Leading Article

Menopause Transition – Physiology, Symptomatology and Management

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Menopause marks the permanent cessation of menstruation (Final menstrual period = FMP) and can only be diagnosed clinically one year after FMP. Menopause heralds the transition in a woman's life from a reproductive state to a nonreproductive one. Across the world menopause occurs in early 50s, and is only truly affected by smoking and medical or surgical induction of the menopausal state. Clinical symptoms of menopause may precede FMP and the physiological changes of menopause transition may begin several years prior to the onset of any manifestation (usually around 45years and 5 to 6 years prior to FMP). It is the depletion of ovarian follicles to a critical level that heralds menopausal transition [1-3].

In order to understand the context in which the physiological changes of menopausal transition are happening, it is necessary to consider the definitions and stages associated with reproductive aging.

The premenopause is the phase of woman's life from the menarche (onset of menstruation) until the beginning of the perimenopausal stage.

The perimenopause comprises the time from a woman's mature reproductive state at the point when she begins to experience variability in the length of her cycle or a characteristic symptoms of the menopausal transition, to the year following her final menstrual period (FMP). It is only following this 12 month period of amenorrhoea that a diagnosis of menopause can be made. The term menopause and postmenopause are often used interchangeably to describe the phase of woman's life from this point[1,3].

Straw Classification

In 2001, the Stages of Reproductive Ageing Workshop (STRAW) met to propose criteria for defining the stages of reproductive life. The STRAW staging system provides healthcare providers and women with a guide in the assessment of fertility and contraceptive requirements. The latest staging is called STRAW+10.

STRAW+10 staging system is divided into 3 phases.

1) the reproductive phase
2) the menopause transition
3) the postmenopausal phase.

The reproductive stage is subdivided into three stages (-5 to -3). The early reproductive stage (-5) refers to the period immediately following menarche, before menstrual cycles become regular.

During peak reproductive stage (-4) menstrual cycles are regular.

The late reproductive stage (-3) marks the time when fertility begins to go into a decline. It is subdivided into 2 stages. During stage -3b, menstrual cycles are regular but Anti Mullerian Hormone (AMH) levels continue to fall (a process that starts from menarche) as a result of a gradual depletion of antral follicular count.

Stage -3a is characterised by subtle changes in menstrual cycle length and flow. FSH levels rise with increasing variability, whilst levels of antral follicle AMH and inhibin B are low[1].

STRAW -2 is the onset of early menopausal transition where cycle variability increases with a persistent difference of 7 days or more in the length of consecutive cycles. Anatomical and biochemical changes are similar to those of stage -3a, but with increasing variability of FSH levels.

The late menopausal transition (STRAW -1) is characterised by an interval of amenorrhoea lasting at least 60 days[1]. There is increased prevalence of anovulation and further variability in cycle length and hormonal levels. During this stage FSH levels are greater than 25 IU/L and are often associated with high Estragon (E2) levels. However E2 levels start to fall over the last 1-3 years. It is during this time that menopausal in particular vasomotor symptoms usually arise.

Late menopausal transition concludes with FMP (STAW 0). Postmenopausal phase starts from FMP (STRAW +1 to +2). STRAW +1 is defined as the early postmenopausal stage. It is subdivided into three stages. Stage +1a lasts 1 year from FMP and the end of this stage is defined as menopause and marks the end of perimenopause. During stages +1a and +1b (which also lasts one year) , FSH levels continue to rise, while E2 levels continue to fall[1-3]. Thereafter the levels of these hormones begin to stabilise. Vaso Motor Symptoms (VMS) are most likely to occur during this period.

Stage +1c marks a period of stabilization in levels of FSH and E2 which lasts between 3 to 6 years.

The late postmenopausal stage (+2) lasts for the remaining life span of a woman, during which FSH levels tend to fall gradually. Generalised somatic ageing processes rather than reproductive ageing characterise this period. However the prevalence of urogenital symptoms increase at this time[1].

Physiological Changes in the Menopausal Transition

During this period, there is a gradual reduction in the number and quality of ovarian follicles to the critical level[2]. Oocyte production stops at 20 weeks of gestational age when the level is 6 to 7 million follicles. Thereafter the level decreases through a combination of follicular atresia and oocyte release, until fewer than 100 follicles remain in each ovary at the onset of perimenopause (menopausal transition). In addition the oocyte and its surrounding layer of granulosa cells are thought to become increasingly incompetent with age[2].

