulcer. There have been reports of osteonecrosis of the jaw (particularly following intravenous bisphosphonate treatment for patients with cancer) and of visual disturbances, which should be reported to the healthcare provider as soon as possible. The level of risk for osteonecrosis in patients being treated for osteoporosis with bisphosphonates is not known, but appears extremely small for at least up to 5 years.

Alendronate and risedronate must be taken on an empty stomach, first thing in the morning, with 8 ounces of plain water (no other liquid), at least 30 minutes before eating or drinking. Patients should remain upright (sitting or standing) during this interval as well. Ibandronate should be taken on the same day each month, at least 60 minutes before first food, drink (other than plain water) or medication of the day. Patients using the liquid formulation should swallow one bottle (75 ml) and follow with at least 2 oz of plain water. Other instructions remain the same. Ibandronate tablets must be taken on an empty stomach, first thing in the morning, with a glass of plain water. Patients must remain upright for at least one hour after taking the medication. Ibandronate, by intravenous injection over 15 to 30 seconds, should be given once every 3 months. Serum creatinine should be checked





before each injection. Zoledronate, 5 mg in 100 ml, is given once yearly by intravenous infusion over at least 15 minutes. Patients may be pre-treated with acetaminophen to reduce the risk of an acute phase reaction (arthralgia, headache, myalgia, fever). These symptoms occurred in 32% of patients after the first dose, 7% after the second dose, and 3% after the third dose.

- **Calcitonin**

Salmon calcitonin is FDA-approved for the treatment of osteoporosis in women who are at least 5 years postmenopausal. It is delivered as a single daily intranasal spray that provides 200 IU of the drug. Subcutaneous administration by injection also is available.

Adverse reactions associated with the injectable form, including local reactions, flushing, and rash, and rare systemic allergic-type reactions have limited its use. Adverse effects are rare with the intranasal formulation and consist mostly of nasal complaints of dryness, soreness, irritation, itching, and epistaxis. Nasal examinations should be performed before treatment begins and whenever nasal complaints occur. Should severe ulcerations of the nasal mucosa develop, the drug must be immediately discontinued.

Calcitonin is thought to have some analgesic effects and has been used for pain management in osteoporotic patients with acute compression fractures. The mechanism underlying this is not well understood, but increases in

Studies in postmenopausal women with low BMD have demonstrated increases in spine BMD of 1-3% after therapy with 200 IU of calcitonin nasal spray. Significant changes in hip BMD have not been seen.

- **Estrogen/Hormone Therapy**

Estrogen/Hormone therapy is approved by the FDA only for the prevention of Osteoporosis. The Woman's Health Initiative (WHI) found that 5 years of HT (Prempro®) reduced the risk of clinical vertebral fractures and hip fractures by 34% and other osteoporotic fractures by 23% (20).

The Women's Health Initiative (WHI) reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli and deep vein phlebitis during 5 years of treatment with Premarin and medroxyprogesterone. Subsequent analysis of these data showed no increase in cardiovascular disease in women starting treatment within 10 years of menopause. In the estrogen only arm of WHI, no increase in breast cancer incidence was noted over 7.1 years of treatment. Because of the risks, ET/HT should be used in the lowest effective doses for the shortest duration to meet treatment goals. When ET/HT use is considered solely for prevention of osteoporosis, the FDA recommends that approved non-estrogen treatments should first be carefully considered.

- **Estrogen Agonist/Antagonist**

Raloxifene – Raloxifene is a selective estrogen receptor modulator which has mixed agonist and antagonist effects on estrogen receptors throughout the body. Raloxifene is approved by the FDA for both prevention and treatment of osteoporosis in postmenopausal women. Raloxifene reduces the risk of spine fracture by 30% in patients with and by 55% in patients without a prior spine fracture, over 3 years.

The Menopause **FOGSI** Focus

Raloxifene decreases low-density-lipoprotein (LDL) cholesterol concentrations by 8-10% but has a neutral effect on triglycerides and does not increase high-densitylipoprotein (HDL) cholesterol. The true effect of raloxifene on cardiovascular outcomes is being tested in a large prospective trial of high-risk post-menopausal women, the Raloxifene Use for The Heart (RUTH) trial

Raloxifene, like estrogen, increases the risk of venous thromboembolism (VTE) up to threefold and is contraindicated in women with a history of thrombosis. The most common adverse effects associated with raloxifene are leg cramps and hot flashes. Raloxifene should not be used in postmenopausal women with hot flashes, since it can make the symptoms worse.

- **Parathyroid Hormone**

PTH(1-34) is approved by the FDA for the treatment of osteoporosis in postmenopausal women at high risk for fracture. PTH (1-34) is an anabolic (bone-building) agent when administered by daily subcutaneous injection. PTH (1-34) in a dose of 20 µg daily was shown to decrease the risk of spine fractures by 65% and non-spine fractures by 53% in patients with osteoporosis, after an average of 18 months of therapy. PTH(1-34) is indicated to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk of fracture.

PTH (1-34) is well tolerated, although some patients experience leg cramps and dizziness. Because PTH (1-34) caused an increase in the incidence of osteosarcoma in rats, patients with an increased risk of osteosarcoma (e.g., patients with Paget's disease of bone) and those having prior radiation therapy of the skeleton, bone metastases, hypercalcemia, or a history of skeletal malignancy should not receive PTH (1-34) therapy. The safety and efficacy of PTH (1-34) has not been demonstrated beyond 2 years of treatment. Since PTH (1-34) is used for a maximum of 2 years, it is common practice to follow PTH (1-34) treatment with an anti-resorptive agent, usually a bisphosphonate, to maintain or further increase BMD.

Combination Antiresorptive Therapy

Several combinations have been evaluated in small randomized controlled trials (e.g., raloxifene-alendronate, risedronate-HRT, and alendronate-HRT). Results of studies evaluating these combination therapies have been conflicting. In some trials, greater increases in BMD were seen with combination therapy compared with either agent alone. The impact of combination therapy on fracture risk is unknown, however. Further studies with fractures as an endpoint are needed before combination therapy can be recommended. Therapy with both a bisphosphonate and HRT or ERT may be appropriate in post-menopausal women with osteoporosis and menopausal symptoms (e.g., vasomotor symptoms).

Monitoring Effectiveness of Treatment

In addition to important lifestyle changes and institution of non-pharmacologic interventions, patients often require the use of FDA-approved pharmacologic therapies for the prevention and treatment of osteoporosis. With use of all therapeutic interventions, it is imperative to ask patients about adherence to their therapy and encourage continued and appropriate compliance with their osteoporosis therapies to reduce fracture risk.





1. Bone Mineral Density
2. Central DXA
3. QCT
4. pDXA, pQCT and QUS.
5. Biochemical Markers of Bone Turnover

Changes in markers of bone turnover can be seen as early as three months. These markers can be used for early monitoring of the response to drug therapy, and their measurement may help with patient compliance. Measurements should be obtained at baseline and repeated after three to six months of therapy. Decreases of approximately 50% from baseline values are expected with antiresorptive drug therapy.

Conclusion

When pharmacologic agents are required to prevent or treat osteoporosis, bisphosphonates have shown the greatest benefit in preventing bone loss and decreasing fracture rates. If these agents are not tolerated well, SERMs may be considered for prevention and SERMs or calcitonin for treatment. Estrogen should not be used for the sole purpose of osteoporosis prevention; however, short-term use is acceptable for women who are also having vasomotor symptoms or in whom the benefits outweigh the risks. PTH may offer another treatment alternative.

Osteoporosis needs lifelong management and adherence to therapy is a must to gain benefit and reduce risk of fractures.

Increasing knowledge of the mechanisms that regulate bone cell activity will provide sources for potential new therapeutic strategies. Thus future approaches may include local regulators such as cytokines (which are essential in bone metabolism), modification of hormone receptors and pharmacogenetics.

Suggested Reading

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The Menopause **FOGSI** Focus

14

Anabolic Drugs and Newer Therapies in Treatment of Osteoporosis



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Introduction

In the present perspective, the goals of treatment of Osteoporosis should be to -

- Prevent fractures
- Stabilize / achieve an increase in bone mass
- Relieve symptoms of fractures and skeletal deformity
- Maximize physical function (e.g. halt progressive deformity)

Over the past two decades, therapies for osteoporosis have evolved very fast. Anabolic drug therapy is the most recent medication that has been approved by FDA.

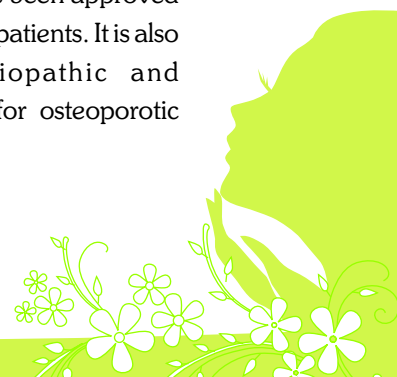
FDA approved Anabolic drug therapy^{1,2}

Teriparatide (Recombinant Human Parathyroid Hormone (PTH 1-34)

FDA has approved Teriparatide for the treatment of postmenopausal osteoporosis and in men with idiopathic or hypogonadal osteoporosis who are at high risk for fracture or who have failed or been intolerant of previous osteoporosis therapy. The recommended dose is 20mcg daily subcutaneously. This has been shown to reduce the risk of vertebral and non-vertebral fractures in postmenopausal women by 65% and 54% respectively over a 19 month treatment period (level 1 evidence). Observed side effects have been mild and transient and include nausea and orthostatic hypotension. Transient and asymptomatic hypercalcemia has also been observed. Teriparatide is contraindicated in patients with Paget's disease, with open epiphysis, with a history of irradiation involving the skeleton or with an undefined elevation of alkaline phosphatase of skeletal origin. Efficacy and safety of Teriparatide have been assessed for two years and are presently unknown thereafter. Pretreatment measurement of serum levels of PTH, 25 hydroxycholecalciferol, creatinine, calcium and phosphorus is recommended. Monitoring patients on treatment for hypercalcemia and hypercalcaemia should be considered. American Association of Clinical Endocrinologists (AACE) and National Osteoporosis Foundation (NOF) do not recommend concomitant use of antiresorptive agents with Teriparatide at present as it may alter the BMD and bone turnover response.

Non- FDA approved drugs for Osteoporosis-

Calcitriol²- This synthetic Vitamin D analogue which promotes calcium absorption has been approved by the FDA for managing hypocalcemia and metabolic bone disease in renal dialysis patients. It is also approved for use in hypoparathyroidism both surgical and idiopathic and pseudohypoparathyroidism. No reliable data demonstrate a reduction of risk for osteoporotic fractures.





Other Bisphosphonates² - (Etidronate, Pamidronate, Tiludronate) Most of these bisphosphonates are currently approved for conditions other than Osteoporosis like Paget's disease, hypercalcemia of malignancy and Myositis Ossificans.

PTH (1-34)² - Approved in some European countries for treatment of Osteoporosis in women. In one clinical study PTH (1-84) effectively reduced the risk of vertebral fractures at a dose of 100mcg/day.

Sodium Fluoride² - Through a process that is still unclear, Sodium Fluoride stimulates the formation of new bone. The quality of bone mass thus developed is uncertain, and the evidence that reduces fracture risk is conflicting and controversial.

Tibolone² - This tissue specific agent is indicated for treatment of vasomotor symptoms of menopause and for prevention of Osteoporosis in Europe but is not approved for use in the USA.

Strontium Ranelate – Strontium is adsorbed onto the bone surface and increases bone strength by being incorporated in a dose dependent manner into bone tissue to change the crystal structure but without altering mineralization⁽³⁾. In a randomized controlled trial of postmenopausal women with osteoporosis treatment with Strontium Ranelate increased BMD in a dose dependent way by 1.4%-3% per year compared with placebo⁽⁴⁾. New vertebral fractures were reduced by 44% after 2 years in women on the highest dose (2gm). The treatment was well tolerated and the larger dose was suggested for clinical use. The use of Strontium normally regarded as a trace element may offer an alternative way of decreasing bone resorption; however at present, Strontium is not approved for use.

Growth factors - Identification of factors that act on receptors for osteoclast attachment or function - such as $\lambda\gamma\beta 3$ integrin, receptor activator of nuclear factor kB ligand (RANKL) or the soluble ligand Osteoprotegerin may allow the development of receptor antagonists. Clinical testing of Osteoprotegerin indicates a positive effect on BMD in postmenopausal women⁽⁵⁾.

Cathepsin K - Degradation of bone matrix is mediated by Cathepsin K, an osteoclast protease that appears to act specifically on bone collagen⁽⁶⁾. An inhibitor of Cathepsin K may be useful as an antiresorptive drug.

Cytokines - Most cytokines are implicated as enhancers of osteoclast activity and subsequently of bone resorption. Blockade of cytokine activity especially IL-1 or IL-6 may have effect on bone turnover since tumour necrosis factor α is one of the most important cytokines that modify bone resorption. But relative non-specificity and subsequent effects on other organs may limit their usefulness.

New SERM - Two new drugs for osteoporosis were featured at the International Osteoporosis Foundation (IOF) World Congress on Osteoporosis at Rio de Janeiro, Brazil on May 26, 2004- a new generation SERM, Lasofoxifene and Strontium Ranelate. Lasofoxifene (0.5mg/day) resulted in-

- A significant increase in lumbar BMD (up by an average of 2.2% compared with a fall of -0.25% in the placebo group over the same time frame)
- Significant reduction in biochemical markers of bone metabolism.
- A significant reduction in LDL Cholesterol from an average of 129mg/dl in the placebo group to 106mg/dl.

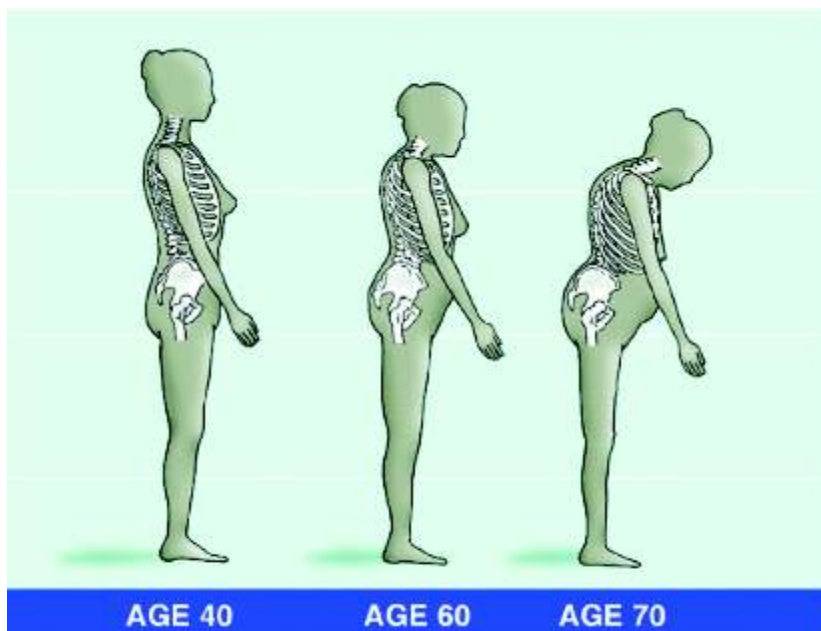
The Menopause **FOGSI** Focus

Other approaches for the future

Future approaches may include genetic modification and pharmacogenetic methods developed as a result of our still increasing knowledge of the genetics of bone diseases. A number of genes have been identified as possibly being associated with Osteoporosis and fractures, although results are inconsistent. Variations in the collagen, estrogen receptor and vitamin D receptor genes merit mentioning as they have been associated with BMD and fractures in elderly women with implications of functional importance for the collagen polymorphism.

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15

Risk Assessment and Investigations - Prior to Starting Hormone Therapy



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With many women in or near menopause and multiple news stories of hormone risks, there has been renewed interest in the treatment of menopause. Each woman entering the menopausal phase is a unique individual who will experience menopause in her own way with regard to developing menopausal symptoms and also in the way she reacts to hormone therapy.

“there are many unanswered questions and many gaps in our understanding of the benefits and risks, so the research studies need to be supported”

– Wall Street Journal, 1/26

Why is RISK ASSESSMENT essential?

It has been estimated that one third of the postmenopausal women in the western countries use hormone therapy to treat symptoms of menopause and prevent chronic conditions. In developing countries also there is an increasing trend in its use. Hormone therapy is a double edged sword it does not suit all women alike and in some the risks may outweigh the benefits. It is important that the benefits and harms of HT based on scientific evidence should be considered when prescribing HT.

It is also important to consider a small group of younger women who enter the transition and experience menopausal symptoms. Starting and continuing HT becomes important in women with premature menopause till they reach the natural age of menopause. The North American Menopause Society released a revised position statement that said

“the benefits of short term hormone replacement therapy for treatment of menopausal women likely outweigh the risks for younger women”

Tailoring an individual program for women, which may include HT and other therapeutic options, is guided by the menopausal risk assessment. It has been seen that women with better socio-economic status, higher education and urban population are more likely to use HT.

Why are INVESTIGATIONS needed?

Starting hormone therapy requires recognition of risk factors as certain conditions warrant the cautious use of hormones like estrogen and progesterone. Some investigations are required before starting and during periodic follow up of women in HT. Clinicians must be aware of the advantages and disadvantages and discuss them thoroughly with their patients. Evaluation of the menopausal women with a stratified risk assessment module helps in individualizing the need for hormone therapy. HT should not be used for treatment of chronic diseases.

