

QUARTERLY MEDICAL REVIEW

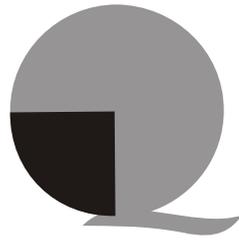
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Current Trends in Management of Menopause

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INTRODUCTION:

The onset of the menopause means permanent cessation of menstruation at the end of reproductive life due to loss of ovarian follicular activity. In other words, menopause is the state in which the ovaries become unresponsive to gonadotropins with advancing age and their function declines resulting in an absence of

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menstrual function. The clinical diagnosis is confirmed following stoppage of menstruation for six consecutive months. As such a woman is declared to have

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attained menopause only retrospectively. Climacteric is the physiologic period when there is regression of the ovarian function and transition from a reproductive to a non reproductive phase in women's life. This is also referred to as the Perimenopause.

The process of menopause does not occur overnight, but rather is a gradual process.

The so-called perimenopausal transition period is a different experience for each woman. This time of change is known as the menopausal transition, and is also called perimenopause by many women and their doctors. It can begin several years before the last menstrual period and lasts for 1 year after the last period. Perimenopause, often accompanied by irregularities in the menstrual cycle along with the typical symptoms of early menopause, can begin up to 10 years prior to the last menstrual period. In the years prior to menopause those encompass the symptoms associated with normal menstrual cycles. This period is marked by irregularity of menstrual cycles.

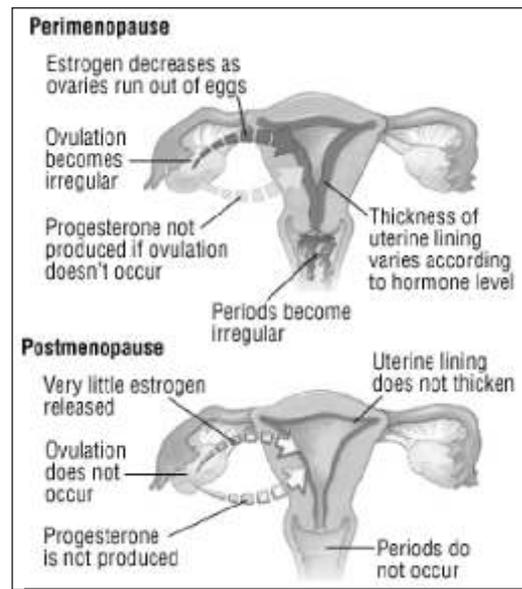
The age at which menopause occurs is genetically predetermined. The mean age of onset of menopause in Indian women is about 44.3 years. In the western world the age range for menopause is between 40 and 61, and the average age for the last period is 51 years. Smoking and severe malnutrition may cause early menopause.

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Two types of menopausal states exist. i.e: physiological menopause and surgical menopause. Physiologic menopause is the result of gradual depletion of functional oocytes within an ovary. Artificial or induced menopause occurs due to either chemotherapeutic agents, extensive irradiation, surgery, infections or in some cases neoplasia when oophorectomy is performed. In rare cases, a woman's ovaries stop working at a very early age, ranging anywhere from the age of puberty to age 40, and this is known as premature ovarian failure.

Spontaneous premature ovarian failure affects 1% of women by age 40, and 0.1% of women by age 30.

The stages of the menopause transition have been classified according to a woman's reported bleeding pattern, supported by changes in the pituitary follicle stimulating hormone (FSH) levels. In younger women, during a normal menstrual cycle the ovaries produce estradiol, testosterone and progesterone in cyclical pattern under control of FSH and leutinising hormone (LH) which are by the pituitary gland. Blood estradiol levels remain relatively unchanged, or may increase approaching the menopause, but are usually well preserved until the late perimenopause. This is presumed to be in response to elevated FSH levels. However, the menopause transition is characterized by marked, and often dramatic, variations in FSH and estradiol levels, and because of this, measurements of these hormones are not considered to be reliable guides to a woman's exact menopausal status.



However, the menopause transition is characterized by marked, and often dramatic, variations in FSH and estradiol levels, and because of this, measurements of these hormones are not considered to be reliable guides to a woman's exact menopausal status.

In contrast to the sudden fall in estradiol during menopause, the levels of total and free testosterone, as well as dehydroepiandrosterone sulfate (DHEAS) and androstenedione appear to decline more or less steadily with age. An effect of natural menopause on circulating androgen levels has not been observed. Thus specific tissue effects of natural menopause cannot be attributed to loss of androgenic hormone production.

Natural or physiological menopause occurs as a part of a woman's normal aging process. It is the result of the eventual depletion of almost all of the oocytes and ovarian follicles in the ovaries

Natural or physiological menopause occurs as a part of a woman's normal aging process. It is the result of the eventual depletion of almost all of the oocytes and this causes an increase in circulating (FSH) and (LH) levels because there are a decreased number of and follicles responding to these hormones and producing estrogen. This decrease in the production of estrogen leads to the perimenopausal symptoms of hot flashes, insomnia and mood changes. Long term effects may include

osteoporosis and vaginal atrophy .

Titus et al. proposed an explanation for the depletion of the ovarian reserve during aging. They found that as women age, double-strand breaks accumulate in the DNA of their primordial follicles. Primordial follicles are immature primary oocytes surrounded by a single layer of granulosa cells. An enzyme system is present in

oocytes that ordinarily accurately repairs DNA double-strand breaks. This repair system is called “homologous recombinational repair”, and it is especially effective during meiosis. Meiosis is the general process by which germ cells are formed in all sexual eukaryotes, and it appears to be an adaptation for efficiently removing damages in germ line DNA.