With decline in antral follicle count in the late reproductive stage and early menopausal transition, there is a reduced amount of inhibin B production by the granulosa cells[2]. Inhibin B usually has a negative feedback mechanism in the pituitary to reduce rising levels of FSH.

Lower levels of inhibin B fail to keep this mechanism in check which leads to higher levels of FSH during the early follicular phase. This in turn leads to increased activity of a single dominant follicle or the recruitment of multiple dominant follicles, and thus higher levels of E2 production. As E2 levels rise to a critical level.

At an earlier stage, the LH surge occurs earlier and the follicular phase is shortened, which in turn reduces the overall cycle length[2]. The luteal phase does not change in duration until later in transition. This shortened menstrual cycle does not occur in all women entering perimenopause.

As women move onto late menopausal transition, menstrual cycle becomes progressively longer in duration. The proportion of cycles which are anovulatory also increases. This may be due to a variety of reasons.

1) A progressive deregulation of positive and negative feed back mechanisms in the hypothalamic pituitary ovarian axis. High levels of E2 which elicits an LH surge in the middle of the cycle has failed.

2) A fall in E2 in the luteal phase has also failed to lower the circulating levels of LH due to hypothalamic-pituitary insensitivity.

3) In the ovary, high levels of FSH may also prevent ovulation occurring inspite of LH surge.

Progesterone levels appear to fall steadily throughout menopausal transition. This may be due to reduced Progesterone production from corpus luteum as well as increase in the frequency of anovulatory cycles[2].

Levels of E2, only falls in the 2 years preceding FMP (this has been noted in the prolonged ovulatory cycles) whilst FSH levels continue to rise. Only 12 months following FMP, the E2 levels are persistently low. In the postmenopausal women, it is the estrone (E1) that predominates in the circulation. This is generated by conversion of Androgens (secreted by adrenal glands and postmenopausal ovaries) in the adipose tissue and liver.

FSH levels undergo slow decline in the late menopausal transition[2]. Whilst there is little change in the levels of testosterone across the transition, levels of SHBG (Sex Hormone Binding Globulin) falls leading to an increased proportion of free testosterone[3].

AMH produced by antral follicles is not directly involved in feedback mechanisms. AMH is high at menarche and then declines after 26 years. It is almost undetectable in the 5 years preceding menopause.

Symptoms of Menopausal Transition

Meopausal transition and postmenopausal period are characterised by broad range of physical and psychological symptoms which can be extremely debilitating.

A woman has about 400000 potential oocytes in her ovaries at menarche. She loses these at a rate of 1000 per month regardless of whether she takes oral contraceptive pills which inhibits ovulation but does not spare oocytes.

Symptoms of menopausal transition also called climacteric, are usually reported as a continuum and can be classified into several types:-

- VASOMOTOR SYMPTOMS:- include hot flushes, palpitations, night sweats, altered sleep pattern and fatigue.

- NEUROMUSCULAR :- these include headaches, joint and muscular pain. other degenerative changes may also occur such as hair and skin changes, which can include a crawling sensation (formication) and itchy skin.

- PSYCHOGENIC :- these include poor concentration, forgetfulness, depression, anxiety, claustrophobia, agoraphobia, irritability, difficulty in coping, tearfulness and lack of drive including sex drive.

- UROGENITAL :- symptoms of vaginal dryness, uterovaginal prolapse and urinary symptoms of urge incontinence / overactive bladder.

- INDIRECT SYMPTOMS :- of menopausal osteoporosis – repeated fractures.

There is a huge variation in the frequency and severity of menopausal symptoms between different women.

About 20% have no significant symptoms, 60% have mild to moderate symptoms and 20% have very severe symptoms.

Menopause induced by surgery or chemo/radiotherapy usually have more severe symptoms.

Vasomotor Symptoms

Hot flushes adversely affect many women in menopausal transition (MT). These symptoms persist for 5 years on average. It is thought that the alpha adrenergic system, specifically noradrenaline, is the chemical trigger triggered by decreasing Estrogen levels. Hot flushes can be aggravated by stress, anxiety, diet, lifestyle and other medications.

Although night sweats can keep women awake at night, insomnia associated with menopause is likely to be due to a separate mechanism (loss of neuronal modulation of energy metabolism), and one can occur without the other[4].