The Menopause **FOGSI** Focus

Table 1: Advantages & Disadvantages of HT

ADVANTAGES OF HT	DISADVANTAGES OF HT
<ul style="list-style-type: none"> • Excellent symptomatic management Hotflushes Night sweats Urinogenital atrophy • ?urinary incontinence Decreased rates of: <ul style="list-style-type: none"> • Colon Cancer • Osteoporosis • ?UTI • ?depression • ?dementia • Preservation of joint movement, teeth, skin • Improved HDL to LDL ratio 	<ul style="list-style-type: none"> • Increased risk of stroke and PE • CHD : doesn't help, might hurt • Increased rates of breast Ca • Increased GB disease • Increased rates of lupus • Vaginal bleeding

History and Physical Examination

The risk assessment of the menopausal woman begins with the history and physical examination. The examiner should ask specifically about classical symptoms of estrogen deficiency including hot flushes, sleep disturbance, palpitations, dry skin, irritable bladder, and dyspareunia. A thorough family history of breast carcinoma, coronary heart disease, osteoporosis, early menopause should be elicited also the use of any unopposed estrogen previously should be kept in mind.

Height, weight, waist circumference, body mass index, waist/hip ratio and blood pressure (who have optimal BP (<130/80) are rechecked every 2yr & those with normal level (<140/90 mm Hg) checked yearly. High blood pressure per se is not a contraindication to starting hormone therapy. should be recorded during the physical examination. It should focus on the genitourinary, neuroendocrine, skeletal, and cardiovascular systems. Special attention should be directed to the thyroid, breast, cardiovascular(cardiac murmurs and arterial bruits), pelvic, and rectal examinations. A screening PAPS smear should be obtained of the exocervix and endocervix using a spatula and cytobrush to for cervical cancer.¹

Assessment should also take into account the women's individual needs and their risk factors.

Risk factors for early menopause:

- Any treatment or surgery that can compromise ovarian functioning
 - Pelvic surgery
 - Chemotherapy, radiation
 - Pelvic endometriosis, adhesions, ovarian surgery
- Familial and genetic factors
 - Estrogen receptor and α polymorphism
- Mean age of menopause due to ovarian failure is significantly advanced upto 4 years in hysterectomized women
- Smoking advances the age of menopause by 2 years
- Recent studies suggest that high levels of galactose consumption and starvation in early childhood may also have an effect.





Risk factors for osteoporosis:

In women without menopausal symptoms, HT should be used only in those women with significant risk for osteoporosis and in whom alternative therapies have been carefully considered.

Table 2: Risk for Osteoporosis

NONMODIFIABLE	METABOLIC / HORMONAL	MODIFIABLE
<ul style="list-style-type: none"> - Approximate risk of fracture doubles every 7yrs - Family h/o osteoporotic fracture esp hip fracture - Personal history of osteoporotic fracture - Untreated early menopause - Ethnicity, genetics 	<ul style="list-style-type: none"> - Leanness - Late menarche / early menopause - Bilateral oophorectomy - Amenorrhea - Hyperthyroidism - Glucocorticoid excess >5mg/day - Cushings syndrome 	<ul style="list-style-type: none"> - Weight-increased risk if thin and decreased if overweight - Excessive weight loss - Smoking - Low calcium intake - Vit D deficiency - Inadequate physical activity - Low bone density

(Modifiable risk factors are those that can be eliminated by a change in lifestyle like regular exercise, healthy food habits, calcium and vitamin supplementation and so on. They bring about a dramatic change when considering cardiovascular diseases, osteoporosis and even urinary incontinence in some.)

In 2005, Osteoporosis Canada Society recommended identifying absolute fracture risk by integrating the key risk factors for fracture; namely, age, BMD, prior fracture, and glucocorticoid use.² The 10-year risk of fragility fractures is thus determined and defined as high if it is greater than 20%, moderate if it is 10% to 20%, and low if it is less than 10%.³ The additional effect of a pre-existing fragility fracture or glucocorticoid use moves the patient 1 risk category higher. These guidelines were based on Swedish data. A more comprehensive calculation of the 10-year absolute fracture risk, now available from the World Health Organization, incorporates additional risk factors: parental history of hip fracture, current tobacco smoking, rheumatoid arthritis or other secondary causes of bone loss, and alcohol intake of 3 or more units daily.⁴ Absolute fracture risk data be used in determining who should be treated, as this will target pharmacologic and hormone therapy at those at an increased risk of fracture.

The goal of management is to prevent fractures and the selection of patients with the highest risk for fracture targets population most likely to benefit from therapy.

Risk factors for coronary heart disease:

Available evidence demonstrates that initiation of HT should be done with caution in women with distressing vasomotor symptoms who are more than a decade after menopause because it may be

The Menopause **FOGSI** Focus

associated with an increased risk of adverse cardiac events. Attention to correction of underlying cardiovascular risk factors before initiation of HT would be important in these isolated cases.

Table 3: Risk factors for Coronary Disease

NON MODIFIABLE	MODIFIABLE
<ul style="list-style-type: none"> - Age, for every 10 year increase in age risk of CHO increases three fold - Family history of premature CHD (MI before 55years in men and 65 years in women) increases risk of MI by two fold 	<ul style="list-style-type: none"> - Cigarette smoking - Physical inactivity - Nutrition - Obesity - Psychosocial factors - Blood pressure - Lipid level - Homocysteine level - Diabetes

Risk factors for Alzheimer's disease:

A better understanding of the factors, or cofactors, that placed the older women at increased risk of dementia would be helpful in identifying women for whom HT may not be advisable.

- age, family history and apolipoprotein E epsilon 4 allele
- may be autosomal dominant, when uncommon forms of illness that appear before the seventh decade of life.
- Dominant inheritance is not characteristic of later onset dementia although family history remains risk factor in this age group
- Poly pharmacy and thyroid disease are two examples of reversible causes of memory loss in older adults.

Investigations to be carried out:

Diagnosis of menopause:

Hormone level may vary between individuals and their level may fluctuate even from one day to next. So, hormone level is not always reliable for diagnosis of menopause.

However the postmenopausal range is

S.FSH >30 IU/L

S.LH >30 IU/L

Screening Tests:

Diabetes -

If FBS is high then repeat fasting glucose. Glucose tolerance test should be done in selected cases.

Hyperlipidemias -

Total cholesterol and high-density lipoprotein (HDL) cholesterol should be measured to help ascertain cardiovascular risk in the menopausal woman. If the total cholesterol concentration is elevated or the HDL cholesterol concentration is low, a 12-hour fasting lipid profile is needed to determine the low-density lipoprotein (LDL) cholesterol.





HDL (>45mg/dl)
Triglycerides (<150mg/dl)
LDL (<130mg/dl)

Repeat measurements every 5 years.

Osteoporosis-

Axial DEXA is best validated as the most accurate method of assessing bone density and diagnosis of osteoporosis. Other investigations include.

- Heel ultrasound
- Biochemical markers of bone turnover
- In few cases homocysteine levels are also checked.

Special circumstances

TSH- for positive history when hot flushes do not subside with hormone therapy

FSH and Estradiol - premature menopause, women on OCP, women who had hysterectomy, doubt as to the cause of secondary amenorrhea. It need not be done in all cases for diagnosis of menopause.

Endometrial biopsy- post menopausal bleeding, recent irregular bleeding, previous use of unopposed estrogen in the presence of uterus. It is also indicated if ET>5mm and also for follow up

Test to assess increased risk of thrombosis - women with previous history of unexplained thromboembolic episodes.

Bone mass measurement - for specific indications only

Liver function tests - in patient with suspected liver disease or recent history of liver disease.

Mammography - Mammography should be performed yearly in perimenopausal and postmenopausal women to obtain a baseline and evaluate for clinically unrecognized breast cancers.

Alternative therapies

Given the negative press on HRT, many women are considering more “natural” therapies. “Bioidentical” botanical and dietary supplement products may be considered more “natural” to consumers, but they are not regulated nor standardized. The most important thing with supplement use in the management of menopause is to know what your patients are taking, the potential adverse reactions, and drug/herb interactions.

Active living, alternative therapies and consumption of food rich in phyto estrogens are some areas which need to be explored in more detail. Benefits and harms need to be re-addressed periodically to apply newly published evidence and to reassess emerging risk, co-morbidities and need of individuals.

Menopause is a physiologic event that gives a woman the opportunity to become involved in a preventive health program. Menopause is not a disease; however, it does cause symptoms in a significant percentage of women. Medical evaluation with an emphasis on health maintenance and lifestyle measures is important for menopausal women.

The Menopause **FOGSI** Focus

Table 4 : Summary

RISK ASSESSMENT	<ul style="list-style-type: none"> • EARLY MENOPAUSE • CARDIOVASULAR • OSTEOPOROSIS • ALZHEIMER`S • FAMILIAL RISK FOR BREAST CANCER
HISTORY AND EXAMINATION	<ul style="list-style-type: none"> • MENOPAUSAL SYMPTOMS • HEIGHT, WEIGHT, BODY MASS INDEX, BP, THYROID, BREAST, CARDIOVASCULAR SYSTEM, PELVIC AND RECTAL • PAPS SMEAR
INVESTIGATIONS	<ul style="list-style-type: none"> • DIABETES - FBS • LIPID PROFILE • AXIAL DEXA FOR BONE DENSITY IN HIGH RISK CASES • OTHERS – <p>FSH/LH IN PREMATURE MENOPAUSE ENDOMETRIAL BIOPSY LIVER FUNCTION TEST MAMMOGRAPHY</p>

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16

Menopausal Hormone Therapy

Preparation, Routes of Administration, Indications & Contraindications

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Introduction:

Menopausal years need special attention due to general health problems along with menopausal changes, which can compound the risks. Menopausal therapy should be part of an overall strategy including lifestyle recommendations regarding diet, exercise, smoking and alcohol for maintaining the health of postmenopausal women. Hormone therapy (HT) must be individualized and tailored according to symptoms and the need for prevention, as well as personal and family history, results of relevant investigations, the woman's preferences and expectations. The risks and benefits of HT differ for women around the time of menopause compared to those for older women. HT includes a wide range of hormonal products and routes of administration, with potentially different risks and benefits. Women experiencing a spontaneous or iatrogenic menopause before the age of 45 years and particularly before 40 are at higher risk for cardiovascular disease and osteoporosis. They will benefit from hormone replacement, which should be given at least until the normal age of menopause.

Counseling should be an important part of the therapy and should be aimed at an holistic approach to these important years. The benefits and risks of HT should be discussed in detail and in simple terms. This allows a woman and her physician to make a well-informed decision about HT. HT should not be recommended without a clear indication for its use.

Indications for HRT

HRT helps to alleviate the unpleasant symptoms associated with the menopause. RCTs have demonstrated the efficacy of HRT in relieving hot flushes, night sweats, and vaginal dryness. A recent meta-analysis has also confirmed that HRT reduces the depressed mood associated with the menopause. Considerable interest has been generated by the more long-term potential benefits of

The Menopause **FOGSI** Focus

HRT therapy, which include a possible reduction in morbidity and mortality from cardiovascular disease (both coronary heart disease and stroke), reduction in morbidity and mortality associated with osteoporosis, and reduction in the cutaneous ageing process. However, evidence and experience in the various studies conducted on menopausal women now have shown that HT is indicated only in symptomatic women.

All menopausal women and especially those taking HT should have at least an annual consultation to include a physical examination, update of medical history, relevant laboratory and imaging investigations and a discussion on lifestyle. There are no reasons to place mandatory limitations on the length of treatment. This should be decided at the discretion of the well-informed hormone user and her health professional, dependent upon the specific goals and an objective estimation of benefits and risks.

Table 1: Initial Workup before Initiating Estrogen Replacement Therapy

- History and physical examination
- Stool examination
- Pap smear
- Mammogram
- SMA
- Lipid profile
- Blood Glucose- fasting and post prandial
- Liver function tests (with past history of liver disease)
- Endometrial biopsy (in high-risk groups)

Preparations of Estrogen and Progestin and dosage:

There are several classes of estrogens. Naturally occurring estrogens, including estradiol, estrone, and conjugated estrogens, are the estrogens generally given for replacement therapy. Synthetic estrogens, including ethinyl estradiol, mestranol, and quinestrol, and the nonsteroidal estrogens, including diethylstilbestrol and chlorotrianisene, typically are **not used** for ERT.

Estrogen can be administered through a variety of routes, including oral, intramuscular, topical, subcutaneous, nasal, and vaginal. Nasal sprays allow direct rapid absorption. Intramuscular injection is convenient, requiring infrequent administration, but immediate reversal is impossible, and tolerance may develop. Moreover, very high circulating levels of estrogen may be achieved soon after administration. Subcutaneous pellets also give sustained release, but immediate reversal may not be possible because retrieval of the pellet is difficult. Estrogen creams are used extensively in France but require a wide area of application. Transdermal patches allow direct absorption, but the effect is not sustained; therefore, the patch must be worn continually and reapplied at appropriate intervals. The most frequent complication of transdermal delivery is skin irritation. Vaginal suppositories and creams permit direct absorption but are unacceptable to many women. A low-dose vaginal ring that delivers 7.5 μgm estradiol per day over a 90-day period provides a local effect without raising serum estradiol levels above the menopausal range. The oral route is most convenient but is the only mode of delivery that significantly affects the liver.





Table 2: Approximately Equivalent Estrogen Dosages

Administration Method	Dosages*
Oral	0.625 mg conjugated equine estrogen
	0.625 - 1.25 mg piperazine estrone sulfate
	1 mg micronized estradiol - 17β
Transdermal	0.05 - 0.1 mg estradiol - 17β

Estrogen administration is associated with a number of side effects that may affect compliance. Initially, most women experience some breast tenderness. If breast discomfort persists, the dosage of estrogen should be reduced. Some women require much higher doses for alleviation of their symptoms; young, surgically oophorectomized women often need twice as much estrogen as those who underwent physiologic menopause. Other side effects include nausea, vomiting, weight gain up to 5 lb, fluid retention, and heartburn. Fluid retention and weight gain often may be abolished by restricting salt intake. The most frequent complaint with hormonal replacement is uterine bleeding. When progesterone is added to the regimen, the incidence of irregular bleeding diminishes markedly.

Table 3: Contraindications to Estrogen Therapy

Strong	Relative
Unexplained vaginal bleeding	Hypertriglyceridemia
Uncontrolled hypertension	Leiomyomas
Impaired liver function	Endometriosis
Active thromboembolic disorders	Gallbladder disease
Porphyria	Pancreatitis
Breast cancer	Migraine headaches
	Strong family history of breast cancer
	Endometrial cancer

Progestin is usually administered only orally. The most commonly prescribed progestin is MPA at a dose of 10 mg. This dose is not well tolerated in as many as 25% of women. Common complaints include bloating, depression, premenstrual tension-like symptoms, acne and breast tenderness. Beginning with a dose of 5 mg and increasing the dose to 10 mg in those women without complaints reduces the number of women discontinuing therapy. It may even be necessary to decrease the dose to 2.5 mg in some women. Norgestrel (150 to 500 μg) and norethindrone acetate (1 to 5 mg) are frequently used in Europe. These 19-norsteroids lower the ratio of high-density to low-density lipoproteins more than MPA and therefore can effect the lipid profile and hence increase the incidence of cardiovascular disease. Micronized progesterone is well absorbed, has little or no effect on the lipid profile and has been approved for use in the United States. Progesterone in vaginal gel form is also available. Many prefer to use the LNG-IUS for preventing endometrial proliferation. Other progestins, such as norgestimate, gestodene and transdermal levonorgestrel and norethindrone acetate are being investigated.

The Menopause **FOGSI** Focus

Treatment Regimens

Many regimens are being used, none of which is physiologic. Estrogen is usually given with a progestin to women with a uterus to prevent endometrial hyperplasia. Estrogen is given alone to women without a uterus to avoid the deleterious effect of progestin on lipoproteins.

Given below are the common regimens.

Regimen	Details	Comments
Sequential	estrogen daily, progestogen for last 10 -14 days of cycle	withdrawal bleeding every month; change to CCEPT after 5 years
Cyclical	estrogen on days 1 - 21, progestogen on days 9 - 21, nothing on days 22 - 28	withdrawal bleeding every month; change to CCEPT after 5 years
Long - cycle	estrogen for 3 months, progestogen in 2nd half month; of third month	withdrawal bleeding every third long - term protection of endometrium uncertain
Continuous combined	estrogen and progestogen continuously	no bleeding should occur, and endometrium should remain atrophic, but many women experience irregular bleeding for the first few months. suitable only for women aged above 54 or postmenopausal
Tibolone	synthetic derivative of testosterone, given continuously	has weak estrogenic, androgenic and progestogenic properties; does not stimulate uterine lining, can be used without progestogen and causes less breakthrough bleeding than other regimens; relieves menopausal symptoms, including bone loss; may not provide the same protection against cardiovascular disease because of its relatively weak estrogenic effects; suitable only for women aged over 54 or who have had no periods for at least 12 months

CCEPT, continuous combined estrogen and progestogen therapy

Alternative Delivery systems for HT

1. Transdermal Administration

The patches first used for transdermal estrogen administration contained an alcohol reservoir; the estrogen was released through a semipermeable membrane attached to the skin with an adhesive. The current generation of patches has the hormones dissolved and distributed throughout the adhesive matrix and hence the skin irritation is less. The patches are designated according to the amount of estrogen delivered per day: 50 and 100 μg .





The effect of steroids on lipids and lipoproteins is determined by the type of steroid, the dose and the route of administration. The advantage of transdermal route is the beneficial impact on the lipoprotein profile. English data indicate that the transdermal administration of 50 g of estradiol twice a week is as effective as 0.625 mg of oral conjugated estrogens, when combined with a progestin in sequential regimens, on bone density and lipids over a duration of 3 years. The transdermal administration of 100 g of estradiol combined with a progestin not only increases bone density, but also reduces the fracture rate in older women who already have significant osteoporosis.

Estradiol Implants

Estradiol pellets are available in doses of 25, 50, and 75 mg for subcutaneous administration twice yearly. The 25-mg pellet provides blood levels in the range of 40 to 60 pg/mL (150 to 220 pmol/L), levels, which are comparable with those obtained with the standard oral dose.

Percutaneous Estrogen

Estradiol delivery can be accomplished by applying a gel (estrogel) to the skin, usually over the abdomen or thighs.

Vaginal Estrogen

Estrogen is absorbed readily from a vagina with immature, atrophic mucosa. The initial absorption is rapid, and relatively high circulating levels of estrogen are easily reached. As the vaginal mucosa cornifies, absorption decreases. This decline takes approximately 3 to 4 months, after which lesser but still significant absorption takes place. European studies demonstrate that vaginal maturation can be achieved with a vaginal ring (that is left in place for 3 months) having incredibly small doses of estrogen, with a low-level absorption that is free of systemic effects. This is an acceptable treatment to relieve atrophic vaginal symptoms in women with contraindications to estrogen treatment.

Progesterone intra Uterine Device – LNG-IUS

The contraceptive levonorgestrel-releasing IUD has been reconfigured in a smaller model releasing as little as 5 μ g of levonorgestrel per 24 hours. The intrauterine presence of the progestin effectively protects the endometrium against hyperplasia and cancer. The local site of action provides endometrial protection and escapes systemic progestin side effects. There is irregular breakthrough bleeding in the first 6 months, and after 1 year, approximately 60% to 70% of the women are amenorrheic. The levonorgestrel device has the advantage of a 10-year duration of use.

Conclusion

Judicious use of HT in women with symptoms is indicated and should not be denied. Relief of mild menopausal symptoms may be achieved by short-term therapy tapering to none. When needed, Ht should be individualized, as there is no one size that fits all. However, HT without any symptoms is no longer indicated. In view of the side-effects with oral HT, alternative routes are now being recommended and seem to have lesser complications due to avoiding the first by-pass by the liver. How long therapy of postmenopausal and oophorectomized women should continue is still a question that's needs to be answered.

The Menopause **FOGSI** Focus

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17 A

Current Recommendations for use of Hormone Therapy at Menopause



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The role of Hormone Therapy at menopause has always evoked a passionate response, be it from the diehard admirers or the critics. The premature release of the results of the Women's Health Initiative which were not completely evaluated and analyzed had a major detrimental effort on the use of Hormone Therapy. However a more detailed sub analysis of the WHI study published in the last three years correlate with the findings of the observational studies on Hormone Therapy. It is clear that appropriately timed Hormone Therapy is safe for healthy women in their early post menopause and decreases total mortality in the age group of 50-59 years(WHI data).

The current recommendations are based on consensus statement issued by International Menopause Society (2007,2008)^{1,2}. North American Menopause Society(2007)³, Indian Menopause Society (2004)^{4,5}.

Indications of use of Hormone Therapy.

- The primary indication remains the treatment of vasomotor symptoms.
- HT is indicated for prevention of bone loss in women with premature menopause and secondary amenorrhea.
- HT should not be recommended without a clear indication for its use.

Issues to be assessed before deciding for Hormone Therapy:

- Age of the woman
- Symptoms of Menopause
- Family history, Past history of medical problems
- Clinical examinations
- Counselling regarding Risk and Benefits
- Routine Screening Tests-CBC, Urine test, Pap smear, S.TSH, Blood Sugar, Lipid Profile, TVS and Mammogram.
- Tests to be done on indication- FSH, Estradiol, Endometrial Biopsy, BMD, tests to assess increased risk of thrombosis.

Hormone Therapy:

- The type, dose, regime and route of Hormone Therapy should be based on patient preference, efficacy in the individual patient, side effects and cost.
- Lower than standard doses of EPT should be considered, such as 0.3 mg of oral conjugated estrogen or 0.25 to 0.5mg of micronized estradiol, but these have not been tested in long-term trials.
- The long term risk/benefit ratio for non oral administration has not been tested.

The Menopause **FOGSI** Focus

- Unopposed Estrogen is prescribed for women with Hysterectomy. Progesterone has to be prescribed along with Estrogen for a woman with uterus.
- Vaginal atrophy may be symptomatic in up to 40% of postmenopausal women, although most women do not seek medical attention for these symptoms. Dryness is the most common symptom of vaginal atrophy.

The current position statement suggests that vaginal lubricants and moisturizers are the first-line therapy for symptoms of vaginal atrophy, and vaginal estrogen therapy should be considered for women with continued symptoms while receiving conservative therapy. All delivery method of vaginal estrogen appears equally effective. Low dose vaginal estrogen does not require progesterone supplements.

Level A evidence refers to data from randomized controlled trials, whereas Level B evidence comes from case control/observational studies.

HT-Quality of Life and Menopause

In symptomatic postmenopausal women, quality of life and sexuality are improved by HT⁶, and, in the presence of symptoms of androgen deficiency, by additional androgen administration.

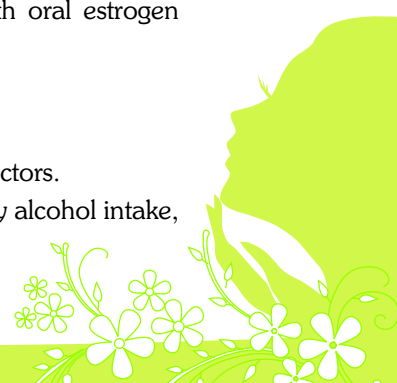
- There is no evidence that so-called 'natural' products and unregulated hormone products (compounded bio-identical) significantly improve quality of life.

HT- Coronary Heart Disease, Stroke and Thromboembolism

- HT in women ages 50-59 years does not increase CHD risk in healthy women and may even decrease the risk in this age group⁷[A].
- Estrogen-alone therapy in the age group 50-59 was associated with significantly less coronary calcification(equivalent to a smaller plaque burden),which is consistent with findings of a lower coronary intervention score in women of this age in the WHI study[A].
- Early harm (more coronary events during the first 2 years of HT) was not observed in the early postmenopausal period. The number of CHD events decreased with duration of HT in both WHI clinical trials[A].
- Data derived from randomized controlled trials in the age group 50-59 are similar to the older observational data suggesting a protective effect of HT on coronary disease[A,B].
- It is unclear at present whether there is a statistical increase in ischemic stroke with standard HT in healthy women aged 50-59. The WHI data showed no statistically significant increase in risk; nevertheless, even if statistically increased, as found in Nurses' Health Study, the low prevalence of this occurrence in this age group makes the attributable risk extremely small[A,B].
- The risk of venous thrombosis approximately two fold higher with standard doses of oral HT, but is a rare event in that the background prevalence is extremely low in a healthy women under 60 years of age[A].
- The risk of venous thrombosis is possibly less with Transdermal, compared with oral estrogen therapy[B].

HT-Breast

- There is wide variation across the world in the incidence of breast cancer and its risk factors.
- There are multiple risk factors for breast cancer, including life-style factors especially alcohol intake,





obesity and lack of exercise. These need to be included during counselling to put the magnitude of risk of HT into an appropriate perspective [B].

- After 5 years' use of combined estrogen and Progestogen, there is a small increase in risk of breast cancer in North American women of about eight extra cases per 10,000 women per year. However, no significant increase was seen in women without prior use of HT in the WHI study[A].
- Estrogen-only use does not cause an increase in breast cancer for up to 7 years⁸. In observational studies, a small increase in the risk with estrogen-alone therapy appears with long-term use⁹[B].
- Women using combined HT before a diagnosis of breast cancer have a reduced mortality[B].
- A decline in the incidence of breast cancer in the USA started before the WHI publication and can be partially related to fluctuation in screening. There has been no decline in breast cancer registration in the UK following the Million Women Study report, nor in Norway, Canada, the Netherlands and countries with stable screening programmes[B].
- Combined estrogen and progesterone therapy may cause increased breast density in up to 50% of postmenopausal women, dependent on the regime (dose, type of progesterone). The effect of estrogen alone is smaller[A].
- The effect on breast density is dose-related. Ultra-low-dose regimes do not cause any perceptible change in density[A].
- The average increase in breast density under standard-dose HT is only about 5-10%[A].
- Increased baseline breast density is a risk factor for breast cancer. There are no data to support a direct association between HT-induced breast density changes and the risk of developing breast cancer.
- Many women who develop breast cancer have no known risk factors other than growing older and most women with known risk factors do not develop breast cancer.
- Individual risk analysis for breast cancer is strongly recommended in clinical practice.

HT-Bone:-

- Overall, HT is effective in the prevention of all osteoporosis-related fractures, even in patients at low risk of fracture[A]¹⁰.
- Although no head-to-head studies have compared HT to bisphosphonates in terms of fracture reduction, there is no evidence to suggest that bisphosphonates or any other antiresorptive therapy are superior to HT.
- It is therefore suggested that, in 50-59 years old postmenopausal women, HT is a cost-effective first-line treatment in the prevention of osteoporotic fractures.
- Even lower than standard-dose preparations maintain a positive influence on bone indices such as bone mineral density[A].
- HT has a positive effect on osteoarthritis and the integrity of intervertebral disks.

HT-Cognition:-

- At present, there is no evidence of substantial cognitive decline across the menopausal transition. However, many women experience cognitive difficulties in association with vasomotor symptoms, sleep disturbances and mood changes[A].
- Verbal memory performance relates with the objective number of hot flushes women experience but not to the number of hot flushes they report.
- Clinical trial findings currently find no cognitive benefit among women initiating HT late in the postmenopausal period (i.e. after age 65).
- Cognitive benefits from estrogen replacement therapy appear to depend on age of initiation¹¹.

The Menopause **FOGSI** Focus

- Observational studies show a decreased risk of Alzheimer's disease in hormone users and typically involve women who initiated estrogen therapy early in the menopausal transition.¹²
- Limited data exist on the effect of Progestogen added to estrogen in the early postmenopause period. Clinical trial data suggest no cognitive benefit with MPA early in the menopause[A].

No Consensus:-

- There is no consensus whether cessation of Hormone Therapy should be abrupt or tapered.

Evidence based prescription of Hormone Therapy is to start early, use minimum effective dose judiciously on indication, after appropriate counseling

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17 B

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Introduction

Tibolone has been classified as a selective tissue estrogenic activity regulator (STEAR)⁽¹⁾

In the light of the results of the Women's Health Initiative (WHI) unopposed estrogen therapy (ET) trial⁽²⁾ and after the criticism^(3,4) of the findings of the Million Women Study (MWS)⁽⁵⁾ there is now room for reformulation of expert advice as to the use of postmenopausal hormone therapy. Tibolone has a different profile to conventional ET, oestrogen-progestogen therapy (EPT) and selective oestrogen receptor modulators (SERMs).

Tibolone has specific effects in different tissues due to tissue-selective metabolism, enzyme regulation and/or receptor binding and activation. After oral ingestion, tibolone is converted to three active metabolites : the 3a - OH-and 3b-OH-tibolone metabolites have oestrogenic effects on the bone, vagina and climacteric symptoms, whilst the D4 isomer has progestogenic and androgenic properties and prevents stimulation of the endometrium. The breast is also not stimulated due to effects on local enzyme activity that inhibit formation of active oestrogens.

1. Efficacy:**1.1 Climacteric symptoms**

Tibolone controls hot flushes, sweating and other typical symptoms such as insomnia, headache and fatigue. It has proved as effective as a range of EPT/ET regimens in relieving climacteric symptoms⁽⁶⁻⁸⁾, although it may have a somewhat slower onset of action, and can be used as add-back therapy to relieve oestrogen-deficiency symptoms in women receiving gonadotrophin-releasing hormone (GnRH) agonist therapy for myomas or endometriosis^(9,10).

1.2 Urogenital symptoms

Tibolone has been shown to reverse vaginal atrophy (increases in karyopycnotic index and cell maturation value) and improve cervical mucus⁽¹¹⁾. Women treated with it have reported significantly less vaginal dryness, dyspareunia & urinary symptoms.

The Menopause **FOGSI** Focus

1.3 **Libido & Sexuality**

With tibolone, sex hormone binding globulin (SHBG) levels are decreased and therefore free testosterone levels are significantly increased as opposed to the decrease observed with standard EPT. DHEAS has also been shown to increase^[12]. In addition, the D4 isomer of tibolone has androgenic effects. These properties of tibolone contribute towards a beneficial effect on sexual well-being, including improvements in sexual desire, arousability, sexual fantasies and vaginal lubrication^[13-15]. Tibolone is more beneficial than oral EPT/ET in this respect.

1.4 **Mood & Depression**

In a comparative study with EPT, tibolone proved more effective in improving mood disorders^[16].



1.5 **Prevention of bone loss**

Randomised, controlled studies have shown that tibolone is effective in increasing bone mineral density (BMD) and preventing bone loss^[17,18]. These beneficial effects are seen over long-term (10 years) treatment^[19] and in both early and late post-menopausal women, women with established osteoporosis and women receiving GnRH agonist treatment^[9,10,20-22].

1.6 **Quality of life**

Beneficial effects of tibolone on climacteric and urogenital symptoms, sleep, sexual drive and mood, combined with low rates of vaginal bleeding and breast tenderness, might be expected to result in an improvement in quality of life.

2. **Safety and tolerability**

2.1. **Breast tolerability**

Tibolone causes significantly less breast tenderness and mastalgia than EPT and women are considerably less likely to stop taking tibolone than EPT for these reasons^[6, 7, 17, 23]

2.2 **Breast Density**

Tibolone does not increase mammographic density^[23,24]. Naturally occurring increased mammographic density is considered to be an independent risk factor for breast cancer.

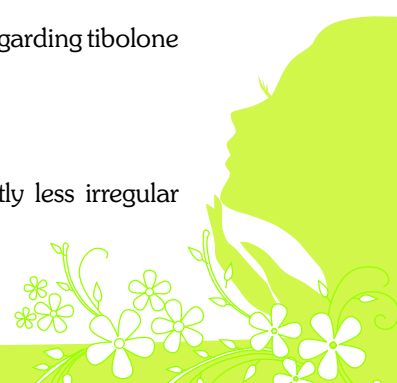
2.3 **Breast safety**

In contrast to EPT, tibolone does not increase breast tissue proliferation whilst stimulating apoptosis^[24,25]. No increased risk of breast cancer has been observed compared with placebo in pooled data from all phase III/IV trials of tibolone (relative risk (RR) 0.50; 95% confidence interval 0.11-2.54)^[26]. The MWS reported an increased RR of breast cancer with tibolone (RR 1.45; 95% confidence interval 1.25-1.67), although this was significantly ($p < 0.0001$) less than that seen with EPT^[5].

Randomised controlled trials are awaited before any firm conclusion can be drawn regarding tibolone and breast cancer.

2.4 **Endometrium**

Randomised controlled studies show that women given tibolone have significantly less irregular



vaginal bleeding and a higher amenorrhoea rate than those given EPT^[6,7,27]. In contrast to EPT, tibolone does not increase the size or volume of myomas^[28]. With it standard endometrial surveillance is not required.

2.5 **Cardiovascular**

Surrogate endpoint studies for arterial & venous thrombo - embolic disease are inconclusive with regard to benefit or risk.

2.6 **Overall tolerability**

Tibolone is well tolerated. It has no major clinical impact on body weight. The most common adverse events are leucorrhoea, abdominal pain, weight increase, vaginal bleeding and breast pain.

It prevents the increase in body fat mass and the decrease in lean body mass that typically occur in postmenopausal women^[29,30]

3. **Contraindications to tibolone**

These should be considered to be the same as for EPT/ET.

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The Menopause **FOGSI** Focus

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17 C**Role of Androgen Replacement****Dr. Sunila Khandelwal**

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Androgens play a primary role in female physiopathology. The age-related decline in the production of ovarian and adrenal androgens may significantly affect women's health.¹ Recognition of cellular action of androgen and decrease in androgen production in women after menopause has led to increase use of androgen replacement therapy for post menopausal women.²

Androgen insufficiency, a cluster of symptoms and physical signs indicative in both peri- and postmenopausal women, include a decrease in mood, diminished energy, depression and impaired sexuality. These women are at increased risk for 'hypoactive sexual desire disorder' (HSDD).

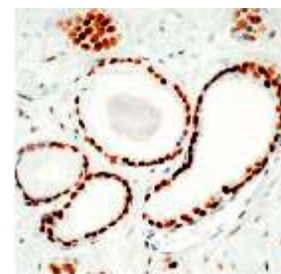
HSDD is a common clinical consequence of Surgical, chemotherapy induced or natural menopause.³

Reliable biological confirmation of female androgen insufficiency is done by using the free testosterone index (the ratio of total plasma testosterone/SHBG).⁴ A value in postmenopausal women below the lower quartile of normal for premenopausal women is confirmatory of female androgen insufficiency.⁵ A Menopause Rating Scale and urogenital problems interview, combined with a "Vaginal Health Index", facilitate early diagnosis and monitoring.⁶

Effects of androgen therapy -

Positive effects: increased libido, mood sense of well being, decreased breast tenderness induced by HRT and an additive effect on ERT induced BMD increments, especially in the spine (both trabecular & cortical).

Negative effects: Long-term use of high doses may result in liver toxicity, Virilizing effects like seborrhoea, androgenic alopecia, acne, mild hirsutism, deepening of voice, clitoromegaly & reversal of the positive effect ERT on lipids (HDL). Contraindications of testosterone therapy are focused similarly to those associated with estrogen therapy.



DHEA use can be beneficial in post menopausal women to compensate for Endogenous age related and accelerated decline in DHEA after surgical menopause. It has anti aging benefits with positive effect on cognition and skeleton. Six weeks DHEA (50 mg / day) has shown remarkable increase in perceived physical and psychological well-being in depressed surgically menopausal women. A synthetic form of this hormone is available as nutritional supplement in tablet (25 mg), capsule (25-50 mg – available in India), cream (1%) and widely used to improve libido & well being in post menopausal women in USA, Europe & Far East. Close monitoring of serum DHEAS and its metabolites should be performed frequently during replacement therapy. However long term safety data for DHEA therapy are lacking.⁷ Researchers argue that, cessation of estradiol secretion by the postmenopausal ovary is a physiological event not a deficiency state. The real deficiency is adrenal.

The Menopause **FOGSI** Focus

They propose that the most physiological intervention is to replace the deficient androgen precursor, DHEA (HPRT). Within the design of a phase III prospective clinical trial involving 218 postmenopausal women, they transvaginal DHEA was administered. Using highly specific and sensitive mass spectrometry to measure circulating sex steroids and combined with traditional vaginal cytology, they demonstrated convincingly that intravaginal DHEA is transformed to estrogen within vaginal epithelium cells and that there is no detectable increase in circulating estradiol. They described relief in symptomatic vaginal atrophy and in estrogen-induced changes in vaginal cytology that are dramatic.⁸

Tibolone possesses some androgenic activity that can be used to treat vasomotor symptoms, psychological and libido problems, and for prevention of osteoporosis. In the absence of availability of other androgen preparations, tibolone can be an option.

As per recommendations of the International Menopause Society, administration of individualized HT (including androgenic preparations) improves sexuality and overall quality of life. Androgen CO-therapy should be administered at the lowest dose for the shortest time that meets treatment goal.⁹

Whom to consider therapy?

Surgical menopause - androgen replacement should be reserved for women with of severe androgen insufficiency due to an established cause and with matching clinical signs and symptoms. In women with bilateral oophorectomy or adrenal failure, androgen replacement has significant beneficial effects, in particular on health related quality of life and sexual function.

Natural menopause - premature natural menopause, especially with unsatisfactory function that are on MHT and present with poor compliance, addition of androgen in moderate dosages for short term (when indicated) promises improved continuation rate.

More research is needed to precisely define androgen insufficiency, recommend an ideal preparation, and to identify to benefits v/s risk of androgen therapy in post menopausal women.

Androgenic preparations¹¹

Preparations	Dose range	Frequency	Route
Methyltestosterone in combination with esterified estrogens	1.25 - 2.25 mg 0.625 - 1.25 mg	Daily	Oral
Methyltestosterone with ethinyl estradiol	3.6 mg - 0.0044 mg	Daily	Oral
Mixed testosterone esters with estradiol*	50 -100 mg/ml 5 mg	4 - 6 weekly	IM
Methyltestosterone alone	5 -10 mg micronized 2.5 mg (cyclodextrin)	Daily Twice/day	Oral SL
Testosterone Undecanoate*	40 mg	Every 2 nd day	Oral
Testosterone implants	50 -100 mg	3 - 6 monthly	SC
Testosterone pellets	75 mg	3 - 6 monthly	SC
Transdermal Testosterone patch*	150 - 300 µg	Every 3 rd day	Topically
Transdermal Testosterone spray*	12.5 mg/spray	Daily	Topical
Transdermal Testosterone gel*	1%	Daily	Topical
Transdermal Testosterone cream*	1%	Daily	Topical
Dehydroepiandrosterone (DHEA)*	25 -50 mg	Daily	Oral
Tibolone (Gonadomimetic) *	2.5 mg	Daily	Oral

* Available in India





Future Perspective

Androgen treatment in postmenopausal women is complex, and it is certain that the debate will continue until more information is gathered to provide a clearer picture as to whether the beneficial effects of androgen therapy on libido are countered by detrimental adverse effects on preexisting conditions such as cancer or cardiovascular disease. An informed consensus can be made when more equitable comparisons are made within and between animal models and clinical trials. Likewise, more emphasis placed on understanding differences in dose, duration, and type of treatment, as well as the method of delivery, and solo versus combined use of androgens with estrogens/progestin's will help to eliminate uncertainties and to eventually establish a general standard of care for androgen therapy.

Androgen replacement therapy is the primary choice, especially in younger women, with either premature ovarian or surgically induced menopause, suffering from loss of well being, fatigue and loss of libido that are not modified by estrogen therapy.

However, since the above conclusions are extrapolated from relatively short-term studies, it is important that long-term safety data be obtained for women given testosterone or DHEA therapeutically.¹⁰

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The Menopause **FOGSI** Focus

18 Role of Phytoestrogen - When & For How Long ?



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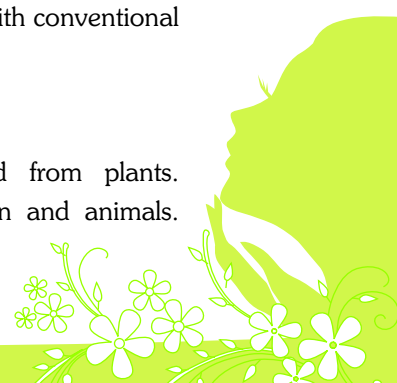
Introduction :

Menopause is an important event in a woman's life but it can be associated with health complaints a decreased quality of life and increased risk for certain diseases like osteoporosis and coronary heart disease. Many women can experience severe adverse health effects during menopause which may persist for several years and can have a large impact on their physical and psychological health as well as well being. With increasing life expectancy approximately one third of woman's life can now be expected to be spent in the postmenopausal years, as a result women are more likely to suffer from menopausal related problems. Estrogen replacement has long been the therapy of choice for the treatment of climacteric symptoms as well as prevention of osteoporosis and reduction in the risk of cardiovascular diseases. In spite of beneficial effects of HRT, there has been always a search for ideal alternative therapy to Hormonal Replacement Therapy (HRT) because of the risk associated with HRT.

In 2002, there was widespread anxiety over the long term safety of HRT after the evidence based findings from the large Women's Health Initiatives (WHI) Studies reported that combined estrogen and progesterone therapy (HRT) increased the risk of CHD, stroke, blood clot and breast cancer. Hence, this has led phytoestrogens as popular alternative to conventional estrogen products and various preparations are marketed as effective in the treatment of menopausal problems. A number of clinical trials have been conducted but it is difficult to assess the effectiveness of phytoestrogens health benefits. If treatment is started, the same precautions should be taken as with conventional estrogen therapy.¹

Phytoestrogens

Phytoestrogens are naturally occurring estrogen like compounds obtained from plants. Phytoestrogens are identified in bile, urine, semen, blood and faeces in man and animals.





Phytoestrogens have 2 – phenylnaphthalene – type chemical structures similar to those of estrogens and bind to estrogen receptors alpha and Beta.² These plant derived estrogens are reported to exert both estrogenic effects in estrogen deficiency and antiestrogenic effects when excess estrogens are present and thus effectively balance the estrogen metabolism in the body. The antiestrogenic activity of phytoestrogens may be due to their competition with endogenous 17β- estradiol for estrogen receptors. Accumulating evidence from molecular and cellular biology experiments, animal studies and to a limited extent human clinical trials reported that phytoestrogens are beneficial in preventing menopausal symptoms, osteoporosis, reducing risk of cardiovascular disease and cancer of breast, endometrium, ovary and colon³

Many of the potential health benefits of phytoestrogens may be due to metabolic properties that do not involve estrogen receptors such as their influence on enzymes, protein synthesis, cell proliferation, angiogenesis, calcium transport, Na⁺ / K⁺ adenosine triphosphatase, growth factor action, vascular smooth muscle cells, lipid oxidation and cell differentiation.⁴

There are two main dietary groups of phytoestrogens available and they are :

- 1) Isoflavones found in beans, pulses, lentils, chickpeas, tofu and soya based products.
- 2) Lignans found in cereals and fruits

Isoflavones are of particular interest to menopausal women as they bind to particular form of estrogen receptors resulting into estrogenic effect in the central nervous system, blood vessels, bones and skin.

Absorption :

Two of the major isoflavones found in humans are genistein and daidzein. Genistein and daidzein are parent compounds. In plants isoflavones are inactive and present in the bound form as glycosides. These plants after ingestion undergo fermentation by intestinal microflora and are converted into active genistein and daidzein which are absorbed by the small intestine and colon and give rise to beneficial effects in the body. Several investigators have reported that individual variability in colonic microflora plays an important role in determining the preferred pathways of isoflavone metabolism and bioavailability of isoflavones.

Sources and Intake levels of phytoestrogens :

The major dietary source of phytoestrogens in most population is soy. Soy beans and their products are consumed by human in many forms including whole soy beans, tofu, tempeh and soy milk. Soy protein, primarily in the form of nontosterilized defatted soy bean flakes can be isolated from the whole bean for consumption through processing. Isolated soy protein which contain up to 50% of phytoestrogen can be consumed through a variety of products, such as baked goods, confections, meat products, texturized foods and nutritional supplements. The concentration of genistein in most soy food materials ranges from 1-2 mg / g protein. Flax is also a concentrated source of phytoestrogens particularly the lignans. Other plant food contain trivial amounts of phytoestrogens compared to soy and flax. Many Asian population that have low rates of breast cancer consume 20 to 50 mg / day genistein, almost entirely derived from soy whereas the dietary intake of genistein in the US has been estimated at 1-3 mg / day.⁵

The Menopause **FOGSI** Focus

Blood Levels⁶

Isoflavones are effective when genistein levels are 25 mmol / L or more. In adults, the plasma half life of genistein / daidzein is 7 to 9 hours. With the high soy consumptions (> 10 mg genistein + > 6 mg daidzein /day) the blood isoflavone concentrations is achieved only up to 1-5 mmol/L. After six weeks of total isoflavones intake of 50 mg/day desired blood plasma concentrations are achieved.

Distribution⁶

All the isoflavones are fat soluble molecules and circulate in blood in the unconjugated (free & active) and the conjugated forms. Free isoflavones are biologically active and are taken up by the tissues. The isoflavones do not bind with serum proteins therefore, miniscule quantities are also sufficient for the effects. They act on

- Reproductive tissue – Uterus, Breast
- Cardiovascular tissue – Arteries, Lipoproteins
- Skeletal tissue – Lipoproteins, Bones

Dosage⁶

In India, Capsules made of soy which contained Isoflavones, Lignane, Calcium & Vitamin C are available. Since then many pharmaceutical companies have come out with preparations containing isoflavones. In UK it is marketed as soy enriched loaf and in USA soy milk has been made popular.

Isoflavones are advised 1 to 2 mg / kg body weight once or twice a day and preferably with high carbohydrate diet. The high carbohydrate diet facilitate conversion of phytoestrogens from soy to active genistein and daidzein forms. A diet rich in fibres especially wheat fibres are found to reduce the bioavailability of genistein. One or two capsules / day along with meals and in combination with diet and exercises are effective for physical, emotional and mental wellbeing.

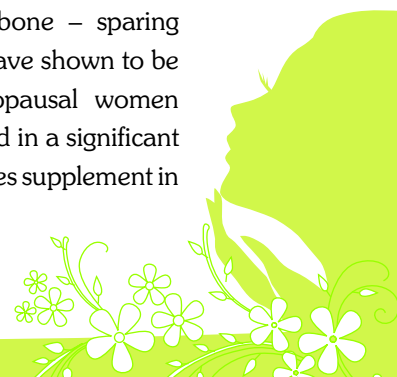
Potential health benefits of Phytoestrogens :

In the treatment of Menopausal symptoms

Phytoestrogens are advised for 30 to 60 days ⁶ In 2004, Buchler H. reported that less than 25% Japanese and oriental women had menopausal complain of hot flushes compared with 80% of American women due to high levels of Phytoestrogens in typical Japanese and Asian diets⁷ However, Murkies et al examined the effect of 45 g/day vs. wheat flour amongst the women with hot flushes and reported that over the 12 weeks study, the number of hot flushes decreased significantly in both groups. Therefore they concluded that the benefit could not be attributed to the soy or its phytoestrogen contents.⁸ In 2004, Kerbs EF et al also reported that in twenty five trials involving 2,348 postmenopausal women for duration of 17 weeks did not improve hot flushes or other menopausal symptoms after consumption of soy foods, soy extract and clove extracts.⁹

For the Prevention of Osteoporosis :

Recently isoflavones have received considerable attention for their potential bone – sparing properties. In daily doses ranging from 200 – 600 mg / day, the phytoestrogens have shown to be effective in promoting bone mass and preventing bone loss.¹⁰ In postmenopausal women consumption of soy protein providing 90 mg isoflavones daily for 24 weeks resulted in a significant increase in lumber spine bone mineral content and BMD¹¹ and a red clover isoflavones supplement in





a form of tablet Promensil providing 57 or 85.5 mg isoflavones per day for 6 months resulted in an increased in BMD of the proximal radius & ulna.¹² In a randomized double blind placebo controlled trial, Charlotte A et al did not observe an increased in lumbar spine BMC or BMD with a daily dose of 80.5 mg. isoflavones in the form of as soy protein given for 24 weeks but they saw a reduction in the extent of bone loss.¹³

Anderson J. J. et al observe in the study of 28 premenopausal women with mean age of 24 years, no significant effects of a soy protein supplement that provided up to 90 mg. of isoflavones for 12 months and they concluded that isoflavones may be beneficial in attenuating age associated bone loss rather than in enhancing peak bone mass in younger premenopausal women.¹⁴

Phytoestrogens and Cardiovascular disease

Several lines of evidence, including epidemiological clinical trial data and basic science suggest that the phytoestrogens decreased the risk of cardiovascular disease. However, this association is confounded by other concomittend dietary differences for e.g. low saturated fat intake in Asian population, making it difficult to attribute the observed differences in disease rates to phytoestrogens intake.

Two proposed mechanisms for the hypocholesterolemic effect of phytoestrogen are the upregulation of LDL receptors and / or the inhibition of endogenous cholesterol synthesis. Isoflavones, particularly genistein have been reported to alter the activity of growth factors and inhibit cell division and proliferation¹⁵ with antithrombolytic effect.¹⁶ However, several clinical trials with phytoestrogens have reported inconsistent serum lipid effects. In one study, hypercholesterolemic, postmenopausal women were randomly assigned to 6 month of 40 gm. protein supplementation / day from casein nonfat dry milk source, an isolated soy protein source or a soy protein source with approximately half of the phytoestrogen content removed. Compared to the casein milk protein both soy products lowered non HDL cholesterol and increased HDL cholesterol significantly.¹¹ While in another study with moderately hypercholesterolemic postmenopausal women were given 45gm/day of either soy flour or wheat flour for 12 weeks and observed significant decrease in the cholesterol in both groups.⁸

Phytoestrogens and Cancer :

Hormone related cancer of breast, ovary, endometrium and colon have been reported to vary from 5 to 20 folds between populations and migrant studies indicated that the differential is largely attributable to environmental factors rather than genetics. The highest rates of these cancers are typically observed in population with Western lifestyles that include relatively high fat, meat based, low fiber diets whereas the lowest rates are observed in Asian Populations with Eastern lifestyles which include plant – based diets with a high content of phytoestrogens.¹⁷ In 1997, Goodman MT et al reported that among the multiethnic population of Hawaii, soy and fiber consumptions were associated with a decreased risk off endometrial cancer, a finding that was limited to women who had never used unopposed estrogens and had never been pregnant.¹⁸ Despite the positive association of the endogenous and exogenous estrogens with the breast, ovarian, endometrial and colon cancers, phytoestrogens are associated with decreased incidence of these cancers. This can be explained by either a lack of estrogenicity or estrogen antagonism at these sites in conjunction with other possible mechanisms. The primary lignans and isoflavones have been shown to exhibit antiestrogenic effects and reduce the proliferation of cells at concentration higher than those achievable under normal

The Menopause **FOGSI** Focus

physiological conditions i.e. > 10 ml / L. The antioxidant properties, inhibition of enzymes associated with cell proliferation and enzymes involved in the production of estrogen from the androgens are other mechanism for anticarcinogenic effects of phytoestrogens.

Recently in 2009, Temfer CB et al concluded in a meta-analysis of randomized trial that based on the available evidence, phytoestrogens supplements have a safe side effect profile with moderately elevated rates of gastrointestinal side effects. Rates of vaginal bleeding, endometrial hyperplasia, endometrial cancer and breast cancer were not significantly increased among phytoestrogen users.²⁰

Conclusion :

Many researchers are of the opinion that there are few risks and many potential benefits from increasing intake of plant based foods which are good sources of phytoestrogens. However, available data do not appear to unequivocally support beneficial effects of phytoestrogens and hence many researchers warn against their wide use in the absence of satisfactory clinical trials. Additionally questions and issues those remain to be the resolved include when to start (perimenopausal or menopausal age), optimal dosages and for how long?

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19

Facts & Myths : WHI**Dr. Jyothi Unni**HOD, Dept of Obs & Gyn,
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Numerous observational studies seemed to show that Hormone Replacement Therapy(HRT) was beneficial for the prevention of age related diseases in women such as coronary artery disease and osteoporosis. However, when two large randomized controlled trials HERS and WHI failed to demonstrate this protective effect, women world over abruptly stopped taking HRT and clinicians were wary of prescribing it, even in women who needed it for symptom control. Most of the observational studies looked at markers such as Lipid profile or Bone Density, whereas the WHI study looked at disease end points.

The Women's Health Initiative (WHI) study was a randomized, double blind placebo controlled trial, conducted in 40 centres in the United States. A total of 16,608 postmenopausal women aged 50-79 years (Mean age 63 years), with an intact uterus were randomized to receive Hormone Replacement Therapy(HRT) or placebo. Participants received conjugated equine estrogens (CEE) 0.625 mg/d, plus medroxyprogesterone acetate(MPA) 2.5 mg/d, in 1 tablet (n = 8506) or placebo (n = 8102).

Another arm of the study recruited 10,739 postmenopausal women,aged 50-79 years with prior hysterectomy. They were randomly assigned to receive 0.625 mg CEE or placebo

The planned duration of this trial was 8.5 years, but the estrogen plus progesterone arm was halted in July 2002 after 5.2 years as it was perceived that the health risks exceeded the benefits. The estrogen alone arm continued till February 2004 (6.8 years)

The results of the CEE+ MPA arm showed an increase in coronary heart disease(CHD),strokes, pulmonary embolism (PE) and invasive breast cancers. There was a decrease in colorectal cancers and hip fractures. When these results were reported in percentages in the lay press, the risks appeared to be alarmingly high. However, the absolute excess risk (or risk reduction) attributable to estrogen plus progesterone was low. Over 1 year, 10,000 women taking estrogen plus progesterone compared with placebo might experience 7 more CHD events, 8 more strokes, 8 more PEs, 8 more invasive breast cancers, 6 fewer colorectal cancers, and 5 fewer hip fractures.

The fallacies of this trial were many. The mean age of the women was 63 years, with 21% of them being in the 70-79 year age group. Most clinicians would prescribe HRT to women between the ages of 45 -55, when symptoms are at their worst. This study had only 287 patients aged 50-54 years and was hence underpowered to test the cardio-protective effect of HRT in women soon after the menopause.

In the study group, 7.7% of them had prior cardio-vascular disease, 36% were hypertensive,10% were overweight and 7% were on statins. Hence they were already an 'at risk' population.

The Menopause **FOGSI** Focus

The WHI study tested only one regime, CEE, 0.625 mg/d, plus MPA, 2.5 mg/d, in postmenopausal women with an intact uterus. The results may not apply to lower doses of these drugs or to other formulations and routes of administration of estrogens and progestogens.

This study could not distinguish the effects of estrogen from those of progestogen. The effects of progestogen may be important for breast cancer and atherosclerotic diseases, including CHD and stroke.

42% of the treatment group dropped out compared with 38% of the placebo group. So, this is one of the rare studies, where there is a higher drop out rate amongst the active preparation group.

As in the WHI estrogen plus progestogen trial, the main hypothesis of the WHI estrogen-alone trial was that hormone therapy would reduce the risk of CHD. This did not happen, although early CHD harm, which could be due to the progestogen, appeared less pronounced.

The estrogen alone arm of the study was discontinued due to increase in stroke risk, without any increase in breast cancer or CHD. There was an increased risk of stroke among women assigned to both estrogen alone or estrogen plus progestogen, and this adverse effect is therefore attributable to the estrogen component of the hormone regimen. It is the only statistically significant adverse effect of estrogen alone. The rate was 0.12% additional strokes per year of treatment, which is quite low.

In younger women however, i.e women aged 50-59 years, there was a 42% decrease in CHD (16Vs29), 28% decrease in breast cancer (25Vs35) and a 41% decrease in colo-rectal cancer (8Vs 15). There was a 22% increase in Venous Thrombo-embolism (18 Vs 15) and an 8 % increase in strokes. Unfortunately, the numbers in this age group were small, so no definite conclusions can be drawn.

Subsequently, several authors have looked at various aspects of the WHI data as well as designed studies of HRT in women in the early post menopausal years. Most authors are now of the opinion that HRT, particularly estrogen alone is not only safe, but beneficial in the age group where treatment is usually commenced.

Hormone therapy is the most effective modality for treating menopausal symptoms, and for this indication, women who do not have contra-indications should not be denied HRT. However, estrogen and progestogen do have adverse effects, and the dose should be kept low and the duration of treatment short.

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Introduction:

Postmenopausal HRT has witnessed its rise and fall over past several years. The research has been giving conflicting results and confusing menopause practitioners about various management protocols. As of the early 2000s, after the publication of the principal results of the two large randomized trials, the Heart and Estrogen/Progestin Replacement Study (HERS) in 1998 and the Women's Health Initiative (WHI) trial in 2002, the trend has changed drastically.^{1,2,3} WHI results constituted the direct cause of discontinuation of HRT in approximately 30% of postmenopausal women³. HERS is a study which has given an unexpected set back to HRT for cardioprotection. Thus, it is important to know how HERS and WHI changed our practices

HERS I:⁴

Heart and Estrogen/progestin Replacement Study (HERS) Research Group conducted a Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women⁴. Earlier observational studies^{5,6,7} had found lower rates of coronary heart disease (CHD) in postmenopausal women who take estrogen than in women who do not, but this potential benefit has not been confirmed in clinical trials so they conducted a Randomized, blinded, placebo-controlled secondary prevention trial in Outpatient and community settings at 20 US clinical centers. A total of 2763 women with coronary disease, younger than 80 years, and postmenopausal with an intact uterus participated in the study. Mean age was 66.7 years. Either 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxy progesterone acetate in 1 tablet daily (n = 1380) or a placebo of identical appearance (n = 1383). Follow-up averaged 4.1 years. The primary outcome was the occurrence of nonfatal myocardial infarction (MI) or Fatal CHD. Secondary cardiovascular outcomes included coronary revascularization, unstable angina, congestive heart failure, resuscitated cardiac arrest, stroke or transient ischemic attack, and peripheral arterial disease. All-cause mortality was also considered. 172 women in the hormone group and 176 women in the placebo group had MI or CHD death. Within the overall null effect, there was a statistically significant time trend, with more CHD events in the hormone group than in the placebo group in year 1 and fewer in years 4 and 5. More women in the hormone group than in the placebo group experienced venous thromboembolic events (34 vs 12;) and gallbladder disease (84 vs 62;). There were no significant differences in several other end points for which power was limited, including fracture, cancer, and total mortality (131 vs 123 deaths). They concluded that during an average follow-up of 4.1 years, treatment with oral estrogen plus medroxyprogesterone acetate did not reduce the overall rate of CHD events in postmenopausal women with established coronary disease. The treatment did increase the rate of thromboembolic events and gallbladder disease. Hence starting this treatment for

The Menopause **FOGSI** Focus

the purpose of secondary prevention of CHD was not recommended as there was no overall cardiovascular benefit and a pattern of early increase in risk of CHD events. However, given the favorable pattern of CHD events after several years of therapy, it could be appropriate for women already receiving this treatment to continue.

Table 1. Hazard ratios of HERS trial 1998

Clinical Event	HAZARD RATIO (95% CONFIDENCE INTERVAL) HERS (Estrogen + Progestin)
CHD events	0.99 (0.80 - 1.22)
Stroke	1.23 (0.89 - 1.70)
Pulmonary embolism	2.79 (0.89 - 8.75)
Breast cancer	1.30 (0.77 - 2.19)
Colon cancer	0.69 (0.32 - 1.49)
Hip fracture	1.10 (0.49 - 2.50)
Death	1.08 (0.84 - 1.38)

Table 1 shows hazard ratios of HERS trial. For the primary CHD events, outcome of (myocardial infarction plus CHD death), the three randomized trials (HERS, WHI HRT-EP, and WHI HRT-E) had similar numbers of events and thus similar power. For the other outcomes, the smaller HERS trial had fewer events and less precise hazard ratios. These risks are statistically significant but minimal.

Results from HERS and WHI led the USFDA to require a warning of potential harm and to recommend that estrogen preparations not be used to prevent CHD or be considered first-line therapy for prevention of osteoporosis. a number of professional societies changed their guidelines to recommend that hormone therapy not be used for preventing disease, and when used for treating symptoms that it be at the lowest dose and for the shortest time possible.

Critical analysis of facts about HERS trial:

The mean age of participants in all three randomized trials was in the mid-60s, raising the concern that these results may not apply to treatment begun early in menopause.^{4,8}

A 50% increase in cardiovascular events was seen in the first year, followed by fewer events after 2 years of treatment in the hormone therapy group than in the placebo group. Understanding the cause of this pattern of early increase and late reduction in risk is key to interpreting the HERS results and reconciling them with the large number of observational and other studies of the cardiovascular effects of estrogen. The other is that the pattern of early increase and late reduction in risk is coupled with a gradually progressive beneficial effect due to lipid lowering and other factors is a promising potential explanation.

Why Early Harm and Late Benefit in HERS trial?

- 1] Estrogen plus progestin had no real effect on risk for heart disease, and the observed pattern of changing risk over time was simply the result of chance or confounding
- 2] It may be due to real but opposing effects of this regimen with time, like lipid lowering effects
- 3] Decrease in number of women uniquely at risk for a cardiovascular complication from hormone therapy





Statistical perspective of HERS trial:

- 1] From a statistical perspective, although the final test for trend in the relative hazards over time had a P value of 0.03, this time-trend analysis was not explicitly specified.
- 2] There are also concerns about the validity of the year-specific estimates of relative risk that were used in the time-trend analyses
- 3] Estimates of risk during individual years of follow-up are less precise than for the entire study period. For these reasons, the time-trend analyses should be interpreted with caution
- 4] Because of the statistical uncertainties concerning the time-trend analysis, it is clear that the results need independent confirmation.

Biological Perspective of HERS trial:

- 1] In the biological perspective, it is possible that the estrogen replacement in HERS had no effect on risk for coronary heart disease because it was opposed by a progestin, medroxyprogesterone acetate
- 2] The overall null effect in HERS is later shown to be due to an early adverse and late beneficial effect, and if the cause of the early risk can be identified and prevented, many women may still be able to benefit from estrogen replacement for secondary prevention of coronary heart disease

Risk factors were assessed by a HERS trial group⁹. These researchers found 11 risk factors: 6 noted by history (nonwhite ethnicity, lack of exercise, treated diabetes, angina, congestive heart failure, and more than one previous myocardial infarction) and 5 that were measured (blood pressure, low-density lipoprotein cholesterol level, high-density lipoprotein cholesterol level, lipoprotein(a) level, and creatinine clearance). The annual rate of coronary events was 1.3% in women with no risk factors and 8.7% in women with five or more risk factors (a six-fold increase)

The facts and the myths : comparison of the three landmark trials:

Heart and Estrogen/Progestin Replacement Study (HERS)⁴, 1998 and the Women's Health Initiative (WHI) trial 2002 E+P¹⁰ and E only.2008⁸

Coronary Heart Disease

Given the absence of evidence in all three trials that these hormone regimens prevent CHD in these populations, the previously available evidence in favor of HRT was probably misleading. HRT-EP or HRT-E does not prevent CHD as previously proposed. To the contrary, there may be a small but significant increase in CHD in women taking HRT-EP. Both women with preexisting CHD and healthy women are at risk. HRT-E, on the other hand, does not increase the risk for healthy women

Stroke

Another outcome that is consistent across the three trials is the increased risk of stroke among women assigned to HRT-E or HRT-EP. Increased stroke is possibly attributable to the estrogen component of the hormone regimen, since it is the only statistically significant adverse effect of HRT-E⁴

Pulmonary Embolism

A pattern of increased risk for pulmonary embolism was observed in all three studies^{4,8,10} although the risk was attenuated and not statistically significant in the WHI HRT-E trial.⁸

The Menopause **FOGSI** Focus

Breast Cancer

The findings of the WHI HRT-E trial differed markedly from the findings of the HERS and WHI HRT-EP trials with respect to the breast cancer risk.^{4,8} In the estrogen plus progestin trials (HERS and WHI HRT-EP), the risk for breast cancer was increased about 25%, and in the estrogen-only trial (WHI HRT-E) it was reduced by 23%. Numerous lines of evidence support an increased risk for breast cancer with estrogen exposure, including cell culture studies, animal models, many observational studies, and the fact that estrogen antagonists reduce the risk of developing breast cancer in healthy women. Thus, this discrepancy was somewhat surprising. Nonetheless, the higher risk for breast cancer observed in the estrogen plus progestin trials probably represent a harmful effect of the MPA. The increased risk was statistically significant in WHI HRT-EP. This was matched by a trend of the same magnitude in HERS and supported by evidence from large observational studies suggesting that the addition of MPA or another progestin to estrogen may significantly increase risk for breast cancer

Ovarian Cancer

Dementia

In postmenopausal women 65 years of age or older, HRT-EP significantly increased risk and resulted in an additional 23 cases of probable dementia per 10,000 women per year. Alzheimer's disease was the most common classification of dementia. A similar trend was observed in the HRT-E group, although this did not reach statistical significance.¹² When the data were pooled, HRT significantly increased probable dementia risk¹²



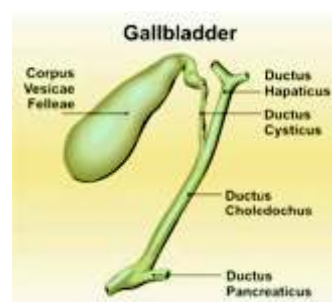
Hyperlipidemia

This rare side effect is observed in patients with severe familial hypertriglyceridemia. An oral estrogen regimen can hasten severe hypertriglyceridemia or pancreatitis in women with severely elevated triglyceride levels¹³. Therefore, estrogen replacement is a relative contraindication in women with substantially increased triglyceride levels. Effect on lipid was studied by a group¹⁴ as Despite the effect of lowering low-density lipoprotein cholesterol (LDL-C) levels and raising high-density lipoprotein cholesterol (HDL-C) levels, combination hormone therapy did not reduce the incidence of coronary heart disease (CHD) events in the Heart and Estrogen/progestin Replacement Study (HERS).

Another group studied Statin therapy¹⁵ in the heart and estrogen/progestin replacement study. Data from HERS supports the use of statins for secondary prevention in postmenopausal women with a history of cardiovascular disease. Statins may attenuate the increased cardiovascular risk of hormone replacement therapy.

Gallbladder Disease

Both WHI trials (HRT-E and HRT-EP) trials showed greater risk of any gallbladder disease or surgery with estrogen¹⁶ In HERS, A total of 147 women (7%) were hospitalized for biliary tract surgery in HERS. Treatment with estrogen plus progestin resulted in a marginally significant 38% increase in the relative risk for biliary tract surgery (P = 0.05). A small absolute difference in risk suggested that for every 185 women treated with estrogen plus progestin, one additional woman had biliary tract surgery per year¹⁷





Urinary symptoms:

Postmenopausal hormones and incontinence: the Heart and Estrogen/Progestin Replacement Study¹⁸. shows that: Incontinence improved in 26% of the women assigned to placebo compared with 21% assigned to hormones, while 27% of the placebo group worsened compared with 39% of the hormone group ($P = .001$). This difference was evident by 4 months of treatment and was observed for both urge and stress incontinence. The number of incontinent episodes per week increased an average of 0.7 in the hormone group and decreased by 0.1 in the placebo group ($P < .001$). this group does not recommend this therapy for the treatment of incontinence.

Benefits of Hormone Replacement Therapy:

Hot Flash

HRT-E or HRT-EP reliably treats hot flashes in most women. Currently, hot flash is the most common indication of a short course of HRT (<5 years).

Fractures

Both HRT-EP and HRT-E significantly decreased hip, vertebral, and other osteoporotic fractures⁸. In this instance, results of observational studies of estrogen and fracture risk and trials using a surrogate end-point (bone mineral density) agree with the results of clinical trials of fracture prevention.

Colon Cancer

Colon cancer was significantly less common with hormone treatment in the WHI HRT-EP study but not in WHI HRT-E for reasons that are not clear.⁸ It is possible that progestin is the protective hormone in this case.

Quality of life:

Hlatky MA, 2002 published results of the HERs study pertaining to quality of life.¹⁹ Women with flushing who were assigned to hormone therapy had improved mental health and fewer depressive symptoms ($P = .01$) over follow-up compared with those assigned to placebo. Women without flushing who were assigned to hormone therapy had greater declines in physical function ($P = .04$) and energy/fatigue ($P = .03$) over follow-up. Quality-of-life scores were significantly lower among patients with older age, diabetes, hypertension, chest pain or heart failure. These differences in quality of life among women classified by clinical characteristics were much greater than the effects of hormone therapy.

As more deliberate and exhaustive analyses of these trials become available, they will likely contribute to new practice guidelines.

Post WHI and HERS Target Groups for HRT

In women with gonadal dysgenesis and surgical menopause, the duration of estrogen deprivation is prolonged. Estrogen replacement is recommended for these patients for the reduction of hot flashes and for long-term prophylaxis against cardiovascular disease, osteoporosis, and target organ atrophy. A low-dose contraceptive may be offered to nonsmoking women until the age of 45. After this age, doses of estrogen equivalent to 0.625 mg of conjugated estrogens may be more appropriate because of a sharp age-related increase in risk for thrombo-embolic events. The clinician should recommend a continuous estrogen-progestin combination to those with a uterus and an estrogen-only regimen to women without a uterus.

The Menopause **FOGSI** Focus

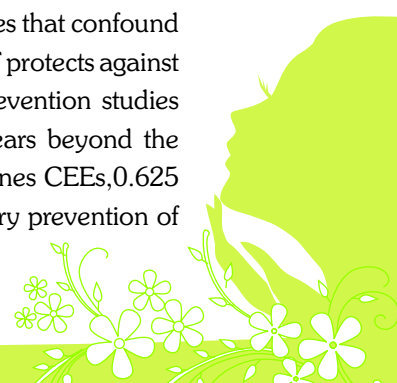
HERS II ::^{20,21}

The Heart and Estrogen/progestin Replacement Study (HERS) was a randomized trial of estrogen plus progestin therapy after menopause. SO HERS II group examined the effect of long-term postmenopausal hormone therapy on common noncardiovascular disease outcomes²¹:: Randomized, blinded, placebo-controlled trial of 4.1 years' duration (HERS) and subsequent open-label observational follow-up for 2.7 years (HERS II). Hence the duration of study was between 1993 and 2000: A total of 2763 postmenopausal women with coronary disease and average age of 67 years at enrollment in HERS; 2321 women (93% of those surviving) consented to follow-up in HERS II. Participants were randomly assigned to receive 0.625 mg/d of conjugated estrogens plus 2.5 mg of medroxyprogesterone acetate (n = 1380) or placebo (n = 1383) during HERS; open-label hormone therapy was prescribed at personal physicians' discretion during HERS II. The proportions with at least 80% adherence to hormones declined from 81% (year 1) to 45% (year 6) in the hormone group and increased from 0% (year 1) to 8% (year 6) in the placebo group. There were 261 deaths among those assigned to hormone therapy and 239 among those assigned to placebo (RH, 1.10; 95% CI, 0.92-1.31). Treatment for 6.8 years with estrogen plus progestin in older women with coronary disease increased the rates of venous thromboembolism and biliary tract surgery. Trends in other disease outcomes were not favorable and should be assessed in larger trials and in broader population.

The Heart and Estrogen/progestin Replacement Study (HERS)⁴ found no overall reduction in risk of coronary heart disease (CHD) events among postmenopausal women with CHD. However, in the hormone group, findings did suggest a higher risk of CHD events during the first year, and a decreased risk during years 3 to 5. To determine if the risk reduction observed in the later years of HERS persisted and resulted in an overall reduced risk of CHD events with additional years of follow-up. The primary outcome was nonfatal myocardial infarction and CHD death. Secondary cardiovascular events were coronary revascularization, hospitalization for unstable angina or congestive heart failure, nonfatal ventricular arrhythmia, sudden death, stroke or transient ischemic attack, and peripheral arterial disease.

Lower rates of CHD events among women in the hormone group in the final years of HERS did not persist during additional years of follow-up. After 6.8 years, hormone therapy did not reduce risk of cardiovascular events in women with CHD. Postmenopausal hormone therapy should not be used to reduce risk for CHD events in women with CHD²⁰

WHI is a tremendously important contribution to our understanding of menopausal therapy. Most, of, earlier cohort, retrospective, and prospective observational studies have demonstrated significant, 40% to 60% reductions in coronary heart disease (CHD) in postmenopausal women taking HRT-E only or combined HRT-EP. These studies also showed reductions in all-cause mortality and osteoporotic fractures, but showed increases in risk of breast cancer on the order of 20% to 30%. Several similar studies have demonstrated reduced incidence of Alzheimer's-type dementia in women who had used HRT-EP versus women who did not. Given the inherent biases that confound observational studies, randomized clinical trials are needed to establish whether HRT protects against cardiovascular disease (CVD) or dementias. The HERS and other secondary prevention studies demonstrated no benefit in women with known CVD initiating HRT 8 to 23 years beyond the menopause Results from WHI indicate that the combined postmenopausal hormones CEEs, 0.625 mg/day, plus MPA, 2.5 mg/day, should not be initiated or continued for the primary prevention of





CHD. In addition, the substantial risks for CVD and breast cancer must be weighed against the benefit for fracture protection in selecting from the available agents to prevent osteoporosis.

Conclusion :

HERS I and II both have not shown any beneficial effect on heart the results must be carefully interpreted. Thus, out of the struggle to interpret the results of HERS, there will emerge new hypotheses, research questions, and paradigms about estrogen and heart disease prevention that will ultimately lead to improvements in the health of all postmenopausal women.

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The Menopause **FOGSI** Focus

21

The Pan-Asia Menopause Study (PAM Study)



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Menopause is the time in a woman's life when her periods cease as the woman's ovaries gradually stop producing estrogen and progesterone hormones. Average age ranges between 47 to 51 years, but perimenopausal symptoms can start several years earlier.

Menopausal symptoms, which affect about 70-80% of women, are believed to be due to the changing hormone levels, particularly estrogen. Leading to altered quality of life. Early menopausal symptoms include physical, sexual and psychological problems

Physical symptoms include:

Hot flushes, night sweats, palpitations, insomnia, joint aches, headaches, anxiety, depression, fatigue, backaches, sleeplessness, lack of concentration & confidence, vaginal dryness, aversion for sex and urinary problems

Later menopausal symptoms include:

Frequency of micturition, urinary infections, dysuria and urinary incontinence. Other symptoms include effects from changes in collagen production, leading to dryer, thinner, less elastic skin, thinning of hair, nails and tendons more prone to bruising, coronary heart disease, Alzheimer's disease and osteoporosis

With the general increase in life expectancy, many women are likely to spend nearly one quarter of their lives or more in the post menopausal period, a state of estrogen deficiency which leads to various problems .





The overall health and well being of middle-aged women has become a major public health concern around the world. World Health Organization defines Quality of life (QoL) as an individual's perception of their position in life in the context of culture and values system in which they live and in relation to their goal expectations, standards and concerns.⁶

The study of QoL in the post menopause has become an essential component in clinical practices. Most studies on QoL of postmenopausal women were conducted in developed countries with different sociocultural realities, which may influence not only the perception of QoL but also the experience of menopausal symptoms. Very little information exists about QoL of postmenopausal women in developing countries.

The Greene Climateric Scale:

The Greene Scale provides a brief measure of menopause symptoms. It can be used to assess changes in different symptoms, before and after menopause treatment.

Three main areas are measured:

- 1) Psychological
- 2) Physical
- 3) Vasomotor.

HRT, or Ovarian Hormone Therapy -

HRT is supplementation of hormones which are deficient in postmenopausal women. The FDA recently adopted the term “menopausal hormone therapy” to replace HRT. When estrogen alone is used, it may also be called “Estrogen Replacement Therapy” (ERT).

"When a subject ceases to be of controversy it ceases to be a subject of interest"

- William Hezlitt

Estrogen perhaps enjoys the status of being one of the most researched molecules in the century and yet the controversies do not cease.

The Women's health initiative was an important national health study taken in the USA focusing on strategies for preventing major causes of death, disability & frailty in older women of all races & socioeconomic background like: Heart disease, breast, colorectal cancer & osteoporosis

15 year study sponsored by National institute of health (NIH) & National heart, lung & blood institute(NHLBI) N= 161,000 women, aged 50-79

Three components : 1) WHI clinical trial 2) Observational study 3) Community prevention study
Primary outcomes were

- a.) Osteoporosis - causes fractures leading to increased disability & debility.
- b.) Heart disease - leading cause of death in postmenopausal women
- c.) Breast cancer -second leading cause of cancer deaths
- d.) Colon cancer-third leading cause of cancer deaths

The Menopause **FOGSI** Focus

Risks Per 10 000 person years on HRT as analysed by WHI investigators

- 8 extra breast cancers
- 7 extra MI
- 8 extra strokes
- 8 extra PE
- 5 fewer hip fractures
- 6 fewer bowel cancers
- Absolute excess risk of events induced in global index 19 per 1000 (as per WHI study)

“Women's Health Initiative” (WHI) investigators found a 34% decrease in hip fractures in postmenopausal women taking estrogen and progestin. Estrogens prevent/slow bone resorption in menopausal women. Bone demineralization occurs earlier in life than one might think!

Generally, estrogens lower LDL, raise HDL, and increase triglycerides

However, the WHI study demonstrated a significant increase in cardiovascular disease: 29% increase in MI, 41% increase in stroke after 5.2 yrs of estrogen + progestin use .

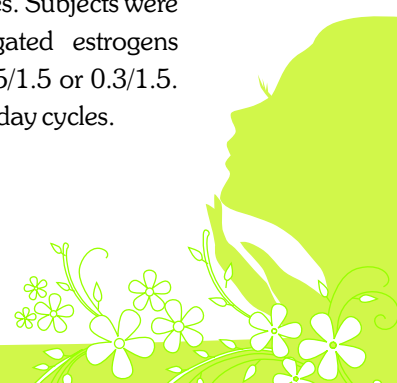
After this study was published and perhaps misinterpreted by the media naturally what followed was the abrupt stoppage of HRT by clinicians for women who were on it, fearing the side effects. Despite the shortcomings of the study it was the failure on part of clinicians to understand the shortcomings of the WHI study and lack of **caution in extrapolating data of post menopausal women to peri & early post menopausal women or women with premature menopause. This resulted in depriving** women who really needed HRT .

So guidelines were later set up to help clinicians decide which women needed HRT and how to assess the **benefits versus risks**.

The WHI study had evoked controversies & raised doubts about the efficacy & safety of Hormone Replacement Therapy (HRT). Most of the studies on Hormone replacement therapy have included Caucasian women having a Western lifestyle so one study which focussed on women in the Asia Pacific region was '**The Pan-Asia menopause study (PAM study)**'

This was a large prospective randomized, 3 arm multi centric clinical trial evaluating 1028 postmenopausal women in 11 Asian countries, to study **the prevalence of vasomotor symptoms in different ethnic groups and** effects and safety, tolerability and side effects of varying doses of Hormone replacement therapy (HRT) on healthy postmenopausal women (40-65 yrs). This would also **assess if lower doses are as effective as the traditional doses of HRT**.

The PAM study was a prospective, three arm, randomized, double-blind clinical trial evaluating 1028 postmenopausal women at 22 investigational centers in 11 Asian countries/territories. Subjects were randomly assigned to one of three doses of continuous combined conjugated estrogens (CE)/medroxyprogesterone acetate (MPA): CE/MPA (in mg/day) = 0.625/2.5, 0.45/1.5 or 0.3/1.5. The treatment period, following baseline evaluations, consisted of six continuous 28-day cycles.





The study compromised of the use of varying doses of HRT for -

- 1) Relief of vasomotor symptoms (VMS) and vaginal atrophy in Asian women of different ethnic background.
- 2) To study differential prevalence of quality-of-life categories (domains) in Asian women and changes after therapy
- 3) Test the hypothesis that reproductive hormone and lipid profiles differ among the nine ethnic groups under investigation in the PAM study.

Arm 1

Objective: To evaluate the efficacy of three doses of estrogen/progestin therapy for relief of vasomotor symptoms (VMS) and vaginal atrophy in Asian women of different ethnic background; to examine the differences in prevalence of VMS amongst ethnic groups.

Methods: A prospective, randomized, double-blind multinational clinical trial in healthy postmenopausal women from 11 Asian countries. Following 2 weeks of baseline observations, the women received one of three conjugated combinations of conjugated estrogens (CEE) and medroxyprogesterone acetate (MPA) (in mg) daily for 24 weeks: doses 0.625/2.5; 0.45/1.5; or 0.3/1.5. The treatment period, following baseline evaluations, consisted of six continuous 28-day cycles. The women recorded VMS and uterine bleeding daily on diary cards translated into 10 languages. Vaginal responsiveness was evaluated by the vaginal maturation index (VMI) at baseline and at week 24.

Results:

Amongst the study population of 1028 postmenopausal women, the VMS-evaluable subpopulation was about 60% of the total population. Hot flush frequency decreased significantly in all the dose groups within 4 weeks of treatment. The VMI shifted significantly from immature (parabasal) to mature (superficial) cells at the end of the treatment. However, uterine bleeding was consistently less frequent in the 0.3/1.5mg group. The percentage of women who reported VMS at baseline differed substantially amongst the different ethnic groups, ranging from 5% in Indonesian women to 100% in Vietnamese women.

Conclusion:

Asian postmenopausal women respond to CE/MPA therapy. The lowest dose is as effective for VMS and vaginal responsiveness as the higher doses, and the lowest dose is associated with the most favorable bleeding pattern. The prevalence of vasomotor symptoms differs among ethnic groups.

Second arm

Objectives - To assess the prevalence of four categories (domains) of menopausal symptoms as markers for quality of life in nine ethnic groups. To evaluate changes in quality of life (MENQOL scores) after therapy with three doses of conjugated estrogens /medroxyprogesterone acetate

Methods - A prospective, randomized, double-blind, multinational clinical trial in 1028 healthy postmenopausal women of nine ethnic groups from 11 Asian countries/regions. Following 2 weeks of baseline observation, the women received one of three conjugated estrogens (CE)/medroxyprogesterone acetate (MPA) doses (in mg) daily for 24 weeks: 0.625/2.5, 0.45/1.5, or 0.3/1.5.

The Menopause **FOGSI** Focus

At baseline and at the end of weeks 4, 12 and 24 following the start of therapy, the study participants were asked to record, on a menopause-specific quality of life (MENQOL) questionnaire, 29 menopausal symptoms, as experienced during the preceding month. The symptoms were categorized into four domains: vasomotor, psychosocial, physical and sexual.

Results - The baseline (pretreatment) symptom scores in each of the four domains varied substantially amongst the different ethnic groups. Overall, Vietnamese and Pakistani women had the highest baseline scores, i.e. were most afflicted by each set of symptoms in a given domain, and Indonesian, Malay, Taiwanese and Thai women were least afflicted. In the overall population, intervention resulted in statistically significant decreases in the scores of all four domains within 4 weeks of intervention. The beneficial effects were similar in the three dose groups.

Conclusions - The prevalence of four domains of menopausal symptoms, varies considerably among ethnic groups of Asian women. The MENQOL scores in the overall population were significantly lowered in the course of the study, indicating an improvement in quality of life. In the absence of a placebo group, the relative contribution of hormones and placebo in our intervention is unknown.

Third arm

Objectives - Significant differences in the prevalence of menopausal symptoms and in lipid profiles have previously been reported for nine ethnic groups of postmenopausal Asian women participating in the Pan-Asia Menopause (PAM) study. Based on these findings, the hypothesis was tested that reproductive hormone profiles differ amongst the nine ethnic groups under investigation in the PAM study.

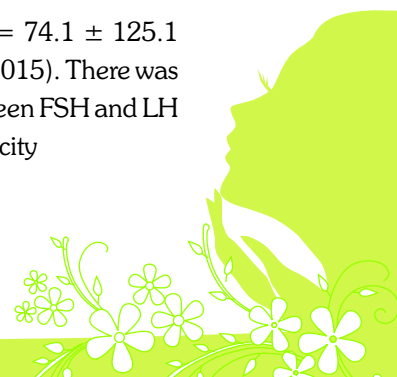
Lipid/lipoprotein profiles, amongst other factors, are associated with the risk of cardiovascular disease which varies in Asian countries, it was hypothesized that lipid profiles differ in ethnic groups of postmenopausal Asian women. To add to the limited body of information currently available, the effects of estrogen/progestin therapy on lipid/lipoprotein profiles in postmenopausal Asian women was also investigated.

Methods:

With the same population under study as mentioned earlier, baseline serum samples from postmenopausal women (n=1020) representing nine ethnic groups were analyzed by electrochemiluminescence immunoassay methods {estradiol (E2), follicle stimulating hormone (FSH) and luteinizing hormone (LH)}

Analysis of lipid profiles was a secondary objective of the PAM study. Total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), very low density cholesterol (VLDC-C), triglycerides and lipoprotein(a) were analyzed at a central laboratory by state-of-the-art methods.

Results The hormone levels for the overall study population (mean \pm SD) were: E2 = 74.1 \pm 125.1 pmol/l (n = 1015); FSH = 81.2 \pm 31.4 IU/l (n = 1013); LH = 36.8 \pm 15.6 IU/l (n = 1015). There was an inverse correlation between log E2 and FSH levels and a positive correlation between FSH and LH levels. The concentrations of E2, FSH and LH were significantly associated with ethnicity





Mean concentrations of total cholesterol, LDL-C, VLDL-C and triglycerides differed significantly among the nine ethnic groups of postmenopausal women. This difference was independent of body mass index and age, two factors that also influenced lipid/lipoprotein profiles. Mean HDL-C concentrations also differed, but this difference was influenced by body mass index in a weak interaction. All three doses of CE/MPA significantly lowered total cholesterol. Treatment with the high and middle doses significantly lowered LDL-C, and increased HDL-C, VLDL-C and triglycerides. The high dose produced a significant decrease in lipoprotein (a).

Conclusion - The levels of FSH, LH and particularly of E2 differ substantially among ethnic groups of postmenopausal Asian women. The clinical significance, if any, of these differences remains to be investigated. The inverse correlation of E2 and FSH levels suggests that E2 at the postmenopausal state still affects pituitary FSH output.

The different lipid/lipoprotein profiles in the nine ethnic groups of postmenopausal Asian women evaluated here suggest a relationship to differences in the prevalence of cardiovascular disease reported for different regions in Asia. However, the reported prevalence data on cardiovascular disease morbidity and mortality in the regions corresponding to the nine ethnic groups are insufficient to allow qualitative comparisons with the lipid profiles shown in our study. The lipid/lipoprotein changes in response to estrogen/progestin therapy observed here are consistent with those reported for Western women.

Conclusions of the PAM study : Prevalence of VMS varied amongst different ethnic groups studied. The lowest dose of (0.3/1.5 mg/d) was as effective as higher doses for VMS. The vaginal maturation index also was comparable to higher doses. The spotting and bleeding patterns were favorable. The breast discomfort was lesser. All the three doses were well tolerated !!

However more data is needed to correlate the differences in the lipid/lipoprotein profiles in the nine ethnic groups of postmenopausal Asian women to differences in the prevalence of cardiovascular disease in different regions in Asia.

Keywords: Menopause; Pan-Asia Menopause Study; Pam Study;
Postmenopausal Asian Women; Hormone Therapy;

Suggested Reading

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The Menopause **FOGSI** Focus

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Publications of the results of the Women's Health Initiative (WHI) study in 2003 & 2004 with estrogen (E) + progestogen (P) arm and the E only arm led to considerable uncertainties about the role of Hormone Therapy (HT) among health professionals and women. Use of tibolone in postmenopausal women was considered to be a good alternative for those postmenopausal women who have concerns about HT.

Tibolone, a synthetic steroid, has a unique clinical profile having estrogenic, androgenic and progestagenic properties. It has specific effects on different tissues as a result of its tissue-selective metabolism, enzyme regulation, and/or receptor binding and activation. It regulates estrogenic activity in a tissue-selective manner, thereby having estrogenic effects on brain, vagina and bone but not on breast or endometrium. However case reports & a few studies have shown presence of endometrial cancer in women on tibolone. Hence questions have been raised as to whether there is an association between use of tibolone and an increased risk of endometrial and breast cancer.

The primary objective of the THEBES study⁽¹⁾ (Tibolone Histology of the Endometrium and Breast Endpoints Study) was to confirm the endometrial safety of oral tibolone (1.25 and 2.5 mg/d) and the secondary objective compare it with continuous combined oral CEE plus MPA (0.625/2.5 mg/d). The vaginal bleeding profile and incidence of breast pain was also studied. The study was a multicentre randomized, active-controlled, double-blind, parallel-group trial wherein a total of 3224 postmenopausal women (aged 45-65 years) with an intact uterus received the medication (tibolone 1.25mg, n=792; tibolone 2.5mg, n = 806; CEE/MPA, n = 1626). Endometrial biopsies were obtained (by pipelle suction curette) at baseline and repeated after 1 and 2 years of treatment. Results of a few important studies including THEBES are given below.

Tibolone and endometrium

An open, prospective comparative study was undertaken by Perez-Medina et al⁽²⁾ in 485 postmenopausal women for a duration of 36 months in which 249 women received 2.5 mg/day of tibolone and 244 women served as controls, receiving continuous-combined HT. Transvaginal ultrasound, hysteroscopy, and directed biopsies were performed before treatment was initiated and at the end of the study. Endometrial polyps were detected in 74 women (33.4%) from the tibolone group and in 22 women (10.8%) from the HT group ($P < 0.01$). The frequency of atrophic polyps was significantly higher in the tibolone group ($P < 0.01$). The study concluded that tibolone increases by threefold the risk for endometrial polyps.

Tibolone Consensus Group⁽³⁾ reported that the endometrial histology in women treated with tibolone showed no hyperplasia and had a high level of atrophic endometrium (level of evidence: proven).

The Menopause **FOGSI** Focus

The Million Women Study⁽⁴⁾ recruited 7,16,738 postmenopausal women out of which 28,028 ie 9 % women had last used tibolone. The MWS estimated an increased risk of endometrial cancer in women who had used tibolone compared with never users of HRT (RR approximately 1.8, 95%CI 1.4 – 2.3). The risk increased with increasing duration of use. Another study that also cautioned that tibolone may be associated with an increased risk of endometrial cancer was the UK General Practice Research Database (GPRD)⁽⁵⁾. This study analyzed data of 4995 women who had used used tibolone as their first HRT product; 10 783 (4.3%) of the users of combined HRT had changed to tibolone at some time during the study period. The adjusted odds ratio of the risk of endometrial cancer in women who had ever used tibolone, compared with users of combined sequential HRT, was 1.54 (95% CI 1.03, 2.32). The authors however mentioned that their data are fragile and residual bias and uncontrolled confounding cannot be excluded and follow-up time was insufficient to draw any firm conclusions.

The secondary objective of the OPAL study⁽⁶⁾ was to assess the effects of tibolone (2.5 mg), continuous combined CEE/MPA (0.625/2.5 mg), and placebo on the endometrium. The study was a 3-year, three-arm, international, randomized, double-blind, parallel group, placebo-controlled clinical trial which enrolled 866 postmenopausal women (aged 45-79 years). At the end of 3 years, data showed no significant differences between the tibolone, CEE/MPA and placebo groups in the incidence of proliferation (1.4%, 4.8%, and 0%, respectively), endometrial hyperplasia (0% in all groups), or cancer (1, 0, and 1 case, respectively) thus demonstrating the endometrial safety profile of tibolone.

In the THEBES study,⁽¹⁾ the incidence and upper one-sided 95% CI for the incidence of abnormal endometrium (hyperplasia or carcinoma), and hyperplasia and carcinoma separately, were calculated at end point, yr 1, and yr 2. The incidence (upper one-sided 95% CI) of abnormal endometrium at end point was 0.0 (0.5), 0.0 (0.4), and 0.2 (0.5) in the tibolone 1.25 mg, 2.5 mg, and CEE/MPA groups, respectively. The study concluded that that there were no cases of endometrial cancer or endometrial hyperplasia in women who used 1.25 or 2.5 mg of tibolone.

Ettinger et al⁽⁷⁾ randomly assigned postmenopausal osteoporotic women (N=3,519) aged 60-85 years (mean 68 years) with a uterus to receive either tibolone 1.25 mg/day, or identical placebo for a 3 year study period to investigate endometrial effects of tibolone. Endometrial thickness was evaluated in all women and histology was examined in 635 participants with unexpected vaginal bleeding or endometrial thickness more than 4 mm. Diagnostic biopsies among 499 women receiving tibolone and 136 who were receiving placebo showed cumulative incidences of endometrial hyperplasia less than 1%. Among the 15% of women whose biopsy showed an endometrial polyp (similar rate in tibolone and placebo), those receiving tibolone were more than twice as likely to show hyperplasia within the polyp. A marginal increase in grade 1 endometrioid adenocarcinoma (P=.06 compared with placebo) was found among women receiving tibolone. The study concluded that tibolone treatment minimally increased endometrial thickness, hyperplastic polyps, endometrial carcinoma, and vaginal bleeding.

Tibolone and breast

The MWS⁽⁴⁾ reported that, compared to never users, the use of various types of estrogen-progestogen combined HRT was associated with a higher risk of breast cancer (RR = 2.00, 95%CI: 1.88-2.12) than use of estrogens alone (RR = 1.30, 95%CI: 1.21-1.40) or use of tibolone (RR=1.45; 95%CI 1.25-1.68). Thus this prospective cohort study that included more than a million women, showed that women using tibolone had nearly 1.5 times the risk of breast cancer as women who never used HRT. The difference was statistically significant.





A randomized double-blind placebo-controlled LIFT⁽⁸⁾ study (n = 4506) on the efficacy of low dose (1.25 mg) tibolone (N = 2249) for the treatment of osteoporosis in elderly women (mean age 68 years), has shown a statistically significantly decreased risk of breast cancer in the tibolone group compared to placebo after an average of 2.9 years of follow-up. The tibolone group had a 3.1 fold decreased risk of invasive breast cancer (RR 0.32, p = 0.015). The incidence of breast cancer observed in the tibolone and placebo arms was 0.91 and 2.85 per 1000 women-years, respectively. The absolute risk decrease is 1.9 cases of breast cancer per 1000 women treated per year. However, the tibolone group had an increased risk of stroke (relative hazard, 2.19; 95% CI, 1.14 to 4.23; P=0.02), for which the study was stopped in February 2006 at the recommendation of the data and safety monitoring board.

The Tibolone Consensus Group⁽³⁾ states that there is inconclusive level of evidence regarding the safety of tibolone. It is shown to cause less breast tenderness and mastalgia than HT and does not increase mammographic density (level of evidence: proven).

Thus, there are controversial reports about tibolone use in terms of efficacy or cancer risks. Only time will tell about the safety profile of tibolone option for treating menopausal women.

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The Menopause **FOGSI** Focus

23 Holistic Approach to Menopause - Diet & Nutrition



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Menopause is a biological phenomenon in the process of ovarian ageing which occurs in around the age of 50 in 50 % of women. Most of the women will spend 1/3 of their life time in the post menopausal period. Therefore apart from management of the menopause related medical problems emphasis should be given on dietary adjustment to fulfill the best potential of the woman's life. Dietary supplementation of micro nutrients is essential for improving their bone mass potential and physical fitness.

Calcium and Vit D: - Post menopausal woman's bone mineral density (BMD) depends on peak bone mass, age at menopause and the rate of calcium loss. Out of these three factors peak bone mineral density is most important factor in the development of post menopausal osteoporosis. Peak BMD depends on the amount of bone mass achieved in young age. There is a clear benefit of calcium and vit D supplementation in post menopausal women as it preserves bone mass, decreases bone turnover⁽¹⁾. Meta analysis of 20 controlled trials of calcium therapy in post menopausal women showed that mean rate of bone loss was 1.17% and 0.13% per year ($p < 0.001$) in 625 untreated women and 857 calcium supplemented women respectively.⁽²⁾



Recommended daily dietary intake of calcium is 1000-1500 mg/day. Increased vit D intake in elderly women when given with calcium preserves bone mass and reduces fracture rate. In double-blind placebo controlled trial, 187 post menopausal women were randomly given 1000 mg calcium per day or 1000mg calcium together with 10000 U vit D. BMD was measured in the forearm, lumbar spine; femoral neck. There was no difference in the change in the BMD between the subjects taking calcium alone or calcium with vit D combined.⁽³⁾



There are insufficient data to show that vit D without calcium supplementation has a protective effect on bones. A supplement of 400-1300 IU of vit D/day is recommended for women who cannot spend 30 minutes/day in sun⁽⁴⁾



Anti-oxidants nutraceuticals:-

Nutraceuticals are nutrients that not only maintain, support and normalize physiological or metabolic functions but also potentiate or antagonize them. Antioxidant nutraceuticals glutathione, selenium and Vit C and E undoubtedly influence and improve many disease process. More research is required in order to clarify the role and importance of these natural substracts with respect to menopausal symptoms and post menopausal health.

Vit C: - Cardiovascular disease is a leading cause of death in post menopausal women. Results from prospective investigatons of the relations between vit C intake and risk of CHD have been inconsistent to date. In 1980, 85118 women were assessed for their vit C intake and other nutrients. They were followed for 16 years for development of CHD –there was a modest significant inverse association between total intake of vit C and risk of CHD (RR 0.73 ;95% cl 0.57-0.94)⁽⁵⁾



Vit E:- It is potent anti oxidant .It prevents oxidation of LDL cholesterol ; so helps In preventing coronary artery disease.600 IU of vit E is recommended for reducing the risk of CAD⁽⁶⁾

**Magnesium: -**

Adequate intake of magnesium is crucial for osteoporosis prevention. Magnesium deficiency can reduce calcium absorption and retention. Magnesium intake of 600 mg is sufficient to maintain an adequate magnesium reserve in bone.

B6, B12 and folic acid: -

Postmenopausal women are more likely to develop Alzheimer's disease than men. This could be because of estrogen deficiency. It has got neuroprotective effects on the ageing brain by protection against beta-amyloid formation, oxidative stress and vascular disease possibly by improving the blood supply and reducing cholesterol. Elevation of homocysteine levels are directly toxic to the vascular endothelial cells – which is one of the important cause of Alzheimer's disease, so adequate intake of B6, B12 and folic acid from the diet will help in conversion of homocysteine to methionine. Phytoestrogens will help in prevention of oxidative stress toxicity.⁽⁷⁾

**Phytoestrogens: -**

Plant based estrogens or Phytoestrogens are used to produce estrogenic effects. Isoflavons and lignans are very popular supplements among the general public. Flex seed, linseed, whole gram cereals are major source of dietary lignans. Legumes such as soyabeans and cloves are a major source of isoflavons 1gm of soya protein gives 1.3 mg of isoflavons. In japense and Chinese women incidence of menopausal symptoms, cardiovascular problems, osteoporosis, endometrial and breast cancer is less as they consume a diet high in isoflavons. Eden(1998) suggests that hot flushes maybe helped by increasing intake of phytoestrogen in daily diet. They are not much helpful for vaginal dryness. In nutritional therapy bioflavonoids combines with vit C, thought to be more effective in

The Menopause **FOGSI** Focus

controlling hot flushes. Mechanism could be - toning of the blood vessels and thereby preventing excessive vasodilatation & consequent sweating, a process normally achieved by circulatory estrogen.

In another study of 40 Gms of soya /day during a 6 month trial revealed an increase in the bone density of 2.2%. Soya protein decreases serum concentration of total cholesterol and triglycerides.⁽⁸⁾ More scientific work on the amount of soya intake that will reduce the risk of cardiovascular diseases, osteoporosis, menopause related symptoms is clearly warranted.

To conclude, for the physical fitness a post-menopausal woman must consume fat free milk, green vegetables, fruits for vit E; dark green leafy vegetables for beta carotene; yellow orange colored vegetables for vit C; amala, citrus fruits, for protein and omega 3 fatty acids ragi, fish, legumes and soybeans in proper proportion.

Apart from this **physical activity** is essential to improve her health outcome.

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24

Holistic Approach to Menopause Exercise in Menopause “How Soon - How Far”

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Menopause is no pause, it is just a continuous life cycle of a woman where some physiological changes are occurring but if we are not careful we can change this phase into a pathological one.

In Holistic approach to menopause mainstay is life style modification not only for Quality of life but also for prevention of diseases.”

Goal and Purpose of Menopause Management

- Health promotion
- Disease prevention
- Disability postponement

And all these can be achieved with timely intervention of exercise and proper diet and calcium and Vit. D

In this mechanized world the only muscles we are moving are our finger tips for various controls and only weight we are carrying is our own body weight so no doubt avoidable morbidity and mortality in all age groups but more so in aging is increasing.

Physical exercise involves many types of exercises but somehow in the present scenario a lay man and for medical practitioners also it just means walking and yoga. But we have to go beyond walking and yoga and strength building exercises to have the maximum impact of exercise.

Advantages of exercise in menopause are many fold and when to start would depend upon what is the clinical problem we are trying to prevent .But as a general rule earlier we start the better it is.

Aging is a complex process involving many variables (e.g., genetics, lifestyle factors, chronic diseases) that interact with one another, greatly influencing the manner in which we age.

- Participation in regular physical activity (both aerobic and strength exercises) from adolescence itself elicits a number of favorable responses that contribute to healthy aging and healthy menopause. Various biological systems of our body respond to exercise and knowledge about these is increasing day by day... Participation in a regular exercise program is an effective intervention/ modality to reduce/prevent a number of functional declines associated with aging.
- Land mark of aging when in our body degenerative changes start is at about mid thirties say around 35 years and beyond .Till the age of 25 years we gain our maximum bone mass and from 25 to 35 years it is a plateau , from 35 onwards age we start losing our muscle mass and our BMD. We lose

The Menopause **FOGSI** Focus

muscle mass at the rate of about 0.4% per year and bone mass at the rate of 0.5 to 0.75% per year and around the year surrounding menopause this loss increases to even 2-4 % per year. It is not only muscle and bone which women lose they lose their collagen tissue also. So if we have not started life style modifications early at least to prevent sarcopenia and osteoporosis we must start at the age of 35 years for reversal of process or slowing down of degenerative changes. For this we have to add strength building and resistance training in our schedule.

- More ever older individuals (including onto- and nonagenarians) **adapt and respond to both endurance and strength training.** Endurance training can help maintain and improve various aspects of cardiovascular function (as measured by maximal VO₂, cardiac output and arteriovenous O₂ difference); as well as enhance sub maximal performance this means that strength and stamina are both increased. **Therefore it is never too late to start.**
- Importantly, reductions in risk factors associated with disease states (heart disease, diabetes, etc.) improve health status and contribute to an increase in life expectancy.
- Kyphosis in menopausal women is a combined effect of weak extensor muscles along with micro fractures of spine because of osteoporosis and women would have to strengthen their back extensors with isotonic exercises along with antiresorptive treatment and Vit.D D and calcium to have the maximum effect.
- Some of the studies also suggest that involvement in regular exercise can also provide a number of psychological benefits related to preserved cognitive function, alleviation of depression symptoms and behavior, and an improved concept of personal control and self-efficacy. Intensity and frequency of hot flushes is also decreased.
- It is important to note that while participation in physical activity may not always elicit increases in the traditional markers of physiological performance and fitness (e.g., VO₂max, mitochondrial oxidative capacity, body composition) in older adults, it does improve health (reduction in disease risk factors) and functional capacity.
- Those who are exercising regularly in them all time mortality are reduced.
- Helps in osteoarthritis in reducing pain, increasing range of motion and increasing thick ness of cartilage.
- Doing exercise in perimenopause and menopausal period reduces incontinence in women at risk of diabetes. In one study it was seen that 38.3% of the women in the lifestyle intervention group had stress or urge incontinence, compared to 48.1% of women on metformin and 45.7% of those on placebo. Stress incontinence was more decreased. Most of the difference in rates of incontinence was attributable to weight loss.
- According to a literature review by Kramer and Wells (1996) sufficient evidence has accumulated to warrant an analysis of the relationship between physical activity and estrogen-dependent cancers like breast and endometrium. The mechanism involved may be any one of the following



- 1) Maintenance of low body fat and moderation of extra glandular estrogen,
- 2) Reduction in number of ovulatory cycles and subsequent diminution of lifetime exposure to endogenous estrogen,
- 3) Enhancement of natural immune function,
- 4) Association of other healthy lifestyle habits.

It is a very well known fact that sooner the better, but for many menopausal conditions women can start even late .

BETTER LATE THAN NEVER

Thus, the benefits associated with regular exercise and physical activity contributes to a healthier, independent lifestyle, greatly improving the functional capacity and quality of life in this population.

Types of Exercises:

Exercises are of following types:

- Aerobic like walking, swimming, these mean repetitive movements of major muscle groups
- Strength building like weight training , and resistance training
- Endurance building brisk walking and weight training.
- Range of movement and stretching exercises e.g. yoga and taichi
- Balance training like taichi and dance.
- Meditation for psychological health



Whenever exercising intensity of exercise is very important and it should be moderate or vigorous intensity .

How Soon?

Prevention should be started as early as possible as quality of bone is better if life style modifications and exercise are started early in life .Some of important facts are:

- Before puberty, bone mineral density in boys and girls is similar.
- However, adolescent females achieve peak bone mass at 11 to 14 years of age and it rapidly declines thereafter,
- Adolescent males continue to increase bone mass until 15 to 16 years of age and then follow a slower subsequent decline
- Central hormonal factors such as estrogen, appropriate nutrition and local mechanical forces positively affect bone mass during growth and development.
- Weight bearing exercises during puberty may improve bone mineral content and result in a greater peak bone mass, which may delay the age at which the osteoporotic fracture limit is reached .Even doing 50 skipping per day is found to give a better bone quality and delays osteoporosis.
- Prolonged periods of inactivity during youth result in higher osteoclastic activity and bone atrophy, which may have a serious negative impact on peak bone mass.
- Sedentary lifestyles in childhood may, therefore, contribute to increasing rates of osteoporosis and its complications later in life.
- To improve good bone health, physicians should recommend appropriate nutrition, including an age-appropriate vitamin D and calcium

The Menopause **FOGSI** Focus

- Regular weight-bearing physical activity and avoidance of tobacco use.
As far as heart risk is concerned we have to check weight and waist ratio even earlier at 3-4 years of age.

If we consider in utero origin of diseases then proper maintenance of BMI during pregnancy is essential so that neither underweight nor overweight children are born.

So exercise is advised during pregnancy also.

Heart risks are being detected by age 7 in overweight kids

Children at risk of future obesity should be examined for body mass index

Rebound. BMI:

Rebound is the age at which body mass index (BMI) reaches its lowest point before increasing through later childhood, adolescence and adulthood. An earlier BMI rebound age is associated with adverse risk factors for heart disease as measured at age 7: higher BMI, higher systolic and diastolic blood pressures, higher serum insulin and leptin levels, higher left ventricular mass and left atrial size. Early BMI rebound age for children is lower than 4.4 years for boys and 4.2 years for girls. Normal values are 4.4 to 6.6 years for boys and 4.2 to 5.7 years for girls. All children who start gaining weight between 3-4 years should be classified as a high risk for future diabetes and heart disease.

This study proves the point that maybe we should start with assessing risk factors much earlier and there comes the corollary that life style modifications like diet and exercise should start very early in life.

How Far:

For prevention of osteoporosis as Bone requires the mechanical challenge of physical activity to remain strong and healthy. An active lifestyle plays an important part in both preventing and treating osteoporosis.

Early prevention:

Achieving a high peak bone mass during childhood and adolescence provides a good foundation for skeletal health in later life. Impact activities such as walking, jogging, soccer, tennis, skipping and dancing help to build a strong skeleton.

BMD preservation in adults:

In early and middle adulthood, the main objective is to maintain bone mineral density. Integrating seasonal and leisure activities into an exercise routine will help to keep up an active lifestyle.

In impact weight-bearing exercises (e.g. jumping, running, racquet sports, step classes), the effect of gravity creates a force that loads and challenges the bones, thus helping to build BMD and prevent osteoporosis. Likewise, muscle strengthening (resistance) exercise has a beneficial effect: when a muscle contracts, it stimulates the bone to which it is attached.

Two sets of eight to 12 repetitions of each exercise twice a week are enough.



Post menopause Women:

They experience significant bone loss immediately after menopause. But research has shown that doing specific exercises (impact weight-bearing and muscle strengthening), especially when combined with appropriate pharmacologic and dietary interventions, can slow down the rate of loss. If bone loss in the spine is minimal and the risk of spinal fracture is low, Pilates and/or yoga can strengthen the back muscles and help maintain good posture.

In the later postmenopausal years, the osteogenic response of bone to exercise is diminished because first, older women are frequently unable to participate in exercise that is vigorous enough to stimulate bone, and second, the response to exercise is not as robust as in premenopausal females. Weight-bearing exercises remain important, although more to minimize bone loss than to increase BMD.

The primary goal of exercise in this age group is to prevent falls and fractures. The specifics of the exercise program need to be based on overall health status (e.g. presence of arthritis, CVD or other medical conditions), balance and the degree of bone loss. Routines that incorporate balance and coordination (such as tai chi and dancing) can be helpful in preventing falls and fractures.

Muscle strengthening exercises:

Large muscle groups, (including back extensors) are also important to improve posture. These can help maintain function and independence and minimize height loss and rounding of the back (kyphosis) caused by compression fractures.

People who have advanced osteoporosis (especially if there is a previous history of spinal fracture) should avoid activities that load the spine during positions of flexion and/or rotation, since these increase the risk of sustaining a vertebral compression fracture.

The following movements should be avoided or done with caution:

- Forward bending of the spine, e.g. toe touches traditional abdominal sit-ups twisting movements (e.g. golf swing)
- Heavy lifting (especially using incorrect techniques such as bending at the waist instead of the knees)
- Yoga positions requiring extremes of spinal flexion

It is always advisable for your patients with osteoporosis to consult a healthcare professional with an expertise in this area (e.g. physical therapist), to help them establish an appropriate routine based on the degree of bone loss and their individual needs.

Studies in old people's homes were done by Fiatarone et al and they showed that it is never too late to start exercising.

- Positive effects of exercise especially strength building exercises have been seen in as old as hundred years. Women can start these exercises as late as 100 years of age and can still get the benefit of exercise by gaining muscle strength. By doing these exercises they were able to perform their routine daily activities and strength and stamina increased for walking and other activities.
- Various studies have proved now that Postmenopausal women who maintain a regular, moderate to vigorous exercise program reduce their risk for breast cancer, even if they did not exercise in the past.
- Women who exercise even after cancer breast treatment have a better quality of life.



The Menopause **FOGSI** Focus

So benefits of exercise start from very early life and go until the time you want to stand erect.

But it is a continuous process so for optimal results aging population should make it an integral part of their life like brushing of teeth.

Everybody should have at least a pair of dumbbell at home so that minimum required exercise can be done.

Exercise Prescription for Total Health in Adults:

- Moderate to severe aerobic activity or brisk walking for 150 min per week or 30 min /day for 5days in a week
Always banking of these activities can be done that means small 10 minutes episodes of activity can be accumulated during a day
- Strength and stamina building exercises should be added for 2 or 3 times in a week of 20 min per session. These exercises should cover all the major muscle groups of body. These exercises can be combined with balancing exercises.
- Meditation and stretching exercises like Yoga should also be included and can be done as a warm up exercise.

Conclusion: Exercise should be made an integral part of life but if not early then start at 35 plus and if not at that time at any age it would be effective and fruitful.

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India is a land of great diversity. There is not only a cultural and traditional divide but also a great difference in the rich and poor, the urban-rural divide and the geographical landscape of the country also changes the life style, food habits and disease spectrum of the people. This large difference reflects upon the medical facilities as well - with state of the art hospitals in the urban cities to primary care centre's with bare minimal facilities in the villages.

To add to this is India's large population that has crossed the one billion mark with over 71 million men and 43million women over 60yrs of age. It is estimated that by the year 2026, more than 103 million women would be over 60yrs of age. The average age of menopause in India is 47.5yrs. presently and the life expectancy about 71yrs . This means that an average Indian woman would be spending about 23.5yrs of her age in menopause. Women's health is linked to family planning in India. Health programmes for women in India are designed and targeted towards reproductive health. (The RCH programme). The older women in India are a medically marginalised group. The medically deprived status of these older women who have reached menopause is a result of the thought of policy makers who have till very recently believed that once a woman's reproductive years are over she no longer needs any specific programmes

With the entire world now waking up to the realization of ageing and the problems that come with this, most world organizations and governments are now gearing up to the needs of geriatric medicine and prophylactic screening programmes for this age group. The Medical Council of India has also issued directives to all medical colleges to have mandatory menopausal clinics in order to cater to the special needs of this group of patients. However, seeing the great diversity that exists in the populations across the country, no definite guidelines have been issued for setting up such a clinic.

This paper attempts to collate the ideas and thoughts of various nations in order to set up **An ideal one stop menopause clinic for the women of India.**

Clinical need :

Essentially these clinics are meant for women who are either approaching (perimenopausal) menopause or are already in their menopause. Perimenopausal women may seek only counseling in order to prepare them for menopause.

The clinic should offer comprehensive patient friendly services under one roof. The medical, para medical and non medical staff must be well informed and updated in menopausal health, they must be sympathetic to the patients and essentially give the same information to them so that the patient is not confused.

The Menopause **FOGSI** Focus

There are three types of patients who would be attending these clinics:

- Symptomless women seeking screening/counselling only
- Women who have problems pertaining to menopause
- Women who have allied problems as well e.g. heart disease.

The Clinic would ideally have to address the following:

1. Evaluating the needs of the individual patient
2. Identification of her menopausal symptoms and evaluation of risk factors
3. Detection of any pathological conditions
4. Treatment of complications

A one stop menopause clinic is therefore a multispeciality, multidisciplinary “centre” comprising of the following clinicians:

- Gynaecologist
- General Physician
- Endocrinologist
- Cardiologist
- Orthopaedic Surgeon
- Neurologist
- Physiotherapist/ yoga instructor
- Nutritionist
- Ophthalmologist
- Urologist
- Dentist
- Psychologist/counsellor

All these must be backed by a good laboratory, Dexa scan, mammography and an ultrasound.

However, passing through this long list of clinicians may be cumbersome and tiresome for elderly women who will soon shy away from this experience. In a govt. set up this would also be expensive for the exchequer and privately unaffordable for the patient. It is therefore mandatory for the gynaecologist to become a “primary care physician” or a specially trained “menopausal medicine practitioner” (training now being conducted by the Indian Menopause Society). Such specialised training will help to both identify problems and treat the simple ones by a single clinician.

Components of screening:

1. Detailed history
2. Detailed clinical examination
3. Yearly Pap smear
4. Ultrasound scan TVS for uterus and ovaries
5. Mammogram
6. Uterine and Endocervical sampling if required
7. Dexascan
8. Haemogram, LFT, Lipid profile, Blood sugar
9. Urine, Stool exam.
10. Special tests like Thyroid profile, FSH, Estradiol if required.





Treatment:

1. Counselling: Counselling is a very important and integral part of a menopause clinic. The patient needs to be counseled preferably in her own language, on the following aspects :
 - The process of menopausal aging and what to expect as she ages
 - The current treatment available for her problems and the side effects
 - Advice on nutrition and life style.
 - Need for yearly screening and follow up

The clinic must have lots of reading material, pamphlets and visuals to inform the patients about all these aspects of menopause. These must be constantly updated in order to share the latest information with the patients.

2. General treatment like vitamins and minerals: Calcium and vitaminD etc.
3. Specific treatment for condition detected
4. Referral to a specialist when required.

It is important for every clinician dealing with elderly women to know that they may require lower dose of medication if they are frail or have a low BMI and drug interaction must be well known before prescribing since they may be on more than one drug for their ailments.

Follow up : Every woman must be asked to come for follow up each year to review her condition and to change/ update her medication if required. A closer follow up e.g. 3-6 months may be required in special cases and must be clearly explained to the patient. If the patient is being put on some treatment e.g. HRT for the first time, she must be called within a month or earlier to review her acceptability and tolerance to the medication and dosage.

Record Keeping: Record keeping, documentation and patient recall system must be perfect so that long term follow up is also possible.

Use of Internet: For the urban literate patients, a clinic website, email services may go a long way in making the clinic truly one stop. All interaction can be carried out on email and may thus save a lot of time. It may also be possible to set up a helpline through this medium or on phone.

Non health needs:

The aging women would have many non health needs which also need to be highlighted and explained by the physician since this is an opportunity to meet this group. The greatest need is to make them aware of housing and environment in order that they do not fall while walking. Non slip flooring and supports in the toilets are essential to prevent hip fractures. Women must be cautioned and trained to meet this challenge. Social support and a caregiver network are also very important to help some of these women tide over the acute stress and depression that they may be going through.

Every clinician wanting to set up a menopausal clinic must ensure that the patient visits are minimal and maximum benefit is gained through just one primary visit each year. A comprehensive, friendly approach would go a long way in popularizing such a venture.

The Menopause **FOGSI** Focus

26

Prevention of Cancers in Menopause



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Introduction :

Menopause is a transition with certain hormonal changes in body. Menopause itself is not associated with an increased risk of developing cancer. However, incidence of most of genital cancers does increase with age and so as with menopause. In addition, changing hormonal milieu of body and use of certain drugs to manage menopausal symptoms may increase or decrease a lady's cancer risk. Many reproductive tract malignancies are preventable. The obstetrician-gynecologist play an important role in counseling patients on lifestyle factors that can reduce the risk of cancer by not smoking, eating high fiber foods, restricting fat intake, exercising daily, pay attention to body changes, and getting regular health check-ups. In this chapter the modalities, which can be used as preventive measures or as screening tools to prevent or to diagnose these malignancies at an early stage, are reviewed.

Endometrial Cancer : Menopause age group constitutes major subset of cancer endometrium patients. Screening of all menopausal females without any symptoms is not recommended. Only high risk patients presenting with post menopausal bleeding, as it is the most common presenting symptom for the endometrial carcinoma precursors and frank malignancies, are to be screened⁽¹⁻³⁾.

Detailed history taking is recommended to exclude any drug intake like HRT and Tamoxifen and finding out high risk factors such as nulliparity, diabetes, obesity, hypertension and the use of unopposed oestrogens⁽⁴⁾.

Bimanual pelvic examination comes next which should be followed by transvaginal ultrasonograph (TVS) if required. On TVS, endometrial thickness of 4mm is the cut-off for further evaluation of endometrium⁽⁵⁾.

For endometrial sampling D & C should no longer be used as a first line investigation because of its low sensitivity^(6,7). Office hysteroscopy with directed biopsy is the gold standard whenever facilities are available.

Females using Tamoxifen should be followed up with more frequent gynecological examination because of 2-6 fold increase risk of endometrial cancer, although regular endometrial sampling is not recommended. Nonetheless, patients presenting with abnormal uterine bleeding should be thoroughly investigated using hysteroscopy and biopsy as first line investigation^(8,9).



Hormone replacement therapy (HRT): ACOG (2004) recommends (grade A) combined HRT can be used for short duration to relieve acute menopausal symptoms with no increased risk of endometrial carcinoma, however, unopposed estrogen is not to be used in women with intact uterus because of increased risk of endometrial carcinoma⁽¹⁰⁾.

Cervical Cancer: According to American cancer society, with a regular 3 yearly Pap smear screening, 70 yrs is the appropriate age of exit from routine cervical cancer screening in women who had 3 or more normal Pap smear in a row and with no abnormality during last 10 yrs.

Pap smear is less efficient at detecting cervical intra-epithelial neoplasia 3 (CIN 3) in older women, more smears are required to detect a case of CIN3 after the age of 50 years,⁽¹¹⁾ but it is more efficient at preventing invasive cancer⁽¹²⁾.

New recommendations are awaited regarding frequency of cervical screening with the possible use of universal HPV screening and during post HPV vaccination era.

Ovarian cancer: Ovarian cancer is the deadliest of all genital cancers mainly because of its late presentation. There is no role of OCPs chemoprevention and prophylactic oophorectomy in menopause age group which is meant for hereditary ovarian cancers that occurs in younger age group.



A variety of modalities have been used to detect ovarian cancer in asymptomatic women and preventing progression to advanced disease:

Pelvic examination: As a screening tool for early stage disease pelvic examination lacks both sensitivity and specificity⁽¹³⁻¹⁵⁾.

Tumor markers: The most extensively investigated is CA125; a cut-off of 35IU is most commonly used. As most of the benign conditions causing increase in CA125 can be excluded in menopausal age group and it is the serial value which is useful, therefore using an algorithm incorporating age and rate of change of CA125 as well as absolute value can be an important progress⁽¹⁶⁾. The use of a combination of markers to increase sensitivity and specificity has been extensively investigated and some of them include CA72-4 (TAG 74), M-CSF, OVX1, LPA, prostacin, osteopontin, inhibin and kallikrein⁽¹⁷⁾. The use of panel of markers as a first-line test in ovarian screening is an attractive concept.

Ultrasound: Although ultrasound alone is not a good modality to detect ovarian cancer in terms of sensitivity and specificity, addition of morphologic index and color flow doppler imaging has enhanced sensitivity and specificity of these modalities^(18,19).

Multimodal screening: various studies⁽²⁰⁻²¹⁾ have shown that the highest positive predictive value can be achieved with multimodal screening, using CA125 as a first-line test, followed by ultrasound if CA125 is abnormal. The use of multimodal screening to detect early ovarian cancer has three main advantages: first, using serum screening as a first line test reduces cost. Second, reserving ultrasound as a secondary test reduces the number of women undergoing transvaginal assessment. Finally, combining different modalities can achieve sensitivity and specificity comparable to that of the most sophisticated protocols utilizing color flow Doppler ultrasound and morphological indices.

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Risk of malignancy index I & II: RMI score=ultrasound score x menopausal score x CA 125 levels in IU/ml

RMI I & II have been introduced, three studies have compared the two RMI scoring schemes, using cut-off RMI score above 200 to indicate high malignancy risk (22, 23). Because of its greater sensitivity, specificity and simplicity, RCOG and ACOG both have recommended use of RMI II for assessment of an ovarian mass to detect ovarian carcinoma at an early stage, therefore improving overall survival rates.

Breast Cancer: Both American cancer society (ACS) and ACOG recommends annual mammography after the age of 40 yrs in an average risk female ⁽²⁴⁾.

Following the release of World Health Initiative data, published in July 2002⁽²⁵⁾ there were concerns regarding use of hormone replacement therapy (HRT) and increased risk of breast cancer. ACOG (2002) recommends that HRT should not be initiated solely for the purpose of prevention of coronary heart disease and should be used for shortest possible duration for amelioration of menopausal symptoms.

Vulvo-vaginal Cancer: Although cancer vulva and vagina are rare, there is a defined premalignant phase called vulvar intra epithelial neoplasia (VIN), and vaginal intraepithelial neoplasia (VAIN) respectively, if identified and managed properly, prevents the development of invasive cancer.

Regular gynecological examination, clinical inspection and biopsy are the hallmark of early diagnosis of high risk vulval lesions. Visual inspection with colposcopy after application of acetic acid is useful. Because of keratinized squamous epithelium of vulva acetic acid needs to be put longer than in cervical lesions, generally it is for five minutes of 5% acetic acid. Extensive evaluation with the colposcope, including perianal region is needed to rule out multicentric lesions.

Pap test screening for vaginal cancer is recommended for women with history of hysterectomy for cervical cancer and CIN.

Colo-rectal cancers: As 90% of population with colorectal carcinoma is above the age of 50 yrs, therefore ACOG (2007) recommends every 10 yearly screening preferably with colonoscopy after the age of 50 yrs, which need to be earlier and more frequent if risk factors are present.

Conclusion: Menopause is the period during which a lady is confronted with multiple changes in her body system because of the changing hormonal milieu, besides her age being the risk factor for developing several genital and non-genital malignancies. Most of these malignancies are not ideally fit for the screening, however early detection can be as good as it would improve their quality of life immensely and the overall survival. To conclude, annual gynecological examination of menopausal age group patients is the single most intervention that needs to be implemented for the best possible results.





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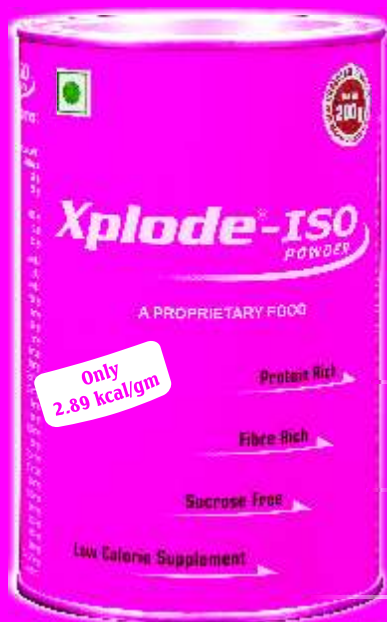


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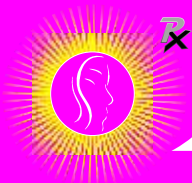
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