Human primary oocytes are present at an intermediate stage of meiosis, termed prophase I. Titus et al. further demonstrated that expression of four key DNA repair genes that are necessary for homologous recombinational repair during meiosis (BRCA1, MRE11, Rad51, and ATM) decline with age in oocytes. This age-related decline in ability to repair DNA double-strand damages can account for the accumulation of these damages, that then likely contributes to the depletion of the ovarian reserve.

SYMPTOMS OF MENOPAUSE

During the menopause transition years, as the body responds to the rapidly fluctuating and dropping levels of natural hormones, a woman may experience a variety of symptoms. Not every woman is affected; and the range of effects and degree to which they appear varies from person to person.

Effects that are due to low estrogen levels (for example vaginal atrophy and skin drying) will continue after the menopause transition years are over; however, many effects that are caused by the extreme fluctuations in hormone levels (for example hot flashes and mood changes) usually disappear or improve significantly once the perimenopause transition is completely over.

All the various possible perimenopause effects are caused by an overall drop, as well as dramatic but erratic fluctuations, in the absolute and relative levels of estrogens and progesterone. Effects such as

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formication (crawling, itching, or tingling skin sensations), may be associated directly with hormone withdrawal. Symptoms vary from woman to woman. They may last 5 or more years. Some women may have worse symptoms than others. Symptoms of surgical menopause can be more severe and start more suddenly. The first thing noticed is the change in the pattern of menses. They might occur more often or less often. Some women might get their menses every 3 weeks. This might last for 1 - 3 years before the menses completely stop.

Symptoms of menopause include:

- Menstrual periods that occur less often and eventually stop
- Palpitations
- Hot flashes, usually worst during the first 1 - 2 years
- Night sweats
- Skin flushing
- Sleeping problems (insomnia)

Other symptoms of menopause may include:

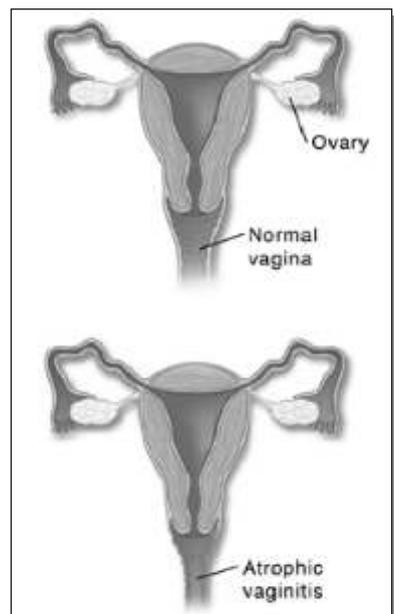
- Decreased interest in sex, possibly decreased response to sexual stimulation
- Forgetfulness (in some women)
- Headaches
- Mood swings including irritability, depression, and anxiety
- Urinary incontinence
- Vaginal dryness and painful sexual intercourse
- Vaginal infections
- Joint aches and pains
- Irregular heartbeat

Vasomotor Symptoms:

The characteristic symptom of menopause is 'hot flush' which begins usually as a pressure symptom in the head in most women. It is a sudden onset of feeling warmth followed by sweating and infrequently associated with weakness, fatigue and vertigo; and may occur in as many as 75% of women and last for as long as 40 years. Low oestrogen level is a prerequisite for hot flush. It coincides with GnRH (LH) pulse secretion known as circorhal secretion. It lasts only for 1-2 minutes and maybe at times unbearable. It is frequently associated with profuse sweating. Sleep may be disturbed due to night sweats. There is peripheral vasodilation with the patient experiencing palpitations and the pulse rate rising by upto 20 beats per minute. The thermoregulatory centre in association with GnRH centre in the hypothalamus has been implicated as a cause of hot flushes.

Urogenital atrophy:

It involves lack of oestrogen support to the vaginal mucosa and the bladder. Symptoms such as thinning of the membranes of the vulva, flattening of



the vaginal epithelium, cervical atrophy, and also the outer urinary tract, along with considerable shrinking and loss in elasticity of all of the outer and inner genital areas are seen. Also there is itching and dryness in the vaginal region leading to dyspareunia or painful sexual intercourse. Atrophy of layers of the uterus also occurs leading to a shrinkage in size and altered consistency of this pelvic organ. Both the endometrium and myometrium thin out and as a result lead to the reduction in size of uterine myomas, adenomyosis and endometriotic lesions if present. Women approaching menopause may experience dysfunctional bleeding due to the hormonal changes that accompany the menopause transition.

In post-menopausal women, genital bleeding is an alarming symptom that requires an appropriate study to rule out the possibility of malignancy, however, spotting or bleeding may be related to a benign sore (polyp or lesion) or functional endometrial response. Other symptoms such as watery discharge, urinary frequency and urgency due to atrophic cystitis, increased susceptibility to inflammation and infection, for example vaginal candidiasis, and UTI are also experienced. Urinary incontinence may worsen the menopause-related quality of life, although urinary incontinence is more related to obstetric events than to menopause. Loss of urethral tone may result in the pouting of the meatus and formation of urethral caruncle causing dysuria and hematuria and tenderness of the meatus.

Skeletal symptoms:

Following menopause there is a decline in collagenous bone matrix resulting in osteoporotic changes. Bone loss increases to 5% per year during menopause as a result of trabecular bone in sites such as the vertebral column and radius (colle's fracture) being sensitive to lack of estrogen. Osteoporosis is most severe in patients with induced menopause e.g: those undergoing oophorectomy. These may lead to back pain, loss of height and kyphosis. Fracture of bones is a major health problem and morbidity and mortality in elderly women following fracture is high.

Skin and soft tissue related symptoms:

Symptoms such as breast atrophy, breast tenderness and swelling, decreased elasticity of the skin, and formication (itching, tingling, burning, pins, and needles, or sensation of ants crawling) can be distressing. Growth of terminal hair over upper lips as a slight moustache and mild balding is seen. Disappearance of cysts and breast pain may be of great relief. Loss of elasticity of the skin around the mouth and eyes leads to wrinkling and furrowing.

Psychological symptoms:

During the phase of menopause women experience a number of psychological symptoms like depression and/or anxiety, fatigue, irritability, memory loss and problems with concentration, mood disturbances, sleep disturbances, poor or light sleep, insomnia, and daytime sleepiness. Cognitive decline may occur after the age of 65 years in part due to decreased oestrogen.

Sexual symptoms:

Sexual symptoms seen are dyspareunia or painful intercourse and decreased libido or desire to perform sexual intercourse.

INVESTIGATIONS DURING MENOPAUSE

Some investigations may be necessary to perform for diagnosis or to help in formulating a treatment plan. Here are the most commonly used investigations and their indications. The pap smear and mammography are strongly recommended as routine screening investigations for all women over the age of 40 years.

Investigations that can be performed:
1. Pap smear
2. Mammogram + Breast ultrasound
3. Hormone levels
4. Lipid profile and fasting glucose
5. Coagulation studies
6. Full blood profile, iron studies
7. Vaginal ultrasound
8. Bone assessment
9. Urodynamic assessment

1. Pap smear

Every two years

If had previous abnormal smear (LSIL or HSIL, or HPV changes) within the last two years

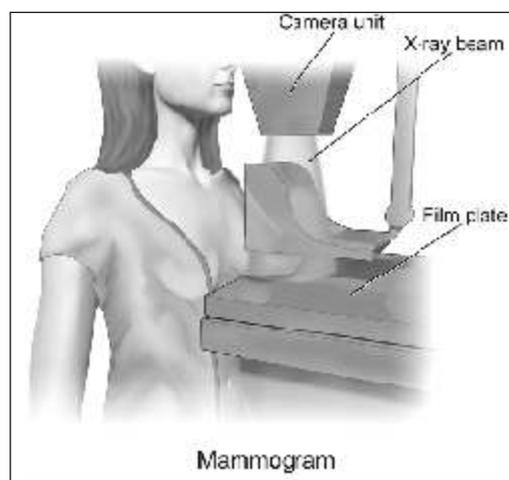
A vault smear every 2 years following hysterectomy if the woman has ever had an abnormal pap smear

If presents with abnormal vaginal bleeding

2. Mammogram ± breast ultrasound

Every two years over the age of 50 years and probably between 40-50 years particularly if post menopausal

If any breast abnormality is found on examination.



3. Hormone levels

FSH/Oestradiol levels:

Have limited use because of the variability day to day in the perimenopause (best taken in early follicular phase i.e. day three of cycle to assess reduced ovarian reserve).

On oral therapy are inaccurate and should not be used as a guideline for determining dosages. Where there is doubt in diagnosis e.g. after hysterectomy with no subsequent menstrual marker.

FSH may be helpful in determining between premature menopause and secondary amenorrhoea in the under - 40 age group.

To track absorption where implant therapy is used, also with implant tachyphylaxis and where absorption with patch or gel use is concerned.

Blood and urine tests can be used to look for changes in hormone levels. Test results can help your doctor determine if you are close to menopause or if you have already gone through menopause.

The levels of the gonadotropins increase in the menopause reaching maximum levels 1 to 3 years after cessation of the menses. FSH levels increase 10 to 20 fold while LH levels are approximately three times the premenopause levels. About 4 years after the menopause there is a slight decline in the peak levels reached. Androgens in the menopause show typical trends. The postmenopausal ovary secretes primarily androstenedione and testosterone however only half the amount of circulating androstenedione is derived from the ovary, the remainder being secreted by the adrenal gland. DHEA and DHEA So₄ are lower than premenopausal levels.

Testosterone levels:

May be appropriate when symptoms of loss of energy, libido and sexual function.

Measure in the morning and after day seven of the cycle; include total sensitive testosterone, and Sex Hormone Binding Globulin (SHBG) and free testosterone to evaluate non-SHBG bound level. A "sensitive" testosterone level may reflect the androgen status more accurately.

Thyroid Stimulating Hormone:

Indicated where there are symptoms of thyroid dysfunction or palpable thyroid, which may manifest around the time of the menopause.

4. Lipid profile & fasting glucose

Especially if risk factors or family history

5. Coagulation studies

Where past history of thrombo-embolism, particularly if spontaneous and/or less than 40 years.

Where family history or known familial disorder.

6. Full blood examination, iron studies

Where abnormal bleeding, especially menorrhagia.

7. Vaginal ultrasound

To assess endometrial thickness where there is abnormal vaginal bleeding: >4-5mm thickness in the post menopausal woman requires endometrial sampling either by endometrial biopsy or hysteroscopy and curettage.

To exclude endometrial pathology such as polyps or submucous fibroids.

To exclude pelvic pathology such as ovarian cysts or fibroids. Referral to a gynaecologist is appropriate for further investigations such as hysteroscopy and endometrial biopsy, where the ultrasound shows an increased endometrial thickening greater than 5mm in the post menopause, pelvic pathology or with any postmenopausal bleeding.

8. Bone Assessment

Bone Density:

There are different techniques for establishing bone density. The most reproducible form is the DXA (dual X-ray absorptiometry), which scans both the lumbar spine and the femoral neck. The test is indicated:

Where there are major risk factors for osteoporosis:

- Family history
- Inadequate amounts of calcium in the diet
- Cigarette smoking
- Alcohol - more than two standard drinks per day
- Caffeine - 5-6 cups/day
- Physical inactivity
- Thin, small body

Hormonal deficiency - late onset of menstrual periods under 16 years, early menopause under 45 years, testosterone deficiency in males.

Long-term use of certain medications such as corticosteroids for rheumatoid arthritis and asthma

Chronic health conditions - rheumatoid arthritis, thyroid disease, malabsorptive disorders, chronic liver disease, chronic kidney disease

Vitamin D deficiency

Bone Metabolism Tests:

Calcium, phosphate, 25hydroxy-vitamin D, thyroid function tests, parathormone when osteopaenia or osteoporosis is detected on bone density.

Urinary or serum bone turnover markers are still controversial. They are mainly used to assess the effectiveness of therapy for osteoporosis and are not recommended routinely.

9. Urodynamic Assessment

Where there is a history of stress and/or urge incontinence, to determine the severity and type of the incontinence. The result will aid in planning and managing the symptoms.

MANAGEMENT OF THE MENOPAUSAL WOMAN

Treatment for menopause depends on many things, including how bad the symptoms are, the overall health, and the patients preference. It may include lifestyle changes and/or hormone therapy.

A. DIET AND LIFESTYLE CHANGES

Hormones are not always needed to reduce symptoms of menopause. There are many steps one can take to reduce symptoms.

Diet changes:

- Avoid , alcohol, and spicy foods.
 - Eat soy foods. Soy contains oestrogen .
 - Get plenty of calcium and vitamin D in food or supplements.
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 - **Eat soy foods. Soy contains oestrogen**
 - **Get plenty of calcium and vitamin D in food or supplements**
 - **Exercise and relax**

Exercise and relaxation techniques:

- Daily exercise is advised for women with menopausal symptoms.
- Strengthen the muscles of your vagina and pelvis.
- Practicing slow, deep breathing whenever a hot flash starts to come on.
- One should try taking six breaths a minute.
- Yoga, tai chi, or meditation are frequently practiced methods for relaxation.

Other tips:

- Dress lightly and in layers.
- Keep having sexual intercourse.
- Use of water-based lubricants or a vaginal moisturizer during coitus.



B. HORMONETHERAPY

Hormone therapy is prescribed if a woman has severe hot flashes, night sweats, mood issues, or vaginal dryness. The patient should be explained about the benefits and risks of hormone therapy. The doctor should be aware of the patient's entire medical history before prescribing hormone therapy (HT).

HRT is the mainstay of treatment of menopausal symptoms which last for 2-5 years in most women. Physicians usually advise to use a 'cyclical combined HRT' preparation. These are of two types:

1. Monthly cyclical HRT - oestrogen is given every day, but progestogen is added for 14 days of each 28-day treatment cycle. This causes a regular bleed every 28 days, similar to a light period. (They are not 'true' periods, as HRT does not cause ovulation or restore fertility. The progestogen causes the lining of the womb (uterus) to build up. This is then shed as a 'withdrawal' bleed every 28 days when the progestogen part is stopped.) Monthly cyclical HRT is normally advised for women who have menopausal symptoms but are still having regular periods. The oestrogen moiety is taken daily and progesterone is added for 10 to 14 days of a month. This regimen mimics the menstrual cycle. A woman experiences withdrawal bleeding at the end of the progesterone.

2. Three-monthly cyclical HRT - oestrogen is given every day and then you also take progestogen for 14 days, every 13 weeks. This means that you have a bleed every three months. This is normally advised for women who have menopausal symptoms but are having irregular periods. Combined HRT. This contains both oestrogen and progestogen.

Routes of administration of HRT include oral medication, gels that one can put on the arms, shoulders or inner thigh every day and skin patches that you put on the back. Pessaries and vaginal rings are also available for use

They may be taken together or separately and the progestogen may be taken every day or for 10 to 14 days of each treatment cycle. The two hormones work in synchrony i.e.: oestrogen stimulates the endometrial lining of the uterus and the release of the egg while progesterone sheds the endometrium

3. Continuous combined therapy HRT. Both oestrogen and progesterone are taken every day. This is ideal for women who do not want to have bleeding or are very sensitive to the effects of progesterone (i.e.: breast tenderness, and bloating).

4 Oestrogen-only HRT. This formulation contains only oestrogen, which helps relieve symptoms of the menopause. However, this formulation causes an increase in the thickness of the endometrium and can lead to hyperplasia and endometrial cancer. This regime is suitable for women who have had a total hysterectomy. The absence of progesterone predisposes the woman from developing endometrial proliferation and cancer if the uterus is not removed.

Methods of taking HRT are as follows:

Routes of administration of HRT include oral medication, gels that one can put on the arms, shoulders or inner thigh every day and skin patches that you put on the back. Pessaries and vaginal rings are also available for use. There is no clear consensus about which delivery method is best. Patches or gels are better for those who have high triglyceride concentrations, are at increased risk of venous thrombosis – including those with hypertension, overweight or smokers, and those who may not absorb tablets adequately. Implants of oestrogen can be inserted underneath the skin over the area of the abdomen with the help of a local anesthetic spray. This implant can last for up to six months and should be replaced as soon as the woman experiences menopausal symptoms. The implant has advantages over other forms of administration as it avoids the liver and does not cause skin irritation as patches can. Because the oestrogen is not passing through the liver, the amount of oestrogen in the implant can be reduced.

Several investigational studies have questioned the health benefits and risks of hormone therapy, including the risk of developing breast cancer, heart attacks, strokes, and blood clots.

Current guidelines support the use of HT for the treatment of hot flashes.

Specific recommendations:

- HT may be started in women who have recently entered menopause.
- HT should not be used in women who started menopause many years ago, except for vaginal creams.
- The medicine should not be used for longer than 5 years.
- Women taking HT have a low risk for stroke, heart disease, blood clots, or breast cancer.

To reduce the risks of therapy, a lower dose or a different preparation (for instance, a vaginal cream or skin patch rather than a pill)

- Frequent and regular pelvic exams to detect problems as early as possible
- Frequent and regular physical exams, including breast exams and mammograms

If a woman has a uterus and decided does not make sense to take, she should also take to prevent cancer of the lining of the uterus (endometrial cancer). If she does not have a uterus, one does not need .

CONCOMITANT TREATMENT OR ALTERNATIVES TO HORMONE THERAPY

There are other medicines available to help with mood swings, hot flashes, and other symptoms. These include:

- Antidepressants, including paroxetine, venlafaxine, bupropion, and fluoxetine
- A blood pressure medicine called gabapentin, a seizure drug that also helps reduce hot flashes

What are the benefits of hormone replacement therapy?

HRT is a safe and effective treatment for most healthy women with symptoms, who are going through the menopause. The risks and benefits of HRT will vary according to age and any other health problems that a women may have.

1. Menopausal symptoms usually ease which can make a big difference to quality of life in some women.

- HRT works to stop hot flushes and night sweats within a few weeks.
- HRT will reverse many of the changes around the vagina and vulva usually within 1-3 months. However, it can take up to a year of treatment in some cases.

HRT can:

- Improve symptoms of vaginal dryness.
- Improve discomfort during sexual intercourse as a result of this vaginal dryness.
- Help to reduce recurrent urine infections.
- Improve any increased frequency of passing urine.
- There is some evidence that HRT itself improves mood or sleep.
- HRT may also help to improve joint aches and pains.
- HRT improves symptoms of vaginal dryness and improves sexual function in many women.

2. Reduced risk of osteoporosis

Women who take HRT have a reduced risk of osteoporosis and subsequently their risk of having fractures due to osteoporosis is also reduced.

3. Other possible benefits

The evidence regarding HRT and cardiovascular disease is still controversial. Recent evidence has demonstrated that HRT does reduce the incidence of cardiovascular disease in women who take HRT under the age of 60 years.

Some studies have shown a reduced risk of Alzheimer's disease and other types of dementia in women who take HRT. However, others contradict this fact, so more work needs to be done in this area. Investigative trials have also shown a reduction in risk of bowel cancer in women who take HRT. However, the evidence for this is still not completely clear.

What are the risks in taking hormone replacement therapy?

1. Venous thromboembolism

The risk seems to be higher with combined HRT compared to oestrogen-only HRT and the risk is also higher in the first year of HRT.

2. Breast cancer

Combined (oestrogen and progestogen) HRT has a higher risk than oestrogen-only HRT. The actual risk of breast cancer with taking HRT is actually very small. It equates to around one extra case of breast cancer per 1,000 women each year. This risk is similar to the risk of breast cancer in women who are obese, those women who have never had children and also those women who drink two to three units of alcohol each day.

3. Stroke

Some previous large studies have shown that there is a small increased risk of stroke in women taking either oestrogen-only or combined HRT. However, there does not appear to be an increased risk of stroke in women who take HRT under the age of 60 years. In addition, this risk is lower in women who use the patch (or gel) rather than tablets. HRT containing lower doses of oestrogen seems to be associated with a lower risk of stroke compared to those containing higher doses.

4. Coronary heart disease

The evidence regarding HRT and cardiovascular disease is still controversial. Recent evidence has demonstrated that HRT does reduce the incidence of cardiovascular disease in women who take HRT under the age of 60 years. Women over the age of 60 years have an increased risk of heart disease.

5. Endometrial cancer

There is an increased risk of endometrial cancer due to the oestrogen part of HRT. However, by taking combined HRT containing oestrogen and progestogen, this risk reduces completely.

6. Cancer of the ovary

It is thought there is a slightly increased risk of developing which decreases after you stop HRT.

Contraindications to the administration of HRT:

- History of endometrial cancer, ovarian cancer or breast cancer.
- History of blood clots (a DVT or a PE).
- History of heart attack, angina or stroke.
- Uncontrolled
- Pregnancy
- Severe liver disease.
- Undiagnosed
- Non-HRT treatments for hot flushes and night sweats

SSRIs and SNRIs

Selective serotonin reuptake inhibitors (SSRIs) are a class of . They include , , and. Several years ago it was noticed as a side-effect that menopausal women who took these drugs for depression had fewer hot flushes. Since then, research trials have confirmed that several SSRIs stop or reduce hot flushes in some (but not all) menopausal women. That is, whether they were depressed or not. A similar antidepressant drug called , a serotonin and noradrenaline reuptake inhibitor (SNRI) antidepressant, has also been shown to have this effect.

How SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs) work to help hot flushes is not clear. When it works, an SSRI or SNRI provides relief from hot flushes almost immediately. A trial of one to two weeks is usually enough to find out whether it is going to work or not. If symptoms improve, a longer course may then be prescribed. The main drawback with these drugs are their side-effects in some women, such as feeling sick (nausea), reduced sex drive (libido) and sexual response. Gabapentin is a drug that is usually used to control epileptic seizures and pain. However, research has shown that it eases menopausal flushing symptoms in some women.

Clonidine

Clonidine, a centrally acting drug shows little evidence that it is beneficial in improving symptoms. It frequently causes side-effects such as dry mouth, drowsiness, dizziness and feeling sick. It is therefore not commonly used any more.

Non-HRT treatments for vaginal dryness

Vaginal lubricants and moisturisers, can help ease vaginal dryness.

Osteoporosis

Prevention of bone disease includes adequate calcium and vitamin D intake. Current medications in vogue are bisphosphonates such as alendronate and risedronate, calcitonin, a peptide hormone which inhibits osteoclast activity, parathormone (PTH 1-34) and selective estrogen receptor modulators (SERMs) which are nonhormonal agents such as raloxifene. Tibolone is a oidal drug that alleviates symptoms as well as preserves bone mineral density. However its long term effect on breast and endometrial cancers remains controversial as shown in the Million Womens Study.

A study group statement in 2012 on Menopause and Hormone Replacement states that Hormone replacement therapy (HRT) is effective for symptomatic relief of menopausal symptoms and its use for this is justified when symptoms adversely affect quality of life. The lowest effective dose for a particular woman should be used for the shortest period necessary and treatment reappraised at least annually. If menopausal symptoms return after stopping HRT, women may wish to consider restarting it and, provided they are fully informed of the risks, it should not be withheld

'Short-duration' HRT may be considered to be use of HRT for up to five years and is usually aimed at relief of menopausal symptoms in women in their early 50s. In some women, symptoms may persist considerably longer than this. If a decision is made to stop HRT, it should be phased out slowly in symptomatic women.

HRT can be used in younger women who have experienced a premature menopause (younger than 40 years), unless contraindicated, for treating menopausal symptoms and preventing osteoporosis until the age of normal menopause, when the therapy should be reviewed.

HRT can be used as 'add-back' therapy when gonadotrophin-releasing hormone (GnRH) agonists are administered to avoid menopausal symptoms.

Local oestrogen replacement may be required for the long term to reverse the symptoms of urogenital atrophy, which is a late manifestation of oestrogen deficiency. It appears to be more effective than systemic therapy. Low-dose vaginal oestrogens can also be used in the management of postmenopausal women with recurrent

While irritative urinary symptoms such as urgency, urge incontinence and frequency and nocturia may be improved by oestrogens, stress incontinence cannot be treated effectively by oestrogens alone, although it may be a beneficial adjunct to surgery.

Women who have experienced a surgical menopause with bilateral oophorectomy may benefit from testosterone replacement in addition to oestrogen specifically to improve libido. The place of testosterone in ovary-intact women with low libido requires further evaluation. Testosterone replacement may be associated with adverse clinical and metabolic side effects and long-term consequences are

unknown.

The overall risk--benefit balance for HRT in women without menopausal symptoms is not generally favorable.

HRT prevents osteoporotic fractures while it is taken although the benefit declines soon after stopping. Its use for this alone is, for most women, not recommended. However, its use in women at very high risk of osteoporosis could be carefully considered, particularly if other therapeutic agents are unsuitable.

Raloxifene, a selective oestrogen receptor modulator (SERM), reduces the incidence of vertebral fractures in women with osteoporosis. There is no current evidence of protection against fractures at the hip or at other sites. Use of raloxifene is associated with reduced risk of breast cancer but increased incidence of vasomotor symptoms.

Most randomised trials and observational studies have indicated that current or recent use of HRT increases risk of breast cancer. However, the risk returns to that of women who have never used HRT soon after it is discontinued. Women must be carefully counseled regarding this increased risk, which appears to be directly related to duration of therapy, not to dose. The evidence suggests that combined oestrogen and progestogen preparations increase the risk of breast cancer more than oestrogen alone. Women taking HRT should be advised to attend regularly for mammographic screening. HRT is contraindicated in women with previous breast cancer.

Women being prescribed, or already taking, combined oestrogen and progestogen preparations should be informed that this therapy may increase the likelihood of both false positive and false negative mammographic screening and that mammography may not detect breast cancer. Approximately one-quarter of women taking combined oestrogen and progestogen preparations will show a significant increase in mammographic density. This increase in density has been shown to reduce the sensitivity of screening mammography and to increase the likelihood that women are recalled for further investigations after mammography (even if they are not found to have breast cancer).

Tibolone has oestrogenic, progestogenic and androgenic properties. It appears to be effective in the treatment of vasomotor symptoms. Recent data suggest that tibolone may also be associated with an increased risk of breast cancer, but less than that associated with combined oestrogen and progestogen preparations.

HRT has been demonstrated in randomised trials not to confer either primary or secondary prevention against ischaemic heart disease or stroke. There is increased risk of stroke and an early excess risk of myocardial infarction in HRT users. The absolute risk of these conditions increases with age. HRT is contraindicated in women with clinical evidence of ischaemic heart disease, cerebrovascular disease or peripheral arterial disease. The metabolic effect of oestrogen can be influenced by the route of administration.

All women commencing HRT should be counseled about the risk of venous thromboembolism (VTE), should be aware of the signs and symptoms of VTE, and should be able to access medical help rapidly if they suspect that they have developed a thrombus. Prior to commencing HRT, a personal history and a family history assessing the presence of VTE in a first- or second-degree relative should be obtained. HRT should be avoided in women with multiple pre-existing risk factors for VTE. Non-oral oestrogen may be associated with lower risk of VTE, compared with oral oestrogen therapy.

Testing for thrombophilia should be discussed with and be available for women with a personal or family history of VTE. It is recommended that, in women with a previous VTE, with or without an underlying heritable thrombophilia, oral HRT should usually be avoided in view of the relatively high risk of recurrent VTE. Universal screening of women for thrombophilic defects prior to or continuing the prescription of HRT is inappropriate. In women without a personal history of VTE but with an underlying thrombophilic trait that is identified through screening, HRT is not recommended in high-risk situations such as type 1 antithrombin deficiency or with combinations of defects or additional risk factors for VTE, and specialist advice should be sought.

It is recommended that, when a woman who is on HRT develops a VTE, HRT should be discontinued. It is recommended that, if a woman is required to be continued on HRT after a VTE, long-term anticoagulation should be considered.

HRT should be considered a risk factor for VTE when assessing women preoperatively. However, HRT does not require to be routinely stopped prior to surgery provided that appropriate thromboprophylaxis, such as low-dose unfractionated or low-molecular-weight heparin, with or without thromboembolic deterrent stockings, is used.

Recent randomised controlled trials in women of 65 years or older reported that HRT does not have a beneficial effect on cognitive function. Also, HRT does not appear to be an effective treatment of established Alzheimer's disease. There is some evidence that use of HRT in women older than 75 years may increase the risk of developing dementia.

HRT should not be used, and is not licensed, as a primary treatment for clinically significant depression or dementia. Some, but not all, studies have shown that HRT appears to improve depressed mood in women with menopausal symptoms.

In women with a uterus, oestrogen-only therapy is associated with a significantly increased risk of developing endometrial hyperplasia and, with continued use, of endometrial carcinoma. This risk remains beyond cessation of therapy.

The addition of progestogen to oestrogen therapy reduces the risk of endometrial disease, but regimens should usually include at least 10 days in each monthly cycle. Postmenopausal women who have been taking sequential oestrogen-progestogen

therapy for more than five years and wish to continue are at increased risk of endometrial carcinoma. They should consider changing to a continuous combined regimen, which appears to confer no increased risk.

Progestogens alone may be effective in treating hot flushes and may be considered a therapeutic option for women who do not want to take, or cannot take, oestrogen. However some evidence suggests that progestogens might increase breast cancer risk even when prescribed without oestrogen. In addition, high-dose progestogens may be associated with increased risk of venous thromboembolism.

There are differences between the progestogens in their metabolic and physiological effects but it is not known if these differences are clinically significant.

Small research studies suggest that the antidepressants venlafaxine*, paroxetine* and fluoxetine* are options for women with hot flushes who are not candidates for oestrogen therapy. These are not contraindicated in women with breast cancer. The additional antidepressant effect of these agents may be beneficial in women who also suffer from mood disorders although they may be associated with loss of libido.

A benefit of up to 50% is seen in trials of many 'alternative' preparations prescribed for vasomotor symptoms, even in placebo groups. Data are lacking regarding the efficacy and safety of topical natural progesterone cream and it cannot be recommended at present for the treatment of hot flushes. Similarly, there is no convincing evidence to support the use of food supplements and herbs.

Education

- The distinction between short-term HRT use for acute relief of menopausal symptoms and the risks and benefits of long-term use should be clarified.
- Where appropriate, women should be advised in terms of absolute risks of the known adverse and beneficial effects of HRT, rather than relative risks.
- With HRT use, women should appreciate the concept of individual needs and risk assessment coupled with population-based evidence.
- Balanced information on HRT should be readily available to both clinicians and the public. Women with menopausal symptoms who choose to take HRT should be supported by well-informed healthcare professionals.
- Accurate information should be available for women and primary care staff on the management of premature menopause.

The terminology for HRT preparations should be clarified and universally adopted.

- Education at undergraduate level should introduce the communication skills necessary to enable doctors to deal with areas of medicine that are not disease-related, such as menopausal problems.
- The primary care team should be able to respond to the challenge of evaluating

and treating menopausal women. There are a number of GPs who have extended their knowledge and skills in the area of women's health and should be considered GP specialists. Further expansion of the GP specialist concept is important and should be supported by the academic colleges and central government.

- Information technology offers enormous potential benefit for service delivery and communication. Investment in this field could assist information flow and decision support and provide for much-needed population-based research in areas such as menopausal medicine.
- The media should make efforts to convey the key messages of the new results from research on HRT accurately.
- New information regarding HRT should be released to experts sufficiently early so that findings can be put into context and cascaded down in sufficient time to allow clinicians to respond appropriately.

Editors of major medical journals should commission balanced editorials to accompany new research findings.

RCOG UPDATE (11 June 2013):

The British Menopause Society (BMS) and Women's Health Concern recently published a literature review of the evidence on the use and effects of HRT. In summary, their key recommendations are:

The decision whether to use HRT should be made by each woman having been given sufficient information by her healthcare professional, including information about complementary therapies and lifestyle and dietary changes.

HRT dosage, regimen and duration should be individualized, with an annual evaluation of the pros and cons.

Arbitrary limits should not be placed on the duration of usage of HRT; if symptoms persist, the benefits of hormone therapy usually outweigh the risks.

HRT prescribed before the age of 60 has a favorable benefit/risk profile.

It is imperative that women with Premature Ovarian Insufficiency (POI) are encouraged to use HRT at least until the average age of the menopause.

If HRT is to be used in women over 60 years of age, lower doses should be started, preferably with a transdermal route of administration.

Research and development of new compounds should continue to maximize benefits and minimize side effects and risks.

NATURAL ALTERNATIVES TO HRT

Phytoestrogens provide an alternative to HRT for many women. The interest in phytoestrogens has developed because of the epidemiological evidence that diets rich in these compounds have led women in Japan and Asia to appear to have a much lower incidence of

Phytoestrogens provide an alternative to HRT for many women

"Western diseases" such as heart disease, osteoporosis, and cancers of breast, colon, and womb. Women in these countries do not appear to suffer the same way with hot flushes and sweats as women do in the western world. Whether one can attain the same protection by starting their diet later in life remains to be seen and the difference may also be related to other factors such as cultural differences in attitude to menopause.

Phytoestrogens have been shown in some clinical trials to reduce hot flushes significantly

Phytoestrogens have been shown in some clinical trials to reduce hot flushes significantly, although many of the trials were undertaken over short periods e.g. 3 months and some trials have shown limited effect. These are plant compounds structurally and functionally similar to 17 β estradiol and bind to estradiol receptors. Phytoestrogens are thought to act as both agonists and antagonists. Several plants possess phytoestrogens, such as black cohosh, dong quai, ginseng, licorice, and wild Mexican yam. Phytoestrogens are non-steroidal, naturally occurring phenolic compounds into various classes that include isoflavones, lignans, coumestans, resorcylic acid lactones, and mycotoxins.

Phytoestrogens are thought to act as both agonists and antagonists. Phytoestrogens are non-steroidal, naturally occurring phenolic compounds

Numerous antiproliferative properties are suggested for phytoestrogens. Genistein inhibits tyrosine protein kinases, which are coded by protooncogenes and play a key role in tumorigenesis. It also inhibits deoxyribonucleic acid (DNA) topoisomerases I and II, and may prevent cell mutations by stabilizing cell DNA. Another mechanism may involve reduction of cell oxidants. Genistein reportedly inhibits formation of tumor promoter-induced hydrogen peroxide and superoxide anion, and it scavenges hydrogen peroxide that is added exogenously to cultured human cells. Daidzein appears to have similar antioxidant activities. Genistein also induces apoptosis; inhibits angiogenesis, subsequent tumor growth, and cell differentiation; and may reduce malignant cell metastasis as a result. These phytoestrogen effects probably are related to relative tissue concentrations. Estrogen concentrations are 40-fold higher in breast fluid aspirates than in serum concentrations; if phytoestrogens can achieve similar relative concentrations, this may account for their protective effects by estrogen receptor antagonism.

The effects of phytoestrogens on menopausal symptoms appear to be promising. Consumption of as little as 30 mg soy isoflavones, in soy protein or as an extract, reduces vasomotor menopausal symptoms by 30–50% including the placebo effect or 10–20% after subtracting the placebo effect. Soy protein and isoflavones work together to lower LDL cholesterol and increase HDL cholesterol. conflicting information regarding the effect of isoflavones on FSH

Soy protein and isoflavones work together to lower LDL cholesterol and increase HDL cholesterol. conflicting information regarding the effect of isoflavones on FSH concentrations, clinical studies illustrate that they increase vaginal maturation

concentrations, clinical studies illustrate that they increase vaginal maturation. Human data regarding the hormones' ability to alleviate menopausal symptoms, their potential reduction in breast cancer risk, and potential increase in BMD are positive. These compelling data, in conjunction with absence of information regarding dosing and long-term effects, should serve as stepping stones for further research evaluating phytoestrogens as alternatives or adjuncts to conventional HRT. No evidence was found of harmful effects on the lining of the womb, stimulation of the vagina or other adverse effects with short-term use.

Phytoestrogens can be taken either by increasing dietary intake or from supplements. To rely on dietary intake alone would involve the ingestion of large amounts of legume food plants, such as peas and beans, with variation in their quantities of phytoestrogens. There are many supplements now available which aim to be equivalent to a typical Japanese diet rich in phytoestrogens.

Four classes of phytoestrogens have been investigated: isoflavones, lignans, flavones and coumestrans. Isoflavones are the most common form and include genistein, daidzein and glycitin.

Phytoestrogens or plant estrogens in our diets

The following foods contain phytoestrogens:

Cereals: oats, barley rye, brown rice, couscous and wheat.

Seeds: sunflower, sesame, pumpkin, poppy, linseeds

Pulses: soya beans and all soya based products

Beans: chickpeas, kidney beans, haricot beans, broad beans, green split peas

Vegetables: red onions, green beans, celery, sweet peppers, sage, garlic, broccoli, tomatoes and bean sprouts.

Soya, Linseed and Red Clover are the richest sources

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Dear Doctor,

Management of menopause has been changing recently due to new clinical trials and studies published providing more information on benefits as well as complications of various treatments and technologies. It gives me a great pleasure introducing this July-September 2014 QMR on Current trends in management of menopause by Dr. Shyam Desai and Dr. Gaurav Desai. Dr. Desai has put together a very balanced and exhaustive review to provide information of the recent updates and understanding of managing menopausal symptoms from an in-depth perspective. This review on the recent trends on management of menopause would be of interest to everybody who is looking for deeper understanding of menopause with the current changing trends.

This booklet is presented to you by **Raptakos, Brett & Co. Ltd.**

We would very much like to have your valuable suggestions and comments to make our future issues more meaningful to you.

We will appreciate if you could spend a few minutes to fill in your comments and mail the same to us. You can also view the QMR on our website: www.raptakos.com and e-mail your feedback to following E-mail id: medical1@raptakos.com

Thanking you

Dr. Aziz Keshvani
Chief Scientific Officer



**Feedback form: July - September 2014:
Current trends in Management of Menopause.**

1. Your comments on this issue of Q.M.R.

2. Please suggest medical topics for our QMR which could be printed in future.

3. Any other suggestions / comments:

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