Neuromascular Symptoms

Joint pain is a common complaint in perimenopausal women. Estrogen is thought to attenuate inflammation and promote cartilage turnover[5].

Headaches and migraine are also common symptoms in the perimenopause. In migraine, continuous hormone replacement therapy should be considered, preferably using a non-oral route and lowest effective dose. Estrogen gives variable results for headaches.

If Estrogen is contraindicated, migraine can be treated with serotonin reuptake inhibitors such as venlafaxine, fluoxetine and paroxetine, which all have shown efficacy[6]. Lifestyle changes alone or in combination with isoflavones may be used for prevention of migraine in MT. Gabapentin also reduces frequency and severity of migraine.

Psychogenic Symptoms

During perimenopause, psychogenic symptoms such as fear of ageing (and wrinkles), changing body shapes, financial pressures, relationship issues, and changing roles with children becoming independent. Estrogen imbalance may aggravate any or all of these. Women who have a past history of depression, or have a history of premenstrual syndrome are more likely to experience psychogenic changes during the perimenopause providing HRT will alleviate Estrogen deficiency, but cannot compensate for many of the factors which may be responsible for low mood. However, certain types of depression which are due to Estrogen deficiency are best treated by HRT[7].

Urogenital Symptoms

Vaginal problems are common and under reported.

Vaginal dryness due to Estrogen deficiency, can cause sexual problems due to lack of lubrication and loss of tissue elasticity.

Loss of normal vaginal secretions can also be associated with an overgrowth of vaginal commensal organisms, resulting in vaginal discharge.

In addition to the vagina, urogenital tract is also affected by lack of Estrogen and this may present as urgency or urge incontinence.

Urogenital problems respond best to local Estrogen therapy. Which includes creams, tablets and vaginal rings. Only Vagifem 10 microgram inserted into the vagina twice a week, is licensed to be used without additional progesterone, lifelong in women with an intact uterus.

Osteoporosis

Women lose 1% of their bone mass each year after ovarian failure and Estrogen replacement can inhibit this.

Quantifying Symptoms

To document the severity of symptoms, a quantitative score sheet has been developed. This enables women to self-score their symptoms on a scale of 0 to 3 and for the total score to be calculated. Not only this allows the severity of symptoms to be accurately assessed, but it also allows follow up of any change / improvements as a result of any therapy.

Menopausal Symptomatology Score Sheet

Symptom	*Score (0 = nil, 1= mild, 2=moderate, 3=severe)*
VASOMOTOR SYMPTOMS	
Hot flushes	
Night sweats	
Crawling feeling under the skin	
Dry skin	
NEURO MUSCULAR SYMPTOMS	
Muscle pains	
Backache	
Headaches	
Joint pains	
PSYCHOLOGICAL SYMPTOMS	
Depression	
Irritability	
Mood swings	
Anxiety	
Inability to sleep	
Tiredness	
Loss of sex drive	
Unloved feelings	
Tearfulness	
UROGENITAL SYMPTOMS	
Dry vagina	
Painful sex	
Urinary frequency/urgency	
Total Score	

Differential Diagnosis

Before we describe a woman's symptoms as being due to climacteric (Menopausal Transition / Perimenopause) we need to be sure we are not missing a medical problem. The three commonest medical problems that can be confused with menopausal symptoms are hypothyroidism, anaemia and depression. Depression is particularly difficult as it is very common in women during perimenopause.

Conclusion

Take a good history about symptoms of menopause.

Using the score sheet is a valuable way of quantifying the symptoms. Take a detailed history with

respect to risk factors for breast cancers, thromboembolic disease and osteoporosis.

Ordering a series of expensive hormone tests in women undergoing physiological menopause is a waste of resources.

Firstly, FSH levels are variable and single raised level is not meaningful.

Secondly, Estrogen levels vary a lot from day to day and its blood level bear no relationship to the symptomatology.

Thirdly the results of hormone tests will not change the management of the patient. This should be determined by the women's symptoms.

The initial prescription of HRT is a therapeutic trial. Using the score sheet is a more objective way of evaluating any improvement in symptoms during treatment. Maximum possible score is 60.

If there is improvement, continue the prescribed treatment. If there is no improvement, a different preparation of HRT could be tried.

References